The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Evidence submitted to the Review following its Oral Hearings

Published May 2019

Contents

Introduction

This document contains information provided to the Independent Medicines and Medical Devices Safety Review in support of, or following, the Oral Hearings held between November 2018 and May 2019. You can find the previous submissions of those that provided them, as well as links to the Oral Hearings, on the Evidence page of the IMMDS Review website.

Disclaimer

The statements made and the opinions expressed in response to the Independent Medicines and Medical Devices Safety Review's ('IMMDSR) Call for Evidence and in the video recording of the IMMDSR's oral hearings are those of the authors. They do not purport to reflect the opinions, views or conclusions of the IMMDSR or its members. The statements and opinions made do not imply the expression of any opinion whatsoever on the part of the IMMSDR concerning the truthfulness, veracity, accuracy or legal status of any statements or opinions made and published on the IMMDSR website. Nor does the IMMSDR accept any legal liability arising from any statements or opinions so expressed and published

WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.

Patient Groups – Hormone Pregnancy Tests

Association for Children Damaged by Hormone Pregnancy Tests

The ACDHPT shared the following:

- Landesarchiv 13198, p82 (p105 original document)
  MHRA Expert Working Group on Hormone Pregnancy Test – Landesarchiv Berlin Files (translated)

Patient Groups – Pelvic Mesh

Mesh Ireland

Mesh Ireland shared the following papers with the Review at the Oral Hearing:

- Kokotovic D, Bisgaard T, Helgstrand F. Long-term Recurrence and Complications Associated With Elective Incisional Hernia Repair. JAMA. 2016;316(15):1575–1582. doi:10.1001/jama.2016.15217
- Ali Azadi, James A. Bradley, Dennis M. O'Connor, Amir Azadi, and Donald R. Ostergard, "Tumor-Like Reaction to Polypropylene Mesh from a Mid-Urethral Sling Material Resembling Giant Cell Tumor of Vagina," Case Reports in Obstetrics and Gynecology, vol. 2017, Article ID 6701643, 4 pages, 2017. https://doi.org/10.1155/2017/6701643.
- Birolini, C., Minossi, J.G., Lima, C.F. et al. Mesh cancer: long-term mesh infection leading to squamous-cell carcinoma of the abdominal wall. Hernia. 2014; 18: 897. https://doi.org/10.1007/s10029-013-1083-x
- Birolini C, de Miranda JS, Rengel L, Teixeira F, Utiyama EM, et al. (2016) Revisiting Mesh-Cancer: An Unusual and Devastating Complication of Chronic Mesh Infection. J Surg Transplant Sci 4(5): 1041.

Welsh Mesh Survivors

Welsh Mesh Survivors provided the Review Panel with a printout highlighting the following two paragraphs in the First Minister's Question Time, in the Meeting of the Scottish Parliament, 25th October 2018:

Jackson Carlaw:

I thank the First Minister for everything that she has said.

For the women concerned, an apology such as the one offered by the First Minister is a necessary cathartic act, but small and practical actions can make a significant change to their lives, too. For example, responsibility for the blue badge scheme rests with the Scottish Government, but many of the women whose mobility has been impaired by mesh are simply not eligible at the moment. To them, access to the blue badge scheme for those in wheelchairs and on crutches would be a hugely welcome and practical advantage.

This might not be the biggest political ask of the day, but it is an important issue to the women involved, and we could resolve to do something about it now. Will the First Minister agree today to instruct ministers and officials to review access to the blue badge scheme and offer those who have had their mobility severely impaired by mesh this singular and practical improvement to their future lives and wellbeing?

The First Minister:

I have a lot of sympathy with the points that Jackson Carlaw has made. I will ask the Cabinet Secretary for Social Security and Older People to work with her officials to look at what action can be taken. I do not want at this stage to give Parliament assurances that I do not know we can deliver on quickly, but I think that it is not necessarily a particularly complicated issue. When it comes to blue badges, local authorities will be relevant in the discussions as well, but I am sure that the cabinet secretary will be happy to talk to Jackson Carlaw about how we can take this forward, once officials have had an opportunity to look at it in more detail.

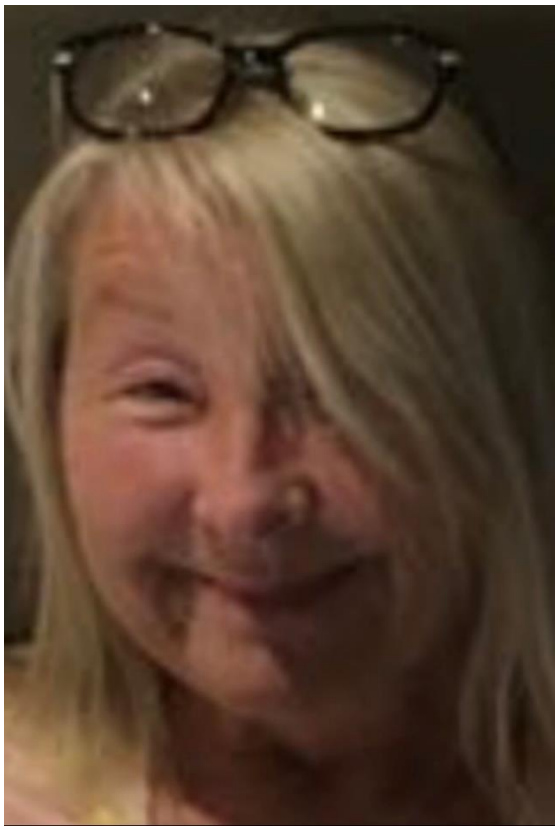
http://www.parliament.scot/parliamentarybusiness/report.aspx?r=11726&mode=html#iob_106167

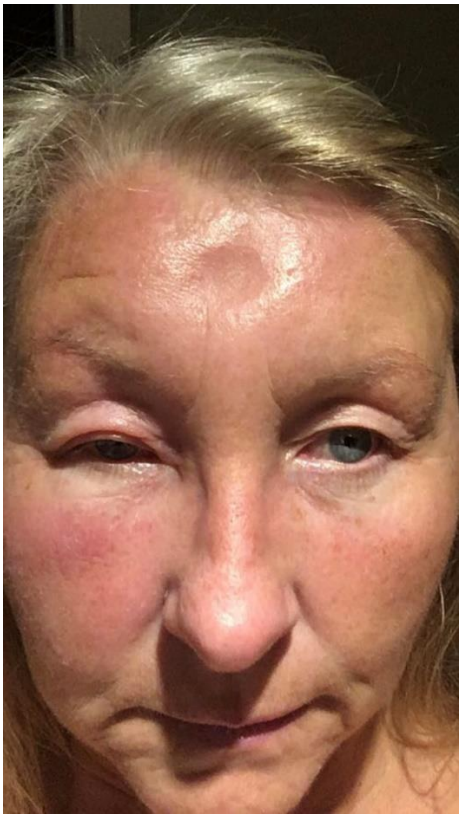
Welsh Mesh Survivors also provided the following links:

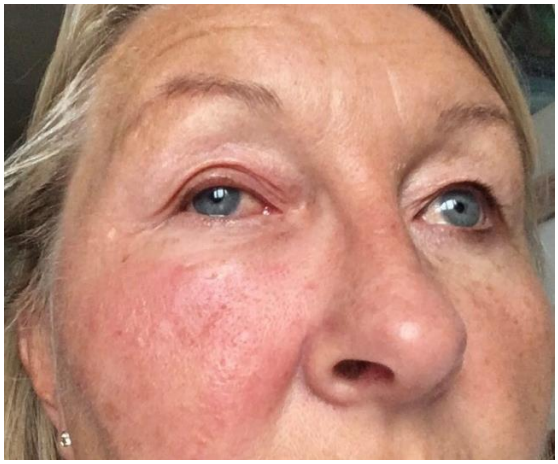
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633602.htm?fbclid=IwAR2fhhr6DgbKnIiGidm8tuxqXcvZKG3ll4GyBg5b-NH_XpEa4OhjLLQM9WE

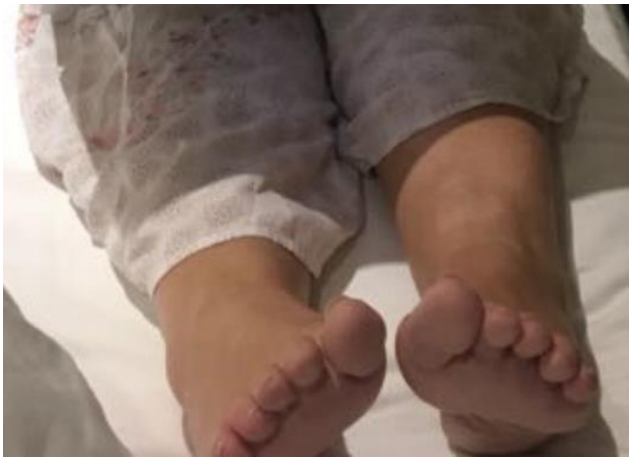
https://www.medicalplasticsnews.com/mpn-north-america/fda-says-more-needs-to-be-done-to-assess-materials-in-device/?fbclid=IwAR068p-tbmEIMbNbIfaxwn16aaPyE6qU3jyLAJo5FkRok3Z66jzvJ62KcCs

Welsh Mesh Survivors have provided these photographs of swelling to the face and body to demonstrate the autoimmune issues raised by a number of Mesh Survivors:









Patient Groups – Sodium Valproate

OACS Ireland

OACS Ireland shared the following with the Review:

Health Service Executive (Ireland) report on prenatal exposure to sodium valproate: *Rapid assessment of the number of women and children exposed to sodium valproate in Ireland 1975-2015*. Available here.

Workshop on Antiepileptic Drug Development. April 15, 1977. Arlington, Virginia. Edited Transcript. US Department of Health, Education, and Welfare Publication No. (NIH) 77-185. Sponsored by the Commission for the Control of Epilepsy and its Consequences (P.L. 94-63)

Clinicians, academics and other individuals – Hormone Pregnancy Tests

Dr Jesse Olszynko-Gryn

Dr Olszynko-Gryn shared the following with the Review:

Subject: Brewer 1975

Attachment: Brewer C. Continued use of hormonal pregnancy test. British Medical Journal 1978; 1 :437 https://doi.org/10.1136/bmj.1.6110.437

Attachment: Primodos Section

Please find attached the 1975 report I mentioned. It is by BPAS, so the sample is 100% biased towards women seeking abortion. The crucial sentence is:

"Although in some cases the GPs may have prescribed HPT in the belief that the pregnancy would be terminated and that teratological risks could therefore be ignored, some of the HPTs were prescribed by GPs who subsequently refused to refer the woman for abortion."

I find the passage suggestive of a range of practices, though it isn't a lot to go on and could be interpreted in different ways. Were some GPs willing to prescribe HPTs as abortifacients, but then not willing to refer their patients for abortion? Or were they prescribing HPTs in good faith, perhaps despite the expectation of their patients?

I have also attached the section of my PhD thesis that discusses HPTs. It includes a discussion of Higgins & Sadler 1960:

"Drs G. L. Higgins and W. R. Sadler, who provided antenatal care to 7,500 patients in Bristol, an industrial city of 500,000, considered the Hogben test 'cumbersome and lengthy' and also noted that 'the collection and transmission of the specimen represent considerable inconvenience to an already busy person.' They decided to give Primodos to 'all women'
(excluding those 'who were clearly pregnant') 'who had amenorrhoea of short duration, after explaining the nature of, and the reasons for, the test (Higgins & Sadler, 1960, 677-678)."

The article is not available online, but you might want to get hold of it to read the whole thing. I haven't looked at it in a while, but my impression is that many GPs, like them, considered HPTs to be more convenient than alternatives - and probably prescribed them mostly in good faith - at least until the early or mid 1960s, when cheaper and more convenient test kits replaced animals. Regional access to legal

abortion after 1968 may also be an important factor, but how much of one would be difficult to reconstruct, geographically, from the patchy historical record.

The Gal passage you referred me to is interesting, and I guess it would help to be able to situate the 19 index and 4 control cases a bit more. Are you able to do this? And is the implication that the women were maybe hoping that the tablets would restore menstruation/terminate an unwanted pregnancy, but also that they were unwilling to take more unambiguous steps in that direction?

Perhaps importantly for your research, the majority of women who had harmless urine tests done in the 1970s also did not want to be pregnant. I have seen market research claiming that in 1978 only 1/3 of women using urine/lab pregnancy tests wanted to be pregnant, whereas 2/3 did not want to be pregnant. These ratios reverse by 1989, by which time successful marketing campaigns for products like Clearblue have effectively convinced married, healthy women hoping to get pregnant that they should use a home test.

So I do think that in the 1960s-70s, many women seeking a pregnancy test did not necessarily want to be pregnant or aren't sure, maybe up to 2/3.
But I also think this was true of urine/lab tests and which one they got depended more on the GP than on any other underlying factor.

Further, I do not think the ratio necessarily implies that many or most HPT users would have knowingly tried to induce a miscarriage by some other means. Some of them might have changed their minds upon a 'positive'
result. Others may have been worried about menopause, which accounted for many of the 'negative' results in reports I have seen (on urine testing).
The only (two) cases I know of for sure of women who knowingly used HPTs in an attempt to induce miscarriage were fairly middle-class metropolitan college students. Here is one of the accounts, also from my PhD thesis:

"In the 1960s, [. . .], a student at Chelsea Art School, was given Amenorone Forte on two separate occasions by her family doctor, 'a refugee from Germany. He was also a dirty old man, but didn't let on to [her] parents about [her] wayward behaviour.' [She] took the tablets, which 'had to be dissolved under the tongue', on the bus to school 'and for weeks afterwards every time [she] got on the bus [she] could taste them - a Pavlovian response!'"

But most of the evidence I have seen for Britain (and some of it is in the attached PhD excerpt) suggests that Primodos was typically prescribed and ingested in good faith, as a diagnostic test for pregnancy. Initially, there was genuine excitement about a cheaper alternative to animals that liberated GPs from dependency on the expensive, distant laboratory. Leading experts in the UK tested HPTs against urine/animal tests, on their patients, and in good faith. I suspect, as I say in the article, that some of these practices may have continued well into the 1960s-70s out of habit.

Campaigners in West Germany, for instance, are upfront about having taken HPTs as abortifacients before abortion was legalised in 1976, a full decade after the British

Abortion Act. But in some ways this suggests that women in Britain may have had less need of abortion pills, especially after 1968.

Historians are fond of saying "It's complicated" and in the case of HPTs I don't think there is a single explanation that covers all prescribing practices or patient expectations that will have shifted, possibly significantly, even between the 1950s and late 1970s. Further, I expect there was a lot of geographical variation (based on economic means, access to laboratory services, access to legal abortion after 1968, and maybe other factors), but also that it will be difficult, maybe impossible, to adequately reconstruct it.

Subject: P.S. Primodos

Attachment: Leddy 'Primodos my recollections'

Attachment: Britton H. G.. Pregnancy Test British Medical Journal 1956; 2 :419 https://doi.org/10.1136/bmj.2.4989.419

P.S. Just a few more thoughts.

First, we (historians) don't know much the history of the informal use of patent medicines ('female pills') or pharmaceuticals as abortifacients. As for the specific question of whether women who took Primodos were more or less likely to take other substances or steps to induce menstruation/miscarriage, all I can say is that I have seen no evidence that this was the case. At least not for Britain.

Like I said, some West German women are open about having used HPTs in the hopes of inducing miscarriage; residual shame is one of the reasons they give for not establishing an advocacy group until very recently. In contrast, the ACDHPT was formed early on, in 1978, evidently by married women who were hoping for pregnancy.

Probably you don't have the resources, but surveying retired GPs and pharmacists would be a good thing to do. Is there a mailing list of retired GPs or med school alumni you could use to this end? Journals like The Practitioner are more useful than the BMJ or Lancet, but more frontline perspectives would help a lot.

Meanwhile, I attach a first-hand account from Bernard Leddy, a pharmacist who remembers regularly dispensing Primodos, evidently in good faith, but with some misgivings.

Also attached is the first published warning against HPTs, in the BMJ. It is a letter from a GP and was overlooked by the MHRA.

P.S. Morning-after pills

P.S. In my recently published book chapter on contraception/abortion I write:

"College physicians who provided the synthetic oestrogen diethylstilbestrol (DES) off-label to 'girls unprepared for the night before' were forced to look elsewhere when longer-term use for other indications was linked to a rare form of vaginal cancer in daughters of women who had taken the drug during pregnancy. Canadian gynaecologist Albert Yuzpe's method of punching out four tablets of oral contraception was authorized in the early 1980s in Britain and West Germany, but not Canada or the United States, where feminists took matters into their own hands by distributing Yuzpe regimen dosages at rape crisis and student health centres."

https://www.people.hps.cam.ac.uk/index/affiliates/olszynkogryn/OlszynkoGryn2018c.pdf

The major histories are Prescott, The Morning After: A History of Emergency Contraception in the United States (New Brunswick, NJ, 2011), and Foster and Wynn (eds.), Emergency Contraception: The Story of a Global Reproductive Health Technology (Palgrave, 2012), which may have a chapter on the UK.

Not sure what, if anything, this says about the off-label use of Primodos and other HPTs as abortifacients, but possibly the evidence points more to higher dosages of oral contraception as the default method?

Subject: Some more data

One more thing is that feminists offered free pregnancy testing services in the 1970s. I've written about this here:

https://www.tandfonline.com/doi/full/10.1080/09612025.2017.1346869

These services were aimed at young, unmarried women who did not want to be pregnant. But the reality was more complex; many women wanted to be pregnant, were unsure or had mixed feelings:

"Aggregated and analysed data confirms that pregnancy testing, if nothing else, was a variable experience. Of the sixty-two positive results obtained by [the Cambridge service] in a single year, twenty women 'wanted to be pregnant,' thirty 'did not' and the rest either 'weren't sure' or didn't say. An analysis of 304 tests performed by the Bristol service found that, while 53% of testees were pleased with a negative result and 43% disappointed with a positive, 37% were pleased with a positive and 13% disappointed with a negative. No older women wanted to be pregnant and sufficiently many were worried about menopause for the group to produce an informational leaflet on the 'Changes in Life'. As expected, young women and girls frequently 'wanted reassurance after "taking a chance,"' or else doubted the effectiveness of the contraceptive they were using. But a substantial group of women in their mid to late twenties were 'keen to start or add to their families' and 'really pleased to get a positive result.'"

I don't think the profile of women who were given HPTs would look significantly different, since my understanding is that the GP's preference, not anything in particular about the women, was the determining factor between whether they were given a urine test or HPT.

Perhaps even something as basic as a list of ACHPT members and whether they were married at the time they were given HPTs would begin to paint a picture.

Subject: Matthew 1956

Another important point, mentioned in my RBMSO article, is that HPTs were considered reliable earlier than urine tests, which were only reliable 2 weeks after a missed period. So if a patient went to her doctor a few days after a missed period, she could be sent home with HPTs right away, but would have to be seen in another couple of weeks for a urine test.

As discussed in my PhD thesis, Matthew (1956) enthusiastically reported the oral administration of Orasecron (Schering UK) in the BMJ as 'a reliable clinical method of diagnosing early pregnancy' (p. 979). He specialised in infertility and had, from the end of the WWII, provided a fertility treatment service for the southeast of Scotland, so it is unlikely that he would have knowingly prescribed abortifacients to his patients, many of whom would have been trying to become pregnant.

Subject: Brewer 1979, follow-up

Colin Brewer has been in touch with me regarding his letter to the BMJ in 1978. He wrote:

"I'd forgotten that it was an actual survey rather than just a case report but there's not much I can add. My guess is that ignorance rather than anything more sinister was the explanation for the persistence of old prescribing and diagnostic habits. Thanks to the NHS payment system - especially before the 1980s introduction of several new item-of-service payments - there was little opportunity to bribe NHS GPs other than in rather non-specific ways such as paying them to go to conferences in pleasant resorts. There were certainly GPs who refused to refer women for abortions and there still are, but not many."

Subject: Primodos publicity material

Attachment: Primodos bookmark

A bookmark,
For evidence of explicit selling points targeting GPs.

Subject: Indications

Another perhaps significant detail to consider is that, as you know, HPTs had two main indications, the diagnostic one for pregnancy testing and the therapeutic one as a treatment for amenorrhea. I believe the MHRA report indicates that many times more pills were prescribed therapeutically than diagnostically. So the women wanting to abort may have approached their doctor saying something more like: ‘My period is late, are there pills I could take?’ vs. ‘I think I may be pregnant, is there a test?’ My impression is that the ACDHPT women come predominantly from the latter category, because they took the HPTs, diagnostically as pregnancy tests. This may help to explain their guilt and frustration. As for women who asked for and were

given Primodos or related products to treat secondary amenorrhea, we simply don't know much about them. They haven't formed a group or come forward with their stories and a large-scale oral history or social survey project would be required to recover their experience and motives, and then only retrospectively. It could be that many of those women didn't want to be pregnant and were hoping that Primodos or Amenorone Forte would induce menstruation/miscarriage. But it is also possible many of these women had not menstruated in months or years and were actively trying to get pregnant, since these types of hormone products were also widely used to treat infertility and to prevent miscarriage. In any case, I would hesitate to leap to conclusions, one way other the other, without much more evidence.

5.4. 'A modern scientific achievement'

An introduction to endocrinology, a handbook published by Organon Laboratories in 1957 explained that 'Menstrogen' provided 'a safe, simple and effective pregnancy test which [did] not depend on laboratory animals.' Rather, it depended on the production of 'cyclic bleeding in cases of amenorrhoea due to endocrine dysfunction.' The 'failure to induce menstruation after four tablets of Menstrogen have been given daily for five days [indicated] a diagnosis of pregnancy.' The handbook argued that the test did not endanger pregnancy 'because the addition and withdrawal of the hormones present in Menstrogen do not interfere with the existing hormonal balance and have no effect on the pregnant uterus' (Organon, 1957, 35). Organon's catalogue, *Everyday treatment of endocrine disorders*, published in 1959 promoted Menstrogen, now also available in ampoules, as a safe and 'speedy diagnostic aid early in pregnancy' (Organon Laboratories, 1959, 83) (**figure 5.8**).

Figure 5.8. Organon advertised Menstrogen as both a treatment for amenorrhoea and a test for pregnancy (*Practitioner*, *184*, April 1960, A98, June 1960, A80).

In 1959, Dr Douglas Hogg, a Newcastle general practitioner, turned to Schering's 'Orasecron' because of the cost (23 shillings), waiting period (at least a week), and 'trouble' of collecting, packaging, and posting the urine for the Hogben test and also because overworked laboratories often requested that general practitioners 'ask for such tests only when absolutely necessary' (Hogg, 1959, 612). Hogg prescribed Orasecron, which he judged simple, cheap, rapid and reliable, to women who suspected pregnancy on the grounds of a missed period, but showed no other clinical symptoms. One of Hogg's patients made the 'veiled suggestion that the drug had produced an abortion' and so he warned the practitioner 'to be guarded in the wording of his instructions to a patient.' In addition to pregnancy diagnosis, Hogg recommended Orasecron as 'a most useful drug when it is necessary for a woman to regulate her periods to prevent menstruation at awkward times such as examinations or sporting events' (Hogg, 1959, 614). Mary Bew, a Belfast practitioner, found Orasecron 'particularly useful as an aid to diagnosis when pregnancy is possible in an unmarried girl' and did not 'suspect that it had interfered with the course of pregnancy in those women who were pregnant' (Bew, 1960, 372).

Dr D. H. Forster, a general practitioner, argued that the Hogben test was 'cumbersome, because a specimen of urine has to be collected, packed and posted, sometimes to a very considerable distance. This specimen may not reach the laboratory intact, and even if intact may be insufficient in quantity. Assuming these obstacles have been overcome, the results are not always accurate, and, in any case, may not be received until ten days or even longer after the patient's first attendance.' In the past few years, he had performed 'hormone tests for pregnancy' on 46 patients using an 'oily injection' of Disecron. In view of 'the distraught state of mind in so many' of his patients, Forster preferred 'to give two daily injections rather than risk an incorrect diagnosis through a misunderstanding by the patient over the dosage of the tablets.' He considered hormone tests to be 'at least as accurate' as the Hogben test and had not 'heard of any foetal abnormalities resulting from its use'. Finally, the basic NHS cost of Disecron, six shillings for two injections, compared 'favourably with the cost of urinary gonadotrophin tests' (Forster, 1959, 242).

Bruce Hobson, Britain's leading proponent of the Hogben test, expressed doubts that Disecron was a 'desirable' alternative to *Xenopus*. He maintained that the Edinburgh station routinely provided reliable results within 24-48 hours (except on weekends) and that urine specimens packed in polyethylene bottles were sure to arrive intact. Though Hobson conceded that Disecron 'might be more convenient for some general practitioners,' he argued that there were few women who, 'when given the alternative of collecting a specimen of urine or of receiving two intramuscular injections, would choose the discomfort of the latter.' Finally, his strongest objection to any 'pregnancy test involving the injection of steroid material when other adequate tests [were] available', was the uncertainty that 'the resulting hormonal imbalance, however small, may not itself cause an abortion in susceptible women' (Hobson, 1959, 409).

But the convenience of pills continued to appeal to GPs and perhaps also to a generation of patients increasingly at ease with prescription drugs. Dr R. J. Kenton, a Glasgow general practitioner, preferred tablets because they required 'less of the general practitioner's time than injections or urinary gonadotrophin tests.' He prescribed a course of four tablets of Primodos, 'one tablet night and morning on each of two consecutive days' to produce 'either withdrawal bleeding (no pregnancy) or no bleeding (indicating pregnancy) within 3-6 days.' As with Disecron, the cost to the NHS of Primodos compared 'favourably with that of gonadotrophin tests' (Kenton, 1959, 409-410) (**figure 5.9**).

Figure 5.9. These two Schering adverts display different marketing tactics: a direct attack ad on the 'slow' toad in fiery red (left) and a subdued blue one playing on the patient's quiet anxiety over a missed period (right). Both ads make prominent use of the question mark (*Practitioner*, 187, July 1960, A49; 184; Schering Archiv).

Dr Albert Davis compared injections of Organon's 'pregnancy test ampoule' (PTA) to the Hogben test in 100 patients from outpatient gynaecological clinics in north and south London 'thus representative of 'the Metropolitan population', including 'women of Northern Mediterranean and African genotypes' (Davis, 1963, 70). Each patient was given a routine examination, a single intramuscular injection of PTA, instructed to bring a urine specimen the next day for a Hogben test, and seen one week later to verify whether the 'presence or absence of bleeding correlated with the Hogben test', which was repeated in cases of disagreement. All patients were seen later 'either for artificial reinstitution of menstruation, or for supervision of their pregnancy if pregnant.' Davis reported in the *Practitioner* that PTA had been correct in all 100 cases, that it was 'utilizable at an earlier stage' than the Hogben test and that 'there had been no adverse effect in cases of established pregnancy' (Davis, 1963, 71).

Gabriel V. Jaffé, a Bournemouth practitioner, used pridostigmine, a cholinergic drug, as a pregnancy test in 100 women with amenorrhoea. He reported in the *Lancet* an overall accuracy of 97% for the 'simple, accurate, and inexpensive' test, which cost 3 shillings under the NHS.[350] Drs G. L. Higgins and W. R. Sadler, who provided antenatal care to 7,500 patients in Bristol, an industrial city of 500,000, considered the Hogben test 'cumbersome and lengthy' and also noted that 'the collection and transmission of the specimen represent considerable inconvenience to an already busy person.' They decided to give Primodos to 'all women' (excluding those 'who were clearly pregnant') 'who had amenorrhoea of short duration, after explaining the nature of, and the reasons for, the test (Higgins & Sadler, 1960, 677-678). Yet cautious views continued to be expressed.

The chapter by Ursula M. Lister on 'the early diagnosis of pregnancy' in *Calling the laboratory* (1962), first published as an article in the *Practitioner*, warned of the possibility that, 'at least in susceptible cases,' 'the hormone balance may be upset and bleeding occur despite a pregnancy.' Although early diagnosis 'may be desired by the patient,' Lister contended that 'a few weeks' delay and re-examination' was 'the best test of all' (Lister, 1962, 86). This view represented the cautious non-interventionist end of the spectrum. But as we have already seen, anxiety-driven demand was only increasing and many GPs felt pressured by their patients to do something. The unknown risks of tablets and injections, on the one hand, and the increasing demand for pregnancy testing, on the other, contributed to an even greater positive presence of *Xenopus laevis* and *Bufo bufo* in women's magazines. In June 1961 an article by Joan Seaward in *Woman* promoted the Hogben test, not Primodos, 'as a modern scientific achievement.' A full-page article conveyed the pros and cons of different tests in the form of a fictionalised encounter between 'Mrs Berry' and her doctor (**figure 5.10**).

"WOMAN" W/E 24TH JUNE 1961

PREGNANCY TEST ★ ★ ★ a modern scientific achievement

GLANCING through the records on his desk, the doctor noted that the last time he had seen the young woman in front of him was when he had attended her for a miscarriage just three years ago.

Both she and her husband had been bitterly disappointed at the loss of what they had hoped would be their first child. And when Mrs. Berry had completely recovered, he had advised her to become pregnant again just as soon as she could.

"Doctor," she began, "since I got over my miscarriage, I never missed a single period—not even a day late. But now I'm a whole fortnight overdue. That could mean I'm pregnant again at last, couldn't it?"

"It could," he answered. "But I won't be able to give you a definite diagnosis today."

Her face fell. "Do you mean you can't tell by examining me?"

"Not yet," he replied. "In any case, it might be unwise for me to do an internal examination very early in your pregnancy. We have to remember that last time you had a miscarriage in the third month, so it's best to take no risks."

What does a pregnancy test involve?

"But doctor," she said, "how much longer must I wait before knowing for certain? It means so much to my husband and me. Couldn't I have one of those pregnancy tests I've heard about?"

"Well yes, Mrs. Berry," he answered, "as your period is two weeks overdue that could be arranged. The laboratory charges a guinea for making the test, but I take it you think it's worth that?"

"Oh yes," she said fervently. "What happens?"

"Well, in the first place, a carefully prepared specimen of your urine is needed and it's essential that your period is at least two weeks overdue, because it's the presence of what we call gonadotrophic hormones in the specimen of urine which gives proof that conception has occurred. And it takes twenty-five to thirty days from time of conception for these hormones to be first manufactured and then carried in sufficient strength in the urine."

"Can you do the test right here in the surgery?"

The doctor shook his head. "It has to be done in a properly equipped laboratory. You see, apart from anything else, the test we use most in this country involves the co-operation of toads!"

"How perfectly extraordinary. How on earth do toads help?"

"In the test, which is called the Hogben test, the urine is injected under the skin of a female toad. If the urine contains gonadotrophic hormones, twelve to twenty-four hours later the toad will begin to produce streams of eggs.

"In another test, called the Galli-Mainini, male toads are used. If the urine injected into them is definitely from a pregnant woman, they produce sperm as the female produced eggs.

"Two other tests—the Ascheim Zondek test for which mice were used and the Friedman test which involved rabbits—have been largely discarded nowadays as although they (like the Hogben and Galli-Mainini tests) are practically a hundred per cent reliable, they take longer to get results and also involve killing the animals concerned, whereas the toads can be used over and over again with no ill effects."

"How amazing," said Mrs. Berry. "Thank you for explaining. Could I ask just one more question? Aren't there some tablets that act like a pregnancy test?"

"The tablets you mean," the doctor answered, "are a combination of two of the ovarian hormones, oestrogen and progesterone. A woman can start taking them when her period is just one week overdue and continue for four to five days. If she is not pregnant, then four to five days after this her period will commence. If she is pregnant, there'll be no bleeding.

"A similar test can be given by means of a hormone injection when the period is one week overdue. Again it's a combination of the same two hormones. And again the period will start after a five day interval if the patient is not pregnant, while there'll be no bleeding if she is.

"But like most doctors I prefer my patients to have the Hogben test. There is still much we have to learn about hormones—although the pregnancy tests are reliable enough.

"And a hormone test wouldn't have got you the result any quicker. You see, for five days of this past week you would have been taking the necessary tablets (for it's these I would have prescribed). Then you would have to wait another five days to see if your period started. Which brings you up to the day after tomorrow.

"As it is, if you take your specimen of urine round to the laboratory tomorrow, which you can do as you live in London, we'll have the result from the Hogben test just twenty-four hours later. So you see you haven't lost time by not coming earlier!"

Hopes confirmed in forty-eight hours

"Here's the necessary pregnancy test form," he said. "I've filled in my part. When you get home, fill in your name, address, age and the number of days your period is overdue. And do adhere strictly to the instructions on the form, won't you?"

"Nothing to drink after your evening meal today so that the morning specimen of urine will be really concentrated. And no aspirin, indigestion mixture or any kind of drug, because that would contaminate the specimen and might possibly harm the toad into which it is injected.

"And finally, use the urine you pass first thing in the morning. Put at least six ounces into a clean glass bottle or jar. See your name is on the bottle. Put the filled-in form, specimen of urine and the fee together, and hand them in at the address on the front of the form. As you'll see, the laboratory is open for specimens from 9 a.m. to 4 p.m. daily except at the weekends. And luckily for you this is only Tuesday!

"Now away you go and try to possess your soul in patience!"

Forty-eight hours later, an ecstatic Mrs. Berry was able to tell her husband a telephone call from the doctor had confirmed she was pregnant.

And just seven months after that she declared herself to be the happiest woman in the world. For she had been safely delivered of a beautiful baby boy.

JOAN SEAWARD

The pregnancy test proved positive —and now the baby they wanted so much is safely in her arms

27

Figure 5.10. The caption reads, 'The pregnancy test proved positive—and now the baby they wanted so much is safely in her arms' (Seaward, 1961, 27).

Three years ago Mrs Berry had miscarried in the third month of her first pregnancy. She and her husband had been 'bitterly disappointed at the loss of what they hoped would be their first child.' Subsequently, Mrs Berry's periods had been regular, but they were now a fortnight overdue. She suspected pregnancy, but her doctor would not risk an internal examination, which could provoke another miscarriage. 'But doctor,' she implored, 'how much longer must I wait before knowing for certain? It means so much to my husband and me. Couldn't I have one of those pregnancy tests I've heard about?' Mrs Berry's doctor informed her that the most popular tests in Britain cost one guinea ('but I take it you think it's worth that') and 'involved the co-operation of toads!' 'How perfectly extraordinary', Mrs Berry replied, 'How on earth do toads help?' The doctor explained how the Hogben and Galli-Mainini tests worked as well as the now 'largely discarded' Aschheim-Zondek and Friedman tests. 'How amazing', explained Mrs Berry, before asking 'just more question' about 'tablets' she had heard of that 'act like a pregnant test'.

'The tablets you mean,' explained the doctor, 'are a combination of two of the ovarian hormones, otestrogen and progesterone. A woman can start taking them when her period is just one week overdue and continue for four to five days. If she is *not* pregnant, then four to five days after this her period will commence. If she *is* pregnant, there'll be no bleeding.' 'A similar test can be given by means of a hormone injection when the period is one week overdue. Again it's a combination of the same two hormones. And again the period will start after a five day interval if the patient is not pregnant, while there'll be no bleeding if she is.' 'But like most doctors', he continued, 'I prefer my patients to have the Hogben test. There is still much we have to learn about hormones—although the pregnancy tests are reliable enough.' Furthermore, he added, 'the hormone test wouldn't have got you the result any quicker. You see, for five days of this past week you would have been taking the necessary tablets (for it's these I would have prescribed). Then you would have to wait another five days to see if your period started. Which brings us up to the day after tomorrow.' Mrs Berry would be able to take her specimen 'round to the laboratory tomorrow,' and would 'have the result from the Hogben test just twenty-four hours later. So you see you haven't lost time by not coming earlier!'

Mrs Berry's doctor handed her the 'necessary pregnancy test form' with his part already completed and instructed her to fill in her name, address, age and the number of days her period was overdue. He instructed her not to drink after her evening meal, to take no aspirin or other drugs that might harm the toad, to collect at least six ounces of concentrated morning urine in a clean glass bottle or jar with her name on it, and to deliver the specimen, completed form, and fee to the indicated address. 'Forty-eight hours later, an ecstatic Mrs. Berry was able to tell her husband a telephone call from the doctor had confirmed she was pregnant.' 'And just seven months after that she declared herself to be the happiest woman in the world. For she had been safely delivered of a beautiful baby boy' (Seaward, 1961, 27). This strong endorsement of the Hogben test in Britain's most prominent women's magazine was a direct response to concerns about hormone tablets and injections.

In the medical press, concerns about withdrawal bleeding tests intensified when Dr Victor Dubowitz, a South African-born paediatrician at the Children's Hospital, Sheffield,[351] warned of a 'possible association between the administration of "Amenorone" for the diagnosis of pregnancy and virilisation in the female infant.' The case, reported in the *Lancet* in August 1962, involved a 34-year-old woman who had become pregnant for the first time after six years of marriage. After missing a second period, she had consulted her GP, who prescribed one tablet of Amenorone daily for three consecutive days. 'This did not produce any vaginal bleeding' and after 'an uneventful pregnancy', the patient gave birth to twins: one 'apparently normal male' and one with 'ambiguous' genitalia. The latter was transferred to the Children's Hospital, where, after performing some tests (a 'buccal smear was chromatin positive' and a 'chromosome karyotype was 46 XX'), Dubowitz concluded that the infant was a 'non-adrenal female "pseudohemaphrodite"'.[352] He 'could only speculate' whether 'masculinisation' ('phallic enlargement') could 'have resulted from the small dose of amenorone' (Dubowitz, 1962, 406).

Dubowitz's speculation planted a new seed of doubt about withdrawal bleeding tests, already suspected by some of inducing miscarriage in pregnant women, that of teratogenicity. Interest in the monitoring of birth defects had 'intensified enormously'

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[351] See Dubowitz, 2005.
[352] Dubowitz, 1962, 405-406. On clinical approaches to sexual ambiguity in the 1950s: Eder, 2010.

in Britain in the 1960s as the direct result of the thalidomide tragedy and German measles epidemics. In 1964 the Ministry of Health set up 'a formal system of registering congenital malformations, with the aim of establishing typical seasonal and regional variations in incidence, and of warning quickly of any unusual increases' (Al-Gailani, 2013, 4). In a review article on the 'problem of teratogenicity' published in the January 1965 issue of the *Practitioner*, Dr Richard Smithells, a Liverpool paediatrician and 'leading British expert on thalidomide diagnostics',[353] explained that

> For the first two weeks of embryonic life pregnancy is usually unsuspected and there is a natural anxiety that during this unguarded fortnight drugs may be taken, anaesthetics administered or x-ray exposures made which would have been avoided had pregnancy been recognized (Smithells, 1965, 104).

But what of withdrawal bleeding tests: drugs intended to be prescribed in the early weeks of pregnancy? Smithells surveyed 189 women who had been prescribed Amenorone Forte or Primodos in 'the first 12 weeks of pregnancies which went beyond the 28th week', but admitted that the 'small group' provided 'no evidence to support [Dubowitz's] suggestion that pregnancy-test drugs are teratogenic.' Nevertheless, he warned that a 'heavy responsibility lies on the shoulders of every practitioner who orders the administration of any drug to a woman in the first twelve weeks of pregnancy' (Smithells, 1965, 108-109).

[353] Smithells 'had set up a congenital abnormalities register and genetic counselling service in Liverpool in 1960': Al-Gailani, 2013, 5.

PRIMODOS MY RECOLLECTIONS:

I finished grammar school in 1970 and was accepted for a place at The London School of Pharmacy to study Pharmacy in what was then a 3 year B.Pharm Honours degree. During my first year I applied and was accepted for summer work in a local pharmacy in my home town. The Pharmacy was [redacted]. The pharmacist owner was [redacted] as he was known to one and all was an excellent teacher with very high professional and ethical standards. I was determined to learn as much as I could as quickly as I could from him. It was a very busy pharmacy which wasn't afraid to undertake any extemporaneous dispensing challenge as we often got dermatology prescriptions from Harley Street in London. It was a time of change in therapeutics as we had an eclectic mixture of 'old' and 'new' drugs. Barbiturates were still widely used and phenobarbitone was often added to drugs as a sedative for example Alupent Sed which was orciprenaline and phenobarbitone syrup which would be regarded as a completely illogical combination these days. It was a time of great change for women also. Less than 10 years earlier the pioneering work of Carl Djerassi had made oral contraception a reality for thousands of women. When I started there was what seemed to me a vast array of oral contraceptives all made by competing pharmaceutical manufacturers. The names were intriguing Gynovlar 21;Anovlar 21;Lyndiol;Volidan; Norinyl 1;Ovulan;Conovid E; Feminor; C-quens and many others which are lost in the mists of time. There were, however, no reliable methods of detecting pregnancy. Pregnancy tests as we now know them were considered science fiction. At college we were told that reliable test involved injecting urine from a female patient into a frog would, if it contained HGC, cause the frog to ovulate. Primodos was presented in a two tablet pack and the instructions were to take one at night and one in the morning. If the patient was NOT pregnant they would start to menstruate. I was never comfortable with the science behind Primodos but there was virtually nothing else if you definitely had to find out if you were pregnant. As my entry into Pharmacy was after the Thalidomide scandal I naturally assumed that any products which presented a similar risk had automatically been withdrawn. From memory we didn't dispense huge quantities of Primodos but there was a regular but low level of prescriptions monthly. I have no recollection at this remove of anybody complaining about the side effects of Primodos in our Pharmacy. I continued working in this Pharmacy in my vacations and then was employed to undertake my pre-registration year. After I qualified I went back to do an M.Sc. and Ph.D. and hardly noticed that during that time Primodos had been withdrawn. The agglutination pregnancy tests were becoming readily available so there was no longer a place for hormonal pregnancy tests like Primodos.

Dr.Bernard Leddy
B.Pharm(Hons),M.Sc,Ph.D,MRCS,CChem,CSci,MRPharmS,MPSI.

Q Pregnant or not?

A The "eyes" have it!

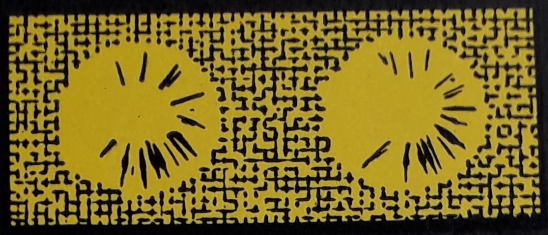
Primodos

SCHERING A. G.
BERLIN

BOOKMARK

When is amenorrhoea due to pregnancy?

The obliging Xenopus Toad can be persuaded to answer this question, at a price, and only after the amenorrhoea has lasted for at least 14 days.



these

TWO TABLETS OF

Primodos

will answer the question **sooner** and at a cost to the N.H.S. of **only 5/-** (less than any other pregnancy test).

Presentation

Tablets containing
5 mg norethisterone acetate
and 0.1 mg
ethinyloestradiol
in packs of 2 (1 Test) and 20

SCHERING A. G. BERLIN

U.K. Subsidiary
Pharmethicals (London) Ltd.,
20, Gerrard Street, London, W.1.

P.T.O.

Clinicians, academics and other individuals – Other

Dr Julia Lake

Julia Lake provided this paper to the Review (which was co-written with Mary Narayn-Lee. The diagram in Appendix 1 was shared during Session 1 of Oral Hearings that took place on the 5th March 2019.

NHS data burden: time to take stock?

> It's a fallacy to think that just having more data and input for your analysis is somehow going to give you more accurate answers.
>
> *Jay Theodore, Chief Technology Officer (ArcGIS) Enterprise) for Esri*

> Modern day information overload stops us sufficiently engaging with our thoughts.
>
> *Sam Owen, 500 relationships and life quotes*

Drowning in data

Information overload is an omnipresent feature of modern life. We are constantly bombarded with data. The NHS is voracious in its demands for evermore data flows which are required, annually, quarterly, monthly, weekly, daily.[1]

Given the pressures on the NHS budget, the time has surely come to pause and reflect on this data industry. What value is being added from all this data and information? We need to start distinguishing between those data flows which contribute to improved clinical services from those data flows which have no value at all i.e. where the collection and submission of the data is an end in itself.

The purpose of this paper is therefore to:

- Raise awareness of the magnitude of the problem by providing an overview of the routine data demands on LTHT.
- Contribute to the emerging national debate on data burden from an acute provider's perspective.
- Support collaborative work with NHS Digital's 'Challenging Burden Service' to identify whether key national clinical audits are providing value for money.

[1] The latest development is to try and introduce near "real time" data flows for Situation Reports - this would mean reporting every 15 minutes.

Increasing data but starved of insight

> Indeed, it could be said that Bristol was awash with data but was, at the same time, singularly uninformed.
>
> *Ian Kennedy, Bristol Royal Infirmary Inquiry, 2001*

Almost 20 years after the publication of the Kennedy report into children's heart surgery at Bristol Royal Infirmary, this observation on data and insight is still pertinent. In fact, it's fair to say that the situation in the NHS has got worse. The Bristol report covered the period 1984 to 1995. Clearly, digitisation of healthcare information has increased dramatically since then, but that doesn't necessarily mean we are now better informed.

Appendix 1 shows the current data traffic applicable to LTHT.[2] This 'infographic' only displays the high level summary of each data collection. Underpinning the individual items are vast swathes of data. For example, the Specialised Services Quality Dashboards relates to 23 specialities and 160 indicators whilst the CQUINs cover 14 overarching goals supported by numerous metrics (see yellow highlight). Can we truthfully say that all these collections are providing us with the insight we need? A recent headline in the Health Service Journal states: "CQUINs should be scrapped or overhauled" as it risks "creating a set of processes with little added value".[3]

The value of information is in its use

> They tell me we're living in an information age, but none of it seems to be the information I need or brings me closer to what I want to know.
>
> *Matthew Flaming, The Kingdom of Ohio*

It is absolutely clear that data is vital to improving patient care. No one would argue against having good quality data to measure and improve services. The challenge, however, is that it is becoming increasingly difficult to identify 'valuable insight' as we are too busy navigating our way through the tsunami of data.

So how can we identify 'value' in terms of information? Amongst the various definitions of 'value', one common thread relates to how the data and information are used. What decisions and actions have been made on the basis of the information? The criterion of "actionable insight" therefore could be the basis of judging which data collections are adding value and which aren't. Information is not a free resource. Can the NHS really afford to collect data which are simply "nice to know"?

The consequence of having an Informatics resource focused on meeting the national demands means there is little resource available to support our local wards & teams in their quality improvement initiatives. Delivering better and safer patient care comes from a Quality Improvement culture which "empowers and enables all staff to make effective and sustainable improvements.[4]

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[2] Note that this will always be a "work in progress" as national bodies and data flows are constantly evolving.
[3] Health Service Journal, 2 July 2018. "'CQUIN should be scrapped or overhauled" say local leaders', by Rebecca Thomas & Lawrence Dunhill.
[4] Quality Improvement in Hospital Trusts, CQC, September 2018

National Clinical Audits (NCA)

Through the work of the LTHT Clinical Information & Outcomes Group (CIOG) we now have corporate oversight of all the national clinical audits we are required to participate in. As one example, our contract with NHS England lists 88 audits which cover 42 surgical and medical specialties, (see yellow highlight in Appendix 1). These audits comprise thousands of individual data items. Staff involved in the collection and submission of the data include: consultants, junior doctors, nurses, allied health professionals, administrators, and information staff. Considerable Trust resources are therefore invested in these audits.

But for the audits to be worthwhile and provide valuable insight, we need to ensure that we measure the right things and collect and submit the data in the right way. Appendix 2 provides an overview of the issues that have been highlighted over the past few years. It has become clear that there are problems with the audit process in terms of clarity of indicator specification, timeliness of reports, duplication & overlap of data items. The risk is that these audits don't focus on the things that truly matter and as a consequence we risk making poorly informed decisions on the back of poor data.

> [NCA] removes that personal sense of ownership for the data that's in there, and then the task of putting the data in is so labour intensive it ends up being delegated. And then I think people are much less interested in what's in there, much less involved in what's going into it, and therefore the quality of what goes in is massively variable.
>
> *Interview extract from clinician regarding NCA*

NHS Digital - Challenging Burden Service

The remit of NHS Digital's Challenging Burden Service (CBS) is to offer:

> "…advice, guidance and support for the health and social care system nationally and locally, on minimising the burden and bureaucracy of data collection with the aim of freeing up time for staff to provide care and to reduce the cost of collections. NHS Digital also has a statutory duty to provide advice to the Secretary of State to minimise burden"

The LTHT Information & Insight team have already met with the CBS. From these early conversations it is evident that NHS Digital does not have oversight of the totality of data burden on specialist acute providers. But does anyone?

Conclusions

"If you don't reveal some insights soon, I'm going to be forced to slice, dice, and drill!"

Hospitals generate and flow enormous quantities of data to national bodies and central repositories. Following national processing masses of data are then fed back to hospitals. Each year this data burden grows and grows.[5]

If 'actionable insight' is the measure of value for these data flows, it would seem that many collections fall short. In fact, the sheer scale of the data avalanche is obscuring the essential insight. The time is now right to take stock of the current culture. We need a robust national conversation to consider how best to harness the power of good quality information to ensure the long-term sustainability of the NHS.

Recommendations

This paper is the starting point for further work to identify those data collections which are not adding value to patient care.

The next steps are to:

- Present the paper to LTHT Information & Insight Group.
- Present the paper to NHS Digital's Data Co-ordination Board whose members include representatives from the Department of Health, NHS England, NHS Improvement, CQC, NICE, PHE and other national bodies.
- Support NHS Digital to assess the value of those national clinical audits which are under their remit.
- Share the paper with commissioners with a view to working collaboratively on reducing data burden.
- Share the paper with the Yorkshire Effective Audit Research Network (YEARN) and other regional groups for their views.

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Contracting Information

Leeds Teaching Hospitals NHS Trust
September 2018

[5] Examples are the 20% increase in mandated National Clinical Audits for Trust Quality Accounts from 51 in 2016/17 to 64 in 2018/19 and on a micro level, the recent increase in data items for the Stroke Audit from 163 questions to 178 questions.


CCG STP WYATT LYPFT LCHC Local drug & alcohol services
Leeds City Council
Cancer Alliance
NHS Improvement
Care Quality Commission
HQIP
NHS Digital
NHSE Specialist Commissioning
NHSE Screening & Dental
PHE
General Medical Council
RCP
Nursing & Midwifery Council
CCG - Operational Standards (eg RTT, Cancer Waits, Cancelled Operations etc)
CCG - National Quality Requirements (eg MRSA, Ambulance handovers, VTE etc)
CQC Visits
GIRFT
NHSI Workstreams
National CQUINs (eg Sepsis, Risky Behaviours etc)
CCG - National Reporting Requirements (eg Activity & Finance, Safety Thermometer, Complaints etc)
CCG - Local Quality Requirements (eg OP Letters < 10 days, TDA No, etc)
CCG - Local Reporting Requirements (eg incomplete pathways snapshot, cancer data etc)
PCAL
Daily SITREPS
Maternity Performance Dashboard
Model Hospital
CCG SDIP - (e.g. Cancer Strategy, Biosimilars, Falls, Maternity etc.)
Surveys (eg FTT, Carer etc)
CCG Data Quality Improvement Plan (eg Cancer Routes, Biologics, Radiology Demand, maternity)
Incident Reporting - (eg Serious Incidents, Never Events
Information Governance toolkit
NHS England Service specifications
Freedom of Information
Long stay dashboard
Public Health England (eg Screening, Immunisation etc)
NHS England Secondary care dental
NHSE Health & Justice
NHSE Armed forces
NHSE Local Quality Requirements (eg targeted service improvement, newly established service etc)
Specialised Services Quality Dashboards
NHSE in year queries
Quality Surveillance Team annual peer review
NHSE CQUINS - (eg Hepatitis C, Medicines Optimisation etc)
OIPP
NHSE - Local Reporting Requirements (eg Neurosurgery/Cardiac incomplete pathways, Paed long term ventilation etc)
Mortality reporting - HSMR & SHMI
NHSE Data Quality Improvement Plan - (eg Drugs / devices / Pharmacia etc)
National Audits and Registries
NHSE SDIP
Statutory Returns
Costs & Transformation (National PLICS)
Reference Costs
Daily A&E Data Flow
Workforce Intelligence

Appendix 2

National Clinical Audits
Assessment of key issues

- ***Data Collection as a bi-product of patient care?***
  In a number of National Clinical Audits many of the requirements are not collected as a routine part of the patient's care, rather they are supplementary data items. Nor do they exist to measure or monitor against a quality goal or benchmark or add any valuable insight into patient outcomes.
- ***Duplication***
  The same clinical data items submitted to a variety of different audits, pertaining to the same patient, during the same period, to different providers/hosts but in different formats or contexts. There is no data linkage.
- ***Large, complex datasets representing little value***
  There are a number of high profile audits encompassing over 150 individual data items. Subsequent reporting is based around a limited number of fields and/or a collection of elements which enable risk adjustment stratification. However, the remaining data items do not add any perceptible value in terms of research, safety or outcomes but remain a requirement and signify a noticeable burden on collection.
- ***Standards & Methodology***
  Standards vary widely across the types of data flows. All too often definitions are vague, the methodology is unclear, clinical procedure codes are not supplied and left to local interpretation. This causes inequality across benchmarking and outcomes cannot be measured accurately.
- ***Collection mechanisms***
  Audits, data-flows, dashboards etc. do not have any standardised collection, validation and submission processes. They range from locally collected data items in clinical or administrative systems exported and uploaded via an xml file to consultants being required to manually enter patient details into an external clinical audit platform or portal. There are examples where the mechanism for collection has not been considered and it has been up to individual Trusts to design and implement a collection tool.
- ***System Limitations***
  System suppliers are often not mandated to make the changes to their clinical/financial or administrative systems in parallel with timelines given to Trusts for providing the data.
- ***Dataset Changes (Version control)***
  Datasets are regularly changed part way through annual reporting periods. This can be difficult to implement on clinical/administrative systems, has a resource implication and causes inconsistencies in reporting/analysis/comparative work.
- ***Short Notice - New Collections***
  On a number of occasions Trusts have received notification of a new or changed dataflow as little as 1 week prior to its compulsory collection and submission window. The pressure to implement a whole new process is considerable often with far reaching consequences.
- ***Consultant Validation***
  Where the data is of a clinical nature it is important that the lead clinician review and sign-off the data. Quite often no consideration is given to administrative

time (non-patient facing time) to complete this task. In return for this investment in time Consultants expect to receive meaningful, timely and useful analysis and this is not the case with a number of National Clinical Audits.

- ***Assurance***
  Most Trusts Informatics Strategy and Data Governance and Assurance Action Plans have at their heart the drive to assure and maximise the use of information in support of clinical & operational management, quality & service improvement and demonstrating externally the quality and effectiveness of the care the Trust provides. Achieving this requires a strong focus on assuring the quality of data through the utilisation of robust and consistent data models and processes, thus ensuring consistent, reliable information is delivered seamlessly to those who need it. With many data flows this central governance does not exist.
- ***Data Quality & Timeliness***
  When poor data quality occurs, this can lead to unrepresentative measures being used by external sources and good services can be suspended due to inaccurate or incomplete data - or worse, failing services can continue to fail without being monitored and targeted for improvement. Therefore, ensuring that data quality is good, and that data assurance is managed from a central co-ordination point for clarity and context (both locally and nationally), is of the utmost importance. In many instances data quality feedback is conveyed to Trusts up to 2 years after the reporting period has ended this is a critically flawed and unhelpful process.
- ***Overlap***
  Audits regularly have an element of overlap with a commissioning feed and/or a CQUIN or quality dashboards, however, the definitions can vary slightly or are not explicitly defined. This can lead to inconsistency across providers as some Trusts will apply the same definitions across all data flows whilst others will adapt to the slight nuance in definition.

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September 2018

Manufacturers – Pelvic mesh

FEG Textiltechnik

Following their attendance at the Oral Hearing sessions (23rd January 2019), FEG Textiltechnik have provided the following documents and further information to the Review.

Introduction

1) FEG Company Sketch
   - Owner-managed / not subjected to investors' expectations
   - Developing and manufacturing of mesh implants; no direct sales but distributors
   - Fully integrated production line – spinning – warp knitting – finishing -> tailored approach: products adapted to the individual requirements of each indication as first USP
   - PVDF as second USP

2) Back to the beginning – important to understand our way of thinking and our philosophy
   - Founded in 1992 as engineering service provider for the technical textile and textile machinery industry
   - By coincidence FEG became project partner in a R&D project funded by one of the big American medical device companies and in cooperation with the university hospital Aachen. Project goal: a new hernia mesh implant
   - Classic engineering approach: compiling a requirement profile based on the state of the art and expert opinions: conclusion: we proposed a large pore (at that time a real innovation) structure made of PVDF monofilament.
   - However: The funding company restricted the choice of material/structure to only PP multifilament (at that time approved and registered material at the funding company)
   - In consequence: Deeply convinced that it is possible to make better meshes we started to develop our own meshes subsequent to the project.
   - Still today, we are an owner-managed company and administered by engineers not by business economists – one example that demonstrates that this makes a big difference: we never developed/made hernia plugs or six arm pelvic floor meshes although we easily could have done technically and although there still is a huge market for these products. However, from the first moment on, we were not convinced that these products will perform safe and efficient. Today there is sufficient evidence that proves we were right with this appraisal.

3) What are the crucial parameters for a good mesh according to the state of the art/what we know today
   - Basically there are two major tool-boxes to adjust the properties of a textile mesh implant: raw material and textile design/structure
   - Essential requirements related to the raw material
     - Long term stability
     - Low foreign body reaction
   - Essential requirements related to the design (present samples to demonstrate the differences)
     - Mechanical properties (strength, elasticity: biomimetic approach -> adapt the textile properties to the properties of the host tissue)
     - Porosity/effective porosity -> large pores -> less bridging -> less shrinkage
     - structure stability – maintaining the porosity under load

- Prof. Klosterhalfen could sum-up his insights based on the analysis of more than 1.000 explants.

Statement: Critical analysis of the current situation – including proposals for improvements

Spitted into three stages:

1. **Premarket stage**

- Strict consideration of the current state of the art regarding raw material and design parameters -> tailored implants
- Equivalence criteria were narrowed down significantly - clinical investigations before approval will become the standard with new MDR
- However, residual risks on the long term will never be excluded 100%. Every approval is based on a risk/benefit ratio.
  Otherwise product developments would take many decades and would require a complete different economic framework (e.g. public funded clinical investigations) – and even in this setting it will not be possible to assess the mesh performance since the measurable clinical outcome is always influenced by the surgeon, the technique, the patient and the medical device. To isolate the mesh impact requires vast number of cases – if possible at all!
- Conclusion: premarket stage was improved significantly by means of the latest regulatory changes – no further improvements necessary or reasonable

2. **Placing on the market/application stage**

- Essential to get good outcomes (4-factors): Only the right surgeon shall place the right implant into the right patient in consideration of the right OP-technique!
- "The right implant" is a matter of the premarket and post market stage and based on a comprehensive and continuous assessment of the product during the products lifetime. Two aspects which should be improved here:
  - "Error culture" and communication between users, patients and manufacturers
  - Clinical assessment on the long term: Only reasonable solution are registries – and there are sufficient examples available to learn which concepts work and which don't:
    - Pure voluntary registry will not gain acceptance (example EURAHS) – so the question is: stick or carrot
    - Voluntary + carrot: works well (example HERNIAMED)
    - Mandatory (stick): works even better (example Danish or Swedish registries)
- "The right surgeon" is a matter of education and referral
  - As manufacturer the opportunities to influence are limited here especially in our situation since we are not in direct contact with the end-user.

  - We train our Distributors – however this is limited to the product specific information
  - Our Distributors are working hard on the establishment of training centres to increase the quality of surgical care (find “most-frequent-users”, “excellent users” who are willed to train their colleagues)
  - Potential improvements: e.g. mentoring program or dedicated centres for education
  - Surgical quality assurance is also a matter which can be addressed by a registries’ data analysis – outcomes of this may go hand in hand with the mentoring program
- To identify “The right patient” is a by-product of registries data analysis. Only a database with vast number of cases allows the identification of certain subgroups at risk.
- “The right OP-technique” is a matter of creative key opinion leaders and a matter of communication and cooperation among these key opinion leaders and if necessary with the manufacturers (in case the technique requires an adopted medical device).
  Important: Standardization should be the primary goal as essential parameter for satisfying clinical results! Not every surgeon should work on new techniques or modifications on his own – this is clearly counterproductive.
  The assessment of different OP-techniques may also be a matter of registries data analysis.

3. **Postmarked stage**

- As mentioned: We definitely need registries under neutral coordination as a key factor for a comprehensive, effective and reliable post-market surveillance on the long term. To establish registries is a common responsibility which will finally enable to assess not only medical devices but also OP-techniques and surgical performance.

Additional Questions

1) **You mentioned in evidence that FEG offers a free analysis of all FEG mesh that has been explanted. How often is that offer taken up and what have you learnt from such analysis? Have there been any surprises?**

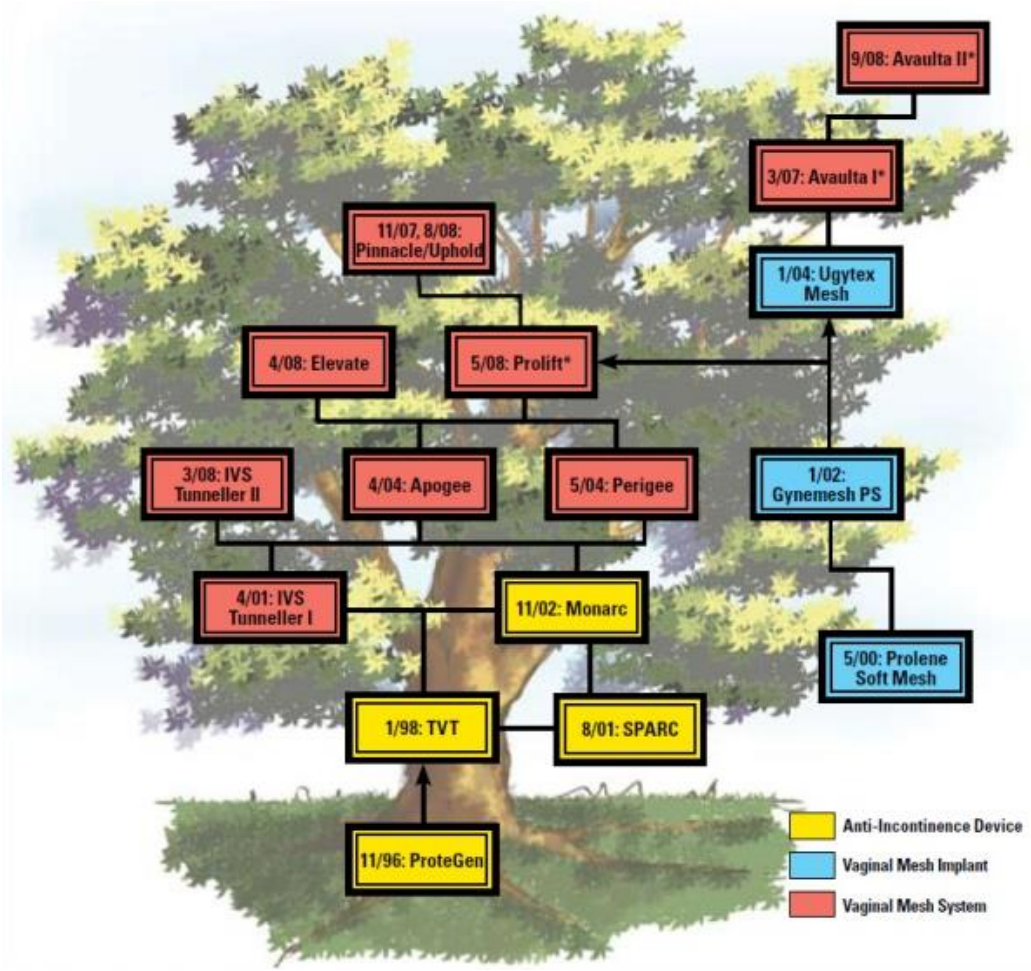
   The offer has been taken up in total only four times for four different products of our urology and gynaecology line (in comparison to 14 explants of our hernia product line, sent in to Prof. Klosterhalfen). The performed histologic tests included the Periodic acid–Schiff (PAS) staining. The analysis of the explants showed no unexpected results:

   All explants showed minimal foreign body reaction and minimal fibrosis. These results underline the high biocompatibility and low foreign body reaction (FBR) of PVDF. Furthermore, there was no recorded nerve lesion, no calcification, no specificity and no malignancy. In two cases there was a reported erosion with a secondary mesh infection and another explant showed a fold in the mesh with no signs of infection. The fourth mesh was explanted due to a high-grade-infection of the used multifilament suture material.
   In conclusion, none of the results of the histologic analyses indicate a clear mesh relation which causes or contributes to the complication.

   In comparison to our 4 + 14 (UroGyn + Hernia) products/explants the total number of explants sent in to Prof. Klosterhalfen exceeds 10.000, mainly PP products/explants.

2) **The DynaMesh range was introduced to market on the basis of equivalence to previous (polypropylene) mesh products. How does this work? (Under the new MDR to demonstrate equivalence, clinical, technical and biological considerations have to be taken into account. On the technical front the claim for PVDF 's USP is an altogether different design, different polymer and with different properties.)**

   Indeed, at the time when we registered our products under the MDD legislation the equivalence criteria were less strict. We would assume that the clinical evaluation of almost all products on the market is based on the equivalence concept. This is not only a European issue – also the FDA allows the use of the equivalence concept (510k) in a rather wide scope. The diagram below demonstrates the variety of equivalences under the FDA system:



https://www.meshmedicaldevicenewsdesk.com/family-tree-of-meshes-from-the-female-patient-april-2009/

In Europe, the equivalence criteria as under the MDD were narrowed down significantly under the new MDR legislation. I assume, all manufacturer are working hard at the moment to switch the clinical evaluation from the equivalence concept to the clinical evaluation based on proper clinical data. This process needs to be completed latest when the products will be registered under the MDR legislation. However, to apply for a MDR certificate requires a Notified Body that is designated according to the MDR. Just recently the first (BSI, UK) of more than 50 Notified Bodies appeared in the nando database (http://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=34) as designated according to the MDR. Others will follow in the next months and year. Due to the time consuming process of designation the MDR allows to place products on the market till latest May 2024 so long as they have a valid certificate according to the MDD. We are currently preparing the MDR compliant documentation for all our products to submit the documents as soon as our Notified Body is designated.

In conclusion: "**How does this work?"** – the equivalence concept did work under the MDD legislation but for the majority of products it does not work any longer under the MDR legislation!

3) You say your products are made from pure, medical grade PVDF. What does medical grade mean in this context? In the case of polypropylene mesh the patient groups have submitted evidence to the Review that no such medical grade exists.

The fact, that patient groups submitted evidence that "medical grade" polymers do not exist might be based on open access information/disclaimer provided by the polymer's manufacturer (material data sheets). To publish such disclaimer in which the use of these polymers for medical applications is prohibited (especially for long term implants) is absolutely right and reasonable. It is irresponsible to generally permit the use of the polymers for such sensitive applications without prior risk consideration and clarifying of duties and responsibilities. Thus, the specific conditions are usually agreed by contract between the polymer supplier and the medical devices' manufacturer.

We are dealing with the problem that there is no clear definition of the term "medical grade". Selected or all of the following aspects may be considered in this context: permanence with respect to formulation, components and manufacturing process; standardized and controlled manufacturing conditions – e.g. use of dedicated production lines to prevent any possible cross-contamination; available test reports for standardized material tests (USP class VI, ISO 10993).

Our understanding of "medical grade" also includes the claim of purity: some polymers necessarily do need certain additives to be process-able on the one side and to perform as required with regard to the applications of use. If the polymer is used for medical applications the amount of additives should be reduced to a minimum and there should be information available about the quantity and quality of added substances. In case of PVDF such additives are not necessary at all.

Investigations on explants with results on polymer properties as degradation

Iakovlev VV, Carey ET, Steege J (2015) Pathology of Explanted Transvaginal Meshes

- The authors aimed to perform a thorough pathological examination of explanted POP meshes and describe findings that may explain mechanisms of complications resulting in product excision. We report a spectrum of important findings, including nerve ingrowth, mesh deformation, involvement of detrusor muscle with neural ganglia, and polypropylene degradation.
- In total, 24 specimens have been analysed
- Average in vivo time since implantation before excision was 2.4 years (range 0.7-5years)
- The devices were of three different manufacturers, where 15 were combination of lightweight and heavyweight meshes, and remaining 9 of all heavyweight design.
- The main reasons for mesh excision reported in the literature are mucosal exposure, pain with dyspareunia, and de-novo or worsening urinary symptoms
- The novel finding of detection of polypropylene degradation in histological sections is interesting. Previous descriptions of cracked surface detected by scanning electron microscopy have been challenged. The degradation bark is easily visible by routine microscopy, yet escaped pathologists for over 50 years.
- Polypropylene degradation may play a role in the continuous inflammatory response, mesh hardening and late deformations. Also, chemical products of degradation need to be studied for their composition and effect on the tissue.

Costello CR, Bachman SL, Ramshaw BJ, Grant SA (2007) Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Res Part B Appl Biomater 83:44–49. https://doi.org/10.1002/jbm.b.30764

- The objective of this study was to determine whether oxidation plays a role in the degradation of polypropylene hernia materials while in vivo
- physiochemical analysis was performed on 14 explanted specimens as well as pristine specimens
- The SEM micrographs displayed images of materials that were vastly different in topology than the pristine materials. The micrographs of explanted polypropylene materials exhibited cracks, surface roughness, and peeling indicative of surface degradation, while the pristine materials appeared smooth.
- results supported our hypothesis and indicated that the explanted polypropylene meshes did undergo degradation while in vivo, most likely due to oxidation

Clavé A, Yahi H, Hammou J-C, et al (2010) Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. International Urogynecology Journal 21:261–270. https://doi.org/10.1007/s00192-009-1021-8

- A sample of 100 implants explanted from patients due to complications was examined to evaluate the relative degradation characteristics of PP and PET prosthetics.
- Poly(ethylene terephtahlate) explants appeared to sustain less degradation in vivo than the PP explants observed in this cohort.

Iakovlev V, Koch A, Petersen K, et al (2018) A pathology of mesh and time: dysejaculation, sexual pain, and orchialgia resulting from polypropylene mesh erosion into the spermatic cord. Annals of surgery 267:569–575

- Field of application: groin henia repair
- 13 PP meshes explanted because of severe chronic post-herniorrhaphy pain
- The records showed that 6 patients reported sexual pain of variable presentation and 3 specifically described dysejaculation.
- Histology demonstrated unequivocal mesh invasion of the spermatic cord, where the initial damage occurred to nerves, then to the smooth muscle of the vas while the lumen remained patent
- In 3 of 6 cases, the vas and other cord structures appeared to be completely invaded by the mesh and replaced by scar tissue.

Iakovlev VV, Guelcher SA, Bendavid R (2015) Degradation of polypropylene in vivo: A microscopic analysis of meshes explanted from patients. J Biomed Mater Res Part B Appl Biomater. https://doi.org/10.1002/jbm.b.33502

- Examination of 164 excised meshes using conventional microscopy and electron microscopy to search for features of polypropylene degradation
- The degraded material, detected by its ability to absorb dyes in the degradation nanopores, formed a continuous layer at the surface of the mesh fibers.
- Several features indicated that the degradation layer formed in vivo: inflammatory cells trapped within fissures, melting caused by cautery of excision surgery, and gradual but progressive growth of the degradation layer while in the body.
- Cracking of the degraded material indicated a contribution to clinically important mesh stiffening and deformation.

Smith SE, Cozad MJ, Grant DA, et al (2015) Materials characterization of explanted polypropylene hernia mesh: Patient factor correlation. J Biomater Appl. https://doi.org/10.1177/0885328215610398

- A total of 30 PP hernia mesh explants were analysed
- The reasons for removal for all 30 explants were indicated as pain, discomfort, and/or hernia recurrence that may cause the mesh to be a potential source of further complications
- The implant duration ranged from 9 to 181 months with a mean of 57 months and a median of 39 months
- The lack of correlation between patient factors and characterization techniques could suggest that PP mesh is extremely susceptible to oxidation regardless of the patient population.

Klosterhalfen B, Junge K, Hermanns B, Klinge U (2002) Influence of implantation interval on the long-term biocompatibility of surgical mesh. British journal of surgery 89:1043–1048

- 76 PP hernia mesh explants
- Median implantation period 18 (2-180 months) months
- Reason for explantations: recurrence, infection, pain
- Long term incorporated PP mesh in humans has a more favourable tissue response with increasing implantation interval
- Sex, age, type of previous operation or location of mesh did not have a significant influence

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Investigations on explants with results on structural mesh parameters as pore size

Klosterhalfen B, Klinge U (2013) Retrieval study at 623 human mesh explants made of polypropylene - impact of mesh class and indication for mesh removal on tissue reaction. Journal of Biomedical Materials Research Part B: Applied Biomaterials n/a-n/a. https://doi.org/10.1002/jbmb.32958

- Field of application: Hernia repair, 623 PP mesh explants
- Half of the meshes were removed after more than 23 month
- Removal for infection showed more IF than for pain or recurrence with significant correlation of inflammatory infiltrate with connective tissue
- large pore meshes showed less inflammatory infiltrate, connective tissue, fistula formation, calcification, and bridging than small pore meshes
- Meshes removed for recurrence showed a lowered collagen 1/3 ratio in 70%

Amid PK (1997) Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1:15–21. https://doi.org/10.1007/BF02426382

- Certain physical properties of biomaterials can lead to undesirable consequences, including increased risk of infection, seroma formation, biomaterial-related intestinal obstruction and fistula formation, and failure of the repair due to shrinkage of the mesh
- Adequate pore size gives sufficient molecular permeability to allow penetration of host proteinaceous material into their pores. Since this results in a rapid fibrinous fixation of the mesh to the tissue and elimination of the dead space between the prosthesis and the host tissue, the chance of seroma formation is minimized. Sufficient molecular permeability also results in formation of proper scaffolcling for future host tissue incorporation which --by filling-up the pores of the mesh and making them inaccessible to bacteria—further decreases the chance of biomaterial related seroma formation and infection

Manufacturers – Sodium Valproate

Sanofi

Following their attendance at the Oral Hearing sessions (18th January 2019), Sanofi have provided the following documents and further information to the Review.

Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence

Response to Follow Up Q1

The Review requested Sanofi to provide the date when enough evidence became available for an association to become causality for congenital malformations and developmental delay.

Introduction

1. While the teratogenic effects of valproate in animals had been underlined in studies, in which doses of valproate, much higher than those prescribed in clinical practice, had been administered to animals, it was not possible to carry out prospective, interventional studies to investigate the effects in humans, for obvious ethical reasons. In these circumstances, the scientific evidence of valproate-related teratogenicity has progressively developed with the accumulation of individual case reports, case series, published studies, and data from registries. Subsequent assessment of aggregated data must take into account the hierarchy of evidence. Prospective randomised controlled trials rank higher than cohort and case-controlled studies and uncontrolled retrospective case series and anecdotal reports rank lowest in the hierarchy, where data are particularly susceptible to bias and confounding and an observed statistical association between an exposure and an outcome does not necessarily mean that a causal relationship is present.

2. Statistical analysis of the data from epidemiological studies can establish only whether or not there is an association between exposure and the observed outcome (i.e. a change in one variable results in change in the other variable). That association may be causal or may be the result of systematic bias or of one or more confounding factors. The criteria listed by Sir Austen Bradford Hill[1] are widely used in epidemiology as a framework with which to assess whether a statistical association may be causal. These criteria include the strength of the association, consistency (whether the same findings have been observed among different populations using different study designs and at different times) and biological plausibility. All the criteria have not been met in relation to valproate. The process of causal inference in the context of multiple confounding factors is complex and arriving at a tentative inference of a causal or non-causal nature of an association requires judgment.

3. In these circumstances, information and warnings regarding the effects of medicinal products may be included in product information (SmPCs and PILs) as a matter of caution, where considered appropriate by the regulatory authorities, even where sufficient evidence to establish a causal relationship is lacking. This approach has formed the basis for the inclusion of warnings in relation to valproate.

4. Finally, in accordance with accepted conventions, causality assessment at an individual case level is based*, inter alia*, on the outcome of the event when the suspect drug is withdrawn (dechallenge) and when it is reintroduced (rechallenge). However, these criteria are not applicable for events occurring after in utero exposure because the drug cannot be withdrawn or reintroduced as the exposure had already taken place during pregnancy.

[1]Hill AB. The environment and disease; association or causation? Proc R Soc Med 1965; 58:295-300

Regarding congenital malformations (CMs):

5. For over forty years the UK Data Sheet for valproate has stated: "women of child-bearing age: this compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings".

6. Reports of congenital malformations in offspring of a small number of epileptic patients receiving antiepileptic therapy during pregnancy were first mentioned in the UK Data Sheet more than thirty years ago. However, at that time the scientific opinion was that there was an increase in the expected incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated. Importantly no congenital malformation is specific to valproate and all types of congenital malformations described individually or collectively in association with exposure to valproate *in utero* are also seen in children who have not been exposed.

7. An evaluation of the occurrence of specific congenital malformations in women exposed to valproate during the first trimester was first mentioned in the UK Data Sheet submitted in January 1989, approved by the Department of Health and Social Services (DHSS) in April 1989. It stated that:

> "*An increased incidence of congenital abnormalities in off-spring born to mothers with epilepsy both untreated and treated has been demonstrated.*
>
> *There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%*".

Regarding neurodevelopmental disorders (NDDs):

8. Neurodevelopmental disorders were not associated with in utero exposure to valproate before early 2000's, as such disorders are generally not recognised until a few years after birth, at which stage multiple confounding factors are present and diagnosis is challenging. As with congenital malformations, neurodevelopmental disorders are not specific to valproate and all such disorders described in association with exposure to valproate in utero are also seen in children who have not been exposed.

9. The first mention of "psychomotor developmental impaired" as being a new area of interest was reported in Sanofi's Periodic Safety Update Report (PSUR) addressed to the regulatory authority in early 2000. The PSUR stated that "*based on current information no definite relationship can be established between valproate and development delay in children exposed in utero to valproate. Nevertheless, this topic will remain under surveillance*".

10. The PSUR addressed to the regulatory authority in early 2001 also referred to "developmental delay in infants exposed to valproate". The PSUR stated that "*Regarding developmental delay, based on data collected through spontaneous reporting, no conclusions concerning a causal relationship between valproate and occurrence of "developmental delay" in children born to mothers exposed to valproate in utero can be drawn*".

11. Following a request by Sanofi, the regulatory authority approved the inclusion of a reference to the potential association between developmental delay and *in utero* exposure to valproate in the UK SmPC, in January 2003. The SmPC stated that "*Epidemiological studies have suggested an association between in utero-exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy*

should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus."

12. The above SmPC statement was mainly based on the following retrospective studies:

    a. In 2001, Adab et al[2] reported on the additional educational needs, examined by postal questionnaire, of children exposed to antiepileptic monotherapy and polytherapy *in utero*. The odds ratio of additional educational needs for all exposed school-age children (n = 400) compared with those unexposed was 1.49 (95% CI 0.83–2.67). The ratio for children exposed to valproate monotherapy was 3.40 (95% CI 1.63 – 7.10). The author's conclusion was "*Although the findings should be treated with caution, they suggest that monotherapy or polytherapy with valproate during pregnancy carries particular risks for the development of children exposed in utero."*

    b. In 2002, Dean et al[3] described 411 women taking antiepileptics in pregnancy between 1976 and 2000. Of 258 women who could be traced, 149 women (58%) participated. Two hundred and ten infants were exposed to monotherapy, and these were compared with 38 non-exposed sibs. Developmental delay, assessed by review of the records with regard to speech, motor or global delay, or special educational needs at school, occurred in 24% of exposed children compared with 10.5% of their non-exposed sibs. Results significantly different from the non-exposed group ($p<0.05$) were seen for those on carbamazepine, valproate, phenytoin, monotherapy and for those on polytherapy. The authors concluded that "*The developmental disorder is likely to have a multifactorial aetiology, but single drug therapy with valproate, phenytoin or carbamazepine and polytherapy are all associated with a substantial risk of developmental delay, even when possible genetic factors are excluded…*"

13. Other studies were also referenced, including Koch (1999)[4] and Wide (2000)[5]

14. As knowledge accumulated over time and the strength of the association increased, this has been reflected by the use of firmer language and additional detail in the SmPC, although this did not refer to a "causal relationship". In 2015, the MHRA approved a revision to the SmPC to strengthen the wording using the phrase "can have":

    a. "*Developmental disorders*

        - *Data have shown that exposure to valproate in utero* ***can have*** *adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.*

        - *Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later,*

[2] Adab N et al. Additional Educational Needs in Children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001;70: 15-21

[3] Dean JC et al. Long-term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet 2002; 39b(4): 251-259

[4] Koch S et al. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia 1999; 40(9): 1237-1243

[5] Wide K et al. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. Dev Med Child Neurol 2000; 42(2):87-92

lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes".

b. The change of the wording about neurodevelopmental disorders was based on the below mentioned epidemiological studies:

- In 2008, Thomas et al[6] observed that 40.8% of children exposed *in utero* to valproate had an impaired mental development quotient defined as score below 84 at Developmental Assessment Scale for Indian Infants (DASII)
- In 2009, Meador et al[7] in the NEAD study observed that 37% of children exposed in utero to valproate had a below average performance (IQ<85) at 3 years of age, and further data, published in 2013, showed that this continued to apply to 16% of such children at 6 years of age.
- In 2010, Bromley et al[8] reported their observation that 29% of children exposed in utero to valproate had a below average performance defined as score below 84 at Griffiths Mental Development scales.
- In 2011, Cummings et al[9] observed that 39.6% of children exposed *in utero* to valproate experienced mild of significant delay defined as score below 1 or 2 SD above the mean.
- In 2013, Meador et al[10] observed that intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics.

[6] Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy Behav 2008 Jul; 13(1): 229-36

[7] Meador KJ et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009 Apr 16;360(16):1597-605

[8] Bromley R et al. Early cognitive development in children born to women with epilepsy: A prospective report. Epilepsia 2010; 51(10): 2058-2065

[9] Cummings C et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child. 2011 Jul;96(7):643-7.

[10] Meador KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52

Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence

Response to Follow Up Q2

The Review requested Sanofi to provide details of the EMA DUS study indicating a good awareness (>90%) of healthcare professionals about the risks of valproate.

A survey was conducted in June-August 2016, to assess the awareness of healthcare professionals of the risks associated with valproate. This followed the previous PRAC referral in 2013-2014 which led to a series of risk minimisation measures being implemented. The design of the survey was approved by the European Medicines Agency (EMA). The statistical analysis and the results were also accepted by the EMA.

This survey targeted physicians who had prescribed valproate within the last 12 months, including GPs, neurologists, psychiatrists and other specialists such as internists and paediatricians. Physicians were identified according to their speciality as specified in the IMS OneKey lists (IMS is a leading market research firm). The physicians were randomly selected according to the procedure in the statistical sampling plan. They were sent an email to present them the survey and invite them to participate. The survey was a primary data collection conducted through a web questionnaire.

The physicians' response rate = physicians who agreed to participate / contacted physicians. (Contacted physicians = physicians who have been reached out to by phone or have opened their email.)

The response rate was 74.6% in United Kingdom.

Among a total of 1,153 physicians who completed the questionnaire 264 were from the UK.

A summary of results from the full cohort is provided below. UK results are presented in brackets:

- 95.5% of participating physicians (97.8% from UK) only prescribed valproate for epilepsy and bipolar disorder in women if other treatments are ineffective or not tolerated;
- 92.1% of participating physicians (92.6% from UK) always informed patients about the risks of taking the drug during pregnancy before prescribing valproate to a female of childbearing potential; and
- 94.4% of participating physicians (98.3% from UK) advised about the use of an effective contraception during treatment before prescribing valproate to a woman of childbearing potential.

Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence

Response to Follow Up Q3

Are there studies that indicate that bipolar disorder as a disease is a potential confounder in trying to establish causal relationship between in utero valproate exposure and malformations as well as developmental delay?

Introduction

In order to answer this epidemiology methodological question, we present in the two following parts (part A) for congenital abnormalities (CA) and (part B) for neurodevelopmental delay (NDD), the key learning of our literature research:

- For both CA and NDD, bipolar disorder (BD) by itself needs to be considered as a potential confounder. Published studies indicate that BD could be a potential confounding factor: it has an influence on the exposure to the treatment of interest (whether valproate or another mood stabilising therapy) and may also influence the occurrence of the outcome under study (CA or NDD).
- For childbearing women with BD, as with epilepsy, the underlying medical disorder of the women can be considered as a confounding factor in the assessment of the causal relationship under study, between the exposure to valproate and the occurrence of CA or NDD. These particular situations for BD childbearing women make the assessment of this relationship a methodological challenge.

Part A: When considering the assessment of the relationship between valproate and CA, BD itself needs to be considered as a confounding factor, as illustrated by the following publications:

1. BD in pregnancy and childbirth: a systematic review of outcomes (Rusner et al. BMC Pregnancy and Childbirth (2016) 16:331)

   An *a priori* protocol was designed and a systematic search conducted in PubMed, CINAHL, Scopus, PsycINFO and Cochrane databases in March 2015. Studies of all designs were included if they involved women with a diagnosis of BD prior to pregnancy, who were pregnant and/or followed up to one year postpartum. All stages of inclusion, quality assessment and data extraction were done by two people. All maternal or infant outcomes were examined, and narrative synthesis was used for most outcomes. Meta-analysis was used to achieve a combined prevalence for some outcomes and, where possible, case and control groups were combined and compared.

   The search identified 2809 papers. After screening and quality assessment (using the EPHPP and AMSTAR tools), nine papers were included.

   Adverse pregnancy outcomes such as gestational hypertension and antepartum haemorrhage occur more frequently in women with BD. They also have increased rates of induction of labour and caesarean section, and have an increased risk of mood disorders in the postnatal period.

   CA (CA) were examined in three studies:

- Jablensky et al. (Am J Psychiatr. 2005;162(1):79–91) found no difference in CA in women with BD (n = 62 out of 1,301, 4.80 %) compared with those with no mental health difficulties (n = 152 out of 3,129, 4.90 %), but is not included in the meta-analysis as the data were not combinable with those from other studies.

- Mei-Dan et al. (Am J Obstet Gynecol. 2015;212(3):367. e361-368.) found that BD presented increased risk for congenital anomalies (n = 90 out of 1859, 5.00 %) compared with the reference group (n = 14,963 out of 432,358, 3.50 %), when adjusted for maternal age and parity (AOR 1.48, 95 % CI 1.20–1.82).

- Bodén et al. (BMJ. 2012;345:e7085) also found the prevalence of CA was 2 % for infants born to women without BD (i.e., the normal population). For women with BD who were not treated with mood stabilisers the rate was 1.90 %, and those women with BD who were treated with mood stabilisers had rates ranging from 0 to 3.50 %, depending on the drug used. When microcephaly was considered separately, 3.9% of untreated women had an affected infant, compared with 2.3% of the women without BD and 3.3% of the treated women. The authors suggested that the increased risk of microcephaly was part of a general foetal growth restriction however and not an isolated phenomenon.

The results of the Bodén and Mei-Dan studies (BMJ. 2012;345:e7085; Am J Obstet Gynecol.2015;212(3):367. e361-368)] were combined in a meta-analysis. This showed that 21,632 women out of 766,750 (2.82 %) without BD had a baby with congenital abnormality, while 175 women with BD, out of 4034 (4.34 %) had a baby with a congenital abnormality. This difference is statistically significant (chi-square = 33.59, $p < 0.0001$, OR 1.56, 95 % CI 1.34 to 1.82).

The authors concluded:

> ***"Babies of women with BD have a higher prevalence of CA (4.34 % versus 2.82 %, two studies, total population 770,784), although the three papers examined differed in their individual findings. The difference is likely due to the smaller sample size in Jablensky's work, at just over 6,000, and to the fact that this cohort included only 55 % of women with pre-existing BD. Other factors include the separation of women treated and un-treated for BD in Boden's study, and the fact that Mei-Dan's study population were women previously hospitalised for BD, so it is likely that they were on medication for their BD symptoms. There are many studies showing that mood stabilisers do cause CA, and that was not the focus of this review. It would appear from the three papers summarised here that women with BD who are not being treated with mood stabilisers in pregnancy might not be at the same level of increased risk of CA".***

Conclusion

There is a heterogeneity of results between studies, which do not demonstrate consistently a significantly higher prevalence of CA in women who have BD.

Nevertheless the data do not exclude a link between BDs and CA. BD can be identified as a potential confounder as it influences the exposure of the women to the treatment of interest (valproate) and, based on the published studies, it may have its own relationship with the occurrence of the outcome under study (CA).

When considering a population of childbearing women with BD, the analysis of the relationship between valproate exposure and CA needs to consider BD as a confounding factor that could impact the assessment of the drug-event relationship under study.

PART B

When considering the assessment of the relationship between valproate and neurodevelopment delay, BD needs to be considered as a potential confounding factor as illustrated by the following publications.

For NDD the situation is different to that for CA, as the recent published literature provides only indirect information on the potential role of BD on the occurrence of NND in children born to a mother suffering from BD. These publications, as detailed below, showed that a cluster of psychiatric conditions, BD, autism and ADH, are linked together when considering family relatives. Based on this cluster it could be hypothesised that a relationship exists between the BD of childbearing women and the occurrence of autism or ADH in their children.

The two papers below seem to indicate that autism or ADH in children born to a mother with BD may be related to common risk factors with BD.

1. Risk and co-aggregation of major psychiatric disorders among first-degree relatives of patients with BD: a nationwide population-based study (Chen MH et al. Psychological Medicine 2018 Nov 12 (epub))

   The authors noted that BD is a highly heritable mental illness that transmits intergenerationally. Previous studies supported that first-degree relatives (FDRs), such as parents, offspring, and siblings, of patients with BD, had a higher risk of BD. However, whether FDRs of bipolar patients have an increased risk of schizophrenia, major depressive disorder (MDD), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) remains unclear.

   Among the entire population in Taiwan, 87 639 patients with BD and 188 290 FDRs of patients with BD were identified in this study. The relative risks (RRs) of major psychiatric disorders were assessed among FDRs of patients with BD.

   FDRs of patients with BD were more likely to have a higher risk of major psychiatric disorders, including BD (RR 6.12, 95% confidence interval (CI) 5.95–6.30), MDD (RR 2.89, 95% CI 2.82–2.96), schizophrenia (RR 2.64, 95% CI 2.55–2.73), ADHD (RR 2.21, 95% CI 2.13–2.30), and ASD (RR 2.10, 95% CI 1.92–2.29), than the total population did. These increased risks for major psychiatric disorders were consistent across different familial kinships, such as parents, offspring, siblings, and twins. A “dose-dependent” relationship was also found between risk of each major psychiatric disorder and numbers of bipolar patients.

   The authors stated that “this study was the first study to support the familial co-aggregation of BD with other major psychiatric disorders, including schizophrenia, MDD, ADHD, and ASD, in a Taiwanese (non- Caucasian) population”.

   This study showed elevated risks of major psychiatric disorders, including ADHD and ASD, in FDRs of patients with BD.

2. Risk of Psychiatric and Neurodevelopmental Disorders Among Siblings of Probands With Autism Spectrum Disorders (Jokiranta-Olkoniemi E et al. JAMA Psychiatry. 2016;73(6):622-629. doi:10.1001/jamapsychiatry.2016.0495)

   Previous research has focused on examining the familial clustering of schizophrenia, BD, and autism spectrum disorders (ASD). Little is known about the clustering of other psychiatric and neurodevelopmental disorders among siblings of persons with ASD.

The objective was to examine the risk for psychiatric and neurodevelopmental disorders among full siblings of probands with ASD. The Finnish Prenatal Study of Autism and Autism Spectrum Disorders used a population-based cohort that included children born from January 1, 1987, to December 31, 2005, who received a diagnosis of ASD by December 31, 2007. Each case was individually matched to 4 control participants by sex and date and place of birth. The siblings of the cases and controls were born from January 1, 1977, to December 31, 2005, and received a diagnosis from January 1, 1987, to December 31, 2009. This nested case-control study included 3578 cases with ASD with 6022 full siblings and 11 775 controls with 22 127 siblings from Finnish national registers. Data were analysed from March 6, 2014, to February 12, 2016.

Among the 3578 cases with ASD (2841 boys [79.4%]) and 11 775 controls (9345 boys [79.4%]), 1319 cases (36.9%) and 2052 controls (17.4%) had at least 1 sibling diagnosed with any psychiatric or neurodevelopmental disorder (adjusted RR, 2.5; 95% CI, 2.3-2.6). The largest associations were observed for childhood-onset disorders (1061 cases [29.7%] vs 1362 controls [11.6%]; adjusted RR, 3.0; 95% CI, 2.8-3.3), including ASD (374 cases [10.5%] vs 125 controls [1.1%]; adjusted RR, 11.8; 95% CI, 9.4-14.7), tic disorders (28 cases [0.8%] vs 24 controls [0.2%]; adjusted RR, 4.3; 95% CI, 2.3-8.2), attention-deficit/hyperactivity disorder (189 cases [5.3%] vs 180 controls [1.5%]; adjusted RR, 3.7; 95% CI, 2.9-4.7), learning and coordination disorders (563 cases [15.7%] vs 697 controls [5.9%]; adjusted RR, 3.2; 95% CI, 2.8-3.6), intellectual disability (104 cases [2.9%] vs 137 controls [1.2%]; adjusted RR, 3.1; 95% CI, 2.3-4.2), conduct and oppositional disorders (180 cases [5.0%] vs 221 controls [1.9%]; adjusted RR, 2.8; 95% CI, 2.2-3.5), and emotional disorders with onset specific to childhood (126 cases [3.5%] vs 157 controls [1.3%]; adjusted RR, 2.6; 95% CI, 1.9-3.4). Autism spectrum disorders were also associated with schizophrenia spectrum disorders, affective disorders, anxiety disorders, and other neurotic and personality disorders among siblings.

The authors concluded:

"Psychiatric and neurodevelopmental disorders cluster among siblings of probands with ASD. For etiologic research, these findings provide further evidence that several psychiatric and neurodevelopmental disorders have common risk factors and/or that their occurrence can be linked together among siblings".

Based on this study a relationship between BD itself and the occurrence of a range of psychiatric and neurodevelopmental disorders, including ADHD and ASD in children born to affected women cannot be excluded.

Conclusion

Our literature review is limited to two recent studies that do not provide definitive proof of a psychiatric cluster of conditions between BD-, autism, ADH and potentially intellectual disability although a relationship seems probable. In these circumstances, a relationship between BD and neurodevelopment delay cannot be excluded.

In the same way as CA, in the case of NDD, BD can be identified as a potential confounder as it influences the exposure of the women to the treatment of interest (whether valproate or another mood stabiliser) and, based on the possible psychiatric cluster of diseases, it may have its own relationship with the occurrence of the outcome under study (autism or ADH).

When considering a population of childbearing women with BD, the analysis of the causal relationship between valproate exposure and NDD needs to consider BD itself as a confounding factor that could impact the assessment of the drug-event relationship under study.

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Response to Follow Up Q4

Future changes to policy – what changes would Sanofi like to see to improve the overall process? Including on transparency of the system.

Like all pharmaceutical companies our products and activities are regulated by the MHRA, the medicines regulatory authority and an executive agency of the Department of Health. We are subject to their supervision and required to comply with their decisions on all medicines-related matters. The Department of Health is responsible for the NHS and the delivery of healthcare to patients. The roles of the Department of Health and MHRA are therefore central to the operation of the medicines healthcare system operates.

Drug safety reporting and other aspects of pharmacovigilance have developed very substantially over the past 45 years as a result of technological advances, increased sophistication of analytic methods and regulatory requirements. We have contributed to this development, within the requirements of the regulatory framework, as this has evolved over time, as has been outlined in our original written submission and in our oral evidence to the Review.

Similarly, society's attitudes to patient information have undergone large changes over this period. This is exemplified by the fact that it is only since 1999 that there has been a regulatory requirement for patient information leaflets to be supplied directly to patients in all packs of medicines (although leaflets were previously provided in relation to certain products, such as valproate, on a voluntary basis) supplementing and reinforcing information provided by healthcare professionals.

While Sanofi does not have overall visibility of the healthcare system or control of its operation, we suggest the following points for consideration by the Review:

1. Increased collaboration by all participants in the healthcare system would be welcome

   Although pharmaceutical companies, directed by the regulatory authorities, play a role in disseminating new safety information through product information updates and risk minimisation activities, the effectiveness of these measures requires the collaboration of every participant in the healthcare chain - regulators, NHS administrators, healthcare professionals in both primary and secondary care, patients and carers - as well as companies.

2. Healthcare professional training, processes and time for implementation of risk minimisation measures

   Healthcare professionals are ultimately responsible for the care that patients receive. They are in direct contact with the patients and are the only ones to have specific information in regard to the health and personal circumstances of the patient. It is the responsibility of healthcare professionals to ensure that each patient receives advice on the most appropriate treatment for his or her condition. This can only be achieved if healthcare professionals are effectively trained on the treatments they use, as knowledge evolves, through appropriate systems and processes, are trained in proper reporting of adverse events and are given adequate time for proper implementation of risk minimisation measures.

3. Greater Yellow Card awareness and adverse event reporting

   In 1963, the Yellow Card Scheme for reporting of suspected adverse drug reactions by doctors was introduced in the UK. This was extended to hospital pharmacists in 1997 and to community pharmacists in 1999. The Scheme was rolled out to the public in 2005 and now permits reporting electronically and via a phone app as well as through a hard copy yellow card form. Healthcare professionals and others

are strongly encouraged to report using the Scheme. However greater awareness of the Scheme and its effective use (including the provision of adequate information for investigation of reports) by all potential participants would be welcome.

Patients could be encouraged to report adverse events directly to the regulator through awareness campaigns.

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Response to Follow Up Q5

What are Sanofi UK's interactions with patient associations and patients – including how Sanofi publicly states this involvement?

Interactions with patient organisations

Sanofi in the UK appreciates the important work patient organisations do to benefit the lives of patients, and we seek to work with them collaboratively and transparently to ensure that the patient voice is at the heart of everything we do. The following response describes Sanofi's interactions generally with patient organisations in the UK; it is not specific to valproate.

We work with patient associations/groups to provide us with valuable, independent and expert knowledge derived from their disease or condition management experience. Collaborating with patients associations/groups contributes significantly to our efforts to improve the quality of patient care, with benefits for individuals and society as a whole. All such interactions are governed by the provisions of the ABPI Code of Practice.

There are four key aspects to our interactions with patient associations/groups:

i. Independence

While collaboration with patient associations is important to the work that we do, we fully recognise and respect their independence. Relationships with patient organisations are disclosed transparently as described below.

ii. Transparency:

Sanofi UK works to strive for the highest standards of transparency and integrity, embracing the spirit and letter of the ABPI Code and UK law. Bringing greater transparency to these already well-regulated and legitimate relationships aims to build greater understanding of the collaboration between industry, healthcare professionals and healthcare organisations.

We believe that transparency reflects on credibility and engenders confidence in our company, and we are committed to complying with all applicable rules and regulations governing transparency.

Sanofi discloses details of its collaborations with healthcare professionals, healthcare organisations and patient associations across Europe. The disclosures include transfers of value made for activities such as research and educational grants to healthcare organisations as well as transfers of value to individual healthcare professionals (HCPs) such as sponsorship to attend educational meetings, speaker fees, consultancy activities and advisory boards.

As a UK affiliate, under both our obligations with the EFPIA Disclosure Code and the Association of the British Pharmaceutical Industry (ABPI) Code of Practice, we list all the transfers of value (payments which can be direct, indirect or in kind) made to healthcare organisations, patient organisations, healthcare professionals and research and development.

The most recent list of payments to patient associations can be found here: https://www.sanofi.co.uk/-/media/Project/One-Sanofi-Web/Websites/Europe/Sanofi-UK/Home/our-responsibility/transparency-in-our-interactions/payment-disclosure-2012-2014/Sponsorship-2017.pdf

iii. Patient Group Charter:

We worked with a number of UK patient organisations to develop a Charter outlining our pledges for working with patients and patient organisations. These include:

- Placing patient needs at the centre of our activities, adopting an inclusive, supportive and collaborative approach which provides mutual benefit.
- Clearly communicate with patients and patient organisations about our activities, how we operate, and why.

In practice this means:

- We respect the independence of a patient organisations and when working collaboratively we commit to clearly communicating and agreeing expectations from the outset of any project.
- We listen to the perspectives of patient organisations, seeking their input at the earliest possible stage when planning our activities.
- We ensure all of our activities adhere to the letter and spirit of the relevant Code of Practice and to UK law.
- We work together to undertake activities and develop resources that reflect patient needs and aim to improve patient outcomes.
- We enter into collaborations based on mutual understanding of teamwork, respect and trust, engaging in honest dialogue.
- We commit to enhance transparency by improving understanding of our objectives and activities, and providing information on why our procedures are in place.
- We commit to open communication about our clinical trial programmes within the scope of the relevant Code of Practice.
- We deliver on the agreement we reach for our projects with patient organisations.

iv. Sanofi Standard Operating Procedures (SOPs):

We have a series of Standard Operating Procedures (SOPs) within the business which helps to govern how we engage patient associations/groups. They are fully complimentary and supportive of the ABPI Code of Practice, but deal with the practical aspects and protocols of who is allowed to initiate engagement with patient associations - led by non-promotional functions such as medical and public affairs.

Patient engagement:

Sanofi is limited by law in its ability to engage directly with patients. In particular, proactive engagement is potentially promotional and in breach of data privacy obligations and is therefore likely to be impermissible. Information provided by Sanofi in relation to its products must always be consistent with the relevant SmPC as approved by the regulatory authorities.

Sanofi operates a reactive Medical Information service, which provides information on Sanofi products to healthcare professionals and members of the public, who request it. We cannot and do not provide advice on personal medical matters in response to requests by individual patients. Such patients are advised to contact their healthcare professional.

Patient experiences contribute significantly to our efforts to improve the quality of patient care. We therefore invite patients to present at internal seminars and conferences to explain their disease or condition and how it impacts them. This is initiated and run through an established patient association at all times. We follow strict rules and procedures for who in the business engages in this type of project and how they go about it (see Standard Operating Procedures above).

We fully uphold and adhere to UK legislation and the ABPI Code of Practice. Our response to Q9 outlines this approach in more detail.

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Response to Follow Up Q6

Patient groups and HCP involvement in the development of the Sanofi-initiated websites to raise awareness of the valproate pregnancy prevention programme

The establishment of websites relating to specific medicines is not unusual. The Human Medicines Regulations 2012 and the ABPI Code of Practice require a clear separation between patient-facing and Healthcare Professionals (HCP)-facing websites in order to ensure that material legitimately provided by pharmaceutical companies to inform HCPs, does not promote their prescription only medicines to patients and the general public.

Upholding the highest standards is a priority for Sanofi. Sanofi UK therefore has initiated the development of two entirely separate valproate websites – one for patients/general public and one for HCPs. We are working with the MHRA in the design and content of both websites, and the launch of the final versions will be subject to their prior approval.

Patient-facing website: *Inside Epilepsy*

The aim of the patient-facing website currently in development is to raise awareness and support implementation of the valproate pregnancy prevention programme (PPP)for Women of Childbearing Potential (WOCBP) and also to raise awareness and generate a better understanding of epilepsy as a condition with epilepsy patients and the general public. The content will be entirely non-promotional, consistent with the SmPC for valproate (as the marketing authorisation holder may not publish information which is inconsistent with the SmPC) and delivered in an engaging way.

Inside Epilepsy will help support families affected by epilepsy by providing appropriate guidance on key topics such as living with epilepsy and valproate risks in pregnancy, as well as featuring resources such as a Shared Decision Making Toolkit to enable patients and healthcare professionals to work together to manage their epilepsy and improve patient care.

We discussed our proposals for phase one of the website with three epilepsy associations. One of the associations provided feedback, which was reflected in the content of the Shared Decision Making Toolkit. Two associations agreed also to include their logos and helpline details on the toolkit as a way for patients to receive further information. It was agreed this was not an endorsement. We expect to launch phase one of the website following approval of its content by the MHRA.

For phase two of the website, we intend to work with an epilepsy association to develop animation content for the website.

We have received expert guidance from a Specialist Epilepsy Nurse throughout the development of the website and plan to continue this collaboration.

HCP-facing website: *Valproate Knowledge Centre*

This website aims to provide educational information regarding epilepsy and valproate treatment to any healthcare professional involved in the prescribing or dispensation of valproate, focusing in particular on the risks of use in WOCBPs and the PPP, but also providing more general information. All content will be consistent with the SmPC for valproate, in compliance with applicable regulations.

The MHRA is involved in the development of the website and we are currently making updates to prepare it for launch, subject to their approval. The launch is currently planned to coincide with the next update to the "Prevent" valproate educational materials.

In developing the HCP website Valproate Knowledge Centre (VKC) we have obtained guidance from a number of HCP experts, starting with an expert faculty meeting comprised of a professor of pharmacy, three specialist epilepsy nurses and a GP with a special interest in epilepsy. This discussion guided the topics that should be covered on the website, the general approach to provision of information and how best to engage HCPs with the site. The content of the site has been developed by Sanofi, much of it based on the "Prevent" educational materials and this has been submitted to the MHRA for approval prior to going live.

In addition to written material which may be accessed via the website, we will also provide educational webcasts, which will be streamed in real time or may be viewed online at a later date. The first webcast currently under development will be entitled "Valproate and women" and will inform HCPs of the latest guidance on the use of valproate from EMA following the PRAC review. The content of the webcast has been developed by Sanofi and has been submitted to the MHRA for approval prior to broadcast.

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Response to Follow Up Q7

Valproate Pregnancy Prevention Plan Best Practice

Sanofi has seen several examples of initiatives in the UK, which share common features. These include the systematic identification in primary care systems of every girl and woman of childbearing age being prescribed sodium valproate, annual recall of all of these patients to valproate-specific clinics in secondary care to ensure that the specialist prescriber and patient consider the risks of using valproate and complete the Risk Acknowledgement Form, and that arrangements are made for women of childbearing potential to receive highly effective contraception whilst taking the drug.

The announcement of the Quality Improvement Domain to be introduced in the 2019-20 Quality and Outcomes Framework of the General Medical Services contract will enhance this, placing a premium on the systems that improve the safety of prescribing of valproate to women of childbearing potential in primary care.

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Response to Follow Up Q8

The Review requested Sanofi to provide information on studies the company is currently pursuing, including those in relation to paternal exposure and potential inter-generational effects.

In the course of the consultations regarding valproate undertaken by the Pharmacovigilance Risk Assessment Committee (PRAC), during the Article 31 referral procedure in 2017/2018, questions other than exposure *in utero* were discussed, notably the potential impact of paternal use of valproate during pregnancy, the potential effect on the third generation offspring and the potential effects on mitochondria (mitochondrial toxicity).

In accordance with PRAC recommendations (8 February 2018), all marketing authorisation holders (MAHs) of valproate products in the EEA are required to conduct further studies (in some cases this means repeating studies which had already been carried out in the past) to characterise the nature and extent of the risk caused by valproate-containing medicinal products. In this context, Sanofi has committed to conduct a preclinical programme to assess the impact of valproate on the epigenome of germ cells. The studies are briefly described below:

1. Studies to be conducted jointly by all MAHS

(a) Extension of the ongoing Drug Utilization Study to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise prescribing patterns.

The main objective of this study is to describe prescribing practices before and after the dissemination of the new RMMs (resulting from the 2018 PRAC recommendations) and to assess the effectiveness of these measures on:

- use of valproate in women of childbearing potential (WCBP)
- use of prior therapy before the initiation of valproate
- compliance with the Pregnancy Prevention Programme (PPP)

(b) Perform 2 surveys (one among healthcare professionals (HCPs) and one among patients) to assess knowledge and behaviour with regard to the PPP as well as receipt/use of Educational Materials (and Direct Healthcare Professional Communication [DHPC] for HCPs). The main study objectives are:

- To assess HCPs' (prescribing physicians and pharmacists) awareness, knowledge and behaviour with respect to the new (2018) RMMs including the new prescribing/dispensing conditions, the PPP and the Educational Materials.
- To assess the awareness, knowledge and behaviour of WCBP treated with valproate with regards to the new (2018) RMMs including the PPP and the Educational Materials.

(c) Conduct an observational study to evaluate and identify the best practices for switching of valproate in clinical practice. The main study objectives are:

- To describe the patterns of valproate use in patients with epilepsy and in patients with bipolar disorder.
- To identify the successful/best switching and discontinuation practices.

(d) Conduct a retrospective observational study to investigate the potential association between paternal exposure and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring.

- There is currently no real-world evidence of an increased risk of congenital malformations and neurodevelopmental disorders including autism in children following paternal exposure to antiepileptic drugs (AEDs).
- The study will be carried out using a retrospective non-interventional longitudinal population-based cohort design conducted using secondary data derived from multiple longitudinal medical records registry databases in selected European Nordic countries.

The protocols of the above-mentioned Post Authorisation Safety Studies (PASSs) are under review by the EMA.

(e) Conduct a PASS preferably based on existing registries to further characterise the foetal anticonvulsant syndrome (FACS) in children with valproate *in utero* exposure as compared to other antiepileptic drugs (AEDs).

The feasibility of this study is under evaluation with the EMA.

2. Preclinical studies to be conducted by Sanofi

(a) Ames test and *in vitro* mouse lymphoma assay to investigate further the possibility of potential gene mutations and clastogenicity according to current standards.

- Genetic toxicology studies in relation to valproate were previously conducted by Sanofi and Abbott between 1977 and 1988. The results of all these studies were negative and no genotoxic potential for valproate was identified. As these studies were conducted, in accordance with applicable standards at the time, it was decided to perform these studies again in accordance with today's standards applicable to the battery of tests performed and the experimental conditions (i.e., Organization for Economic Co-operation and Development test guidelines for genotoxicity and November 2011 ICH S2 guideline).

(b) Study the potential impact of valproate on the epigenome of male and female germ cells.

- This type of study has never been carried out in the field of medicines and there is no precedent for study design. As a result, there are no regulatory guidelines and clear scientific consensus for the evaluation of changes in epigenome of male and female germ cells after exposure to chemicals. After agreeing to conduct such a study, Sanofi therefore convened an external Panel of Experts on epigenetics to help define the most appropriate experimental approaches for a non-clinical epigenetic programme. The results of this work are likely to be useful in guiding studies that may be conducted in relation to other medicines in the future.
- The scientific programme is under discussion with the EMA.

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Response to Follow Up Q9

Governance of promotion

1. Legal requirements

Directive 2001/83/EC on the Community Code relating to medicinal products for human use ("the Directive"), includes at Title VIII, controls on the advertising of medicinal products, including the sponsorship of scientific meetings and hospitality provided to healthcare professionals.

The above provisions of the Directive are transposed into UK law by Part 14 of the Human Medicines Regulations 2012: http://www.legislation.gov.uk/uksi/2012/1916/regulation/300. Further guidance in relation to these provisions is set out in MHRA's "Blue Guide: Advertising and Promotion of Medicines in the UK": https://www.gov.uk/government/publications/blue-guide-advertising-and-promoting-medicines.

The advertising controls under the Human Medicines Regulations 2012 are supervised by the MHRA, although in general complaints are referred to the appropriate self-regulatory body. Breaches of the advertising provisions of the Human Medicines Regulations 2012 may result in criminal sanctions.

2. ABPI Code of Practice

The pharmaceutical industry in the United Kingdom is committed to benefitting patients by operating in a professional, ethical and transparent manner to ensure the appropriate use of medicines. The ABPI Code of Practice ("the Code") is a voluntary self-regulatory code applicable to the promotion of prescription-only medicines, established by the Association of the British Pharmaceutical Industry (ABPI) in 1958 and updated regularly to be consistent with updates in relevant guidelines and legislation, most recently in January 2019. It incorporates the principles set out in corresponding codes issued by International and European pharmaceutical industry associations, and relevant national and European legislation governing the supply and promotion of medicines, most notably the Human Medicines Regulations 2012 (as amended).

The Code is administered by the Prescription Medicines Code of Practice Authority (PMCPA), responsible for provision of advice, guidance and training on the Code as well as managing the complaints procedure. Any complaint made against a company is regarded as a serious matter. Where a company is ruled in breach of the Code, sanctions may be applied, the most extreme being expulsion from membership of the APBI. The MHRA, assumes direct responsibility for monitoring the promotional activities of any company expelled from the ABPI, as it does for those non-member companies which choose not to be subject to the Code.

All ABPI member companies are required to abide by the Code - both in spirit and to the letter. Strong support is given to the Code by ABPI member companies, and by those non-member companies who voluntarily elect to be subject to its requirements. Companies devote considerable resources to ensure that all their activities comply with the Code's requirements. Companies are required to have robust operating procedures that ensure compliance with the Code, (and all relevant legal requirements), and must ensure that all personnel involved in the promotion of medicines to healthcare professionals are trained in the Code's requirements.

A copy of the Code can be obtained from the PMCPA's website: www.pmcpa.org.uk/thecode/Documents/ABPI%20Code%20of%20Practice%202019.pdf.

A Quick Guide to the Code can usually be found at the following page on the PMCPA's website (although at the time of writing this is undergoing revision): www.pmcpa.org.uk/thecode/Pages/Quick-guides-to-the-Code.aspx.

Principles

The fundamental principles upon which the Code is based is that promotion of prescription-only medicines is always appropriate, factual, balanced, fair and capable of substantiation. This applies to both written and spoken communication, and to both company personnel and to third parties acting on the instruction of the company. The detailed provisions of the Code establish the standards by which the pharmaceutical industry operates in a responsible, ethical and professional manner. In exchange for a legitimate right to promote medicines to healthcare professionals, the industry has to recognise the special nature of the products that it promotes (through their direct impact on the human condition), and the need to balance the requirements of patients, healthcare professionals and members of the public.

The best demonstration of this ethos is clause 2 of The Code: "***Discredit to, and Reduction of Confidence in, the Industry"***. A ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances. Examples of activities that are likely to be ruled a breach of clause 2 include activities that prejudice patient safety and/or public health.

3. Interactions with patients/members of the public

The Review specifically requested details of the legal and code provisions which regulate interactions between pharmaceutical companies and members of the public, including patients.

Part 14 of the Human Medicines Regulations 2012 (which re-enacts earlier legislation) includes provisions relating to the advertising of medicinal products to members of the public. Clarification of these provisions is found in MHRA's Blue Guide at chapter 4 and annex 3 includes guidance for the pharmaceutical industry on medicines which are promoted for use during pregnancy.

The Code sets out several principles that companies are required to follow when dealing with patients/members of the public who are not themselves healthcare professionals. These are detailed in *Clause 26: Relations with the public and the media.*

This section of the Code sets out the requirements for the industry when interacting with patients. It reinforces legislation that prohibits the advertising of prescription only medicines to members of the public. The provision of factual information about disease or a particular medicine is permitted, provided the requirements of the Code are respected.

The full text from the 2019 edition of the Code is presented below for reference. The Code itself contains further supplementary information about these clauses that often places the requirement in context, a good example being that provided for Clause 26.4: "*The intention behind this prohibition is to ensure that companies do not intervene in the patient/doctor or patient/prescriber relationship by offering advice or information which properly should be in the domain of the doctor or other prescriber.*"

"Clause 26 - Relations with the Public and the Media

26.1 Prescription only medicines must not be advertised to the public. This prohibition does not apply to vaccination campaigns carried out by companies and approved by the health ministers.

26.2 Information about prescription only medicines which is made available to the public either directly

or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product.

Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

26.3 Any material which relates to a medicine and which is intended for patients taking that medicine must include the statement below or a similar one:

'Reporting of side effects'

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report side effects directly via the Yellow Card Scheme at [a web address which links directly to the MHRA Yellow Card site].

By reporting side effects you can help provide more information on the safety of this medicine.'

When the material relates to a medicine which is subject to additional monitoring an inverted black equilateral triangle must be included on it together with the statement below or a similar one:

'This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See [a web address which links directly to the MHRA Yellow Card site] for how to report side effects.'

26.4 Requests from individual members of the public for advice on personal medical matters must be refused and the enquirer recommended to consult his or her own doctor or other prescriber or other health professional.

26.5 Companies are responsible for information about their products which is issued by their public relations agencies."

4. Sanofi's processes

Sanofi is committed to following the highest ethical standards in the promotion of its products to healthcare professionals. All requirements of the Code are embedded in Sanofi UK's standard operating procedures, and Sanofi UK has a rigorous Ethical Leadership programme, the successful completion of which is required before staff are able to undertake responsibility for the generation, review and approval of promotional materials and activities. Staff are required to complete training on the standard operating procedures for all activities they undertake before being authorised to perform any particular task, and this training is recorded and measured to ensure compliance. Compliance with all ethical standards is led by a Medical Governance function that operates independently of the commercial business, and is overseen by the Compliance Committee at board level in the UK.

All promotional materials used in the UK are reviewed by a cross functional team to ensure compliance with the Code, before being certified for use by an experienced, senior physician within the company. Promotional activities undergo a similar rigorous assessment before being approved by an appropriately experienced senior member of staff.

Ensuring that all our activity is aimed at improving the health of those who take our medicines is a fundamental principle followed at Sanofi, and the company recognises that this can only be achieved if it maintains the highest standards in the promotion of our products to healthcare professionals.

Professional and Trade Bodies

Pan–college guidance

A number of Professional Bodies brought to our attention the following Pan-college Guidance Document on Valproate Use in Women and Girls of Childbearing Years, published on 29th March 2019:

https://www.rcgp.org.uk/-/media/Files/CIRC/Epilepsy/RCGP-pan-college-valproate-march-2019.ashx?la=en

Association of British HealthTec Industries (ABHI)

Following their attendance at the Oral Hearing sessions (5th March 2019), ABHI have provided the following documents and further information to the Review.

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Evidence for the Independent Medicines and Medical Devices Safety Review
Submitted by the Association of British HealthTech Industries (ABHI)

About ABHI

ABHI is the UK's leading industry association for health technology (HealthTech).

ABHI supports the HealthTech community to save and enhance lives. Members, including both multinationals and small and medium enterprises (SMEs), supply products from syringes and wound dressings to surgical robots and digitally enhanced technologies. We represent the industry to stakeholders, such as the government, NHS and regulators. HealthTech plays a key role in supporting delivery of healthcare and is a significant contributor to the UK's economic growth. HealthTech is now the largest employer in the broader Life Sciences sector, employing 121,000 people in 3,500 companies, with a combined turnover of £22.2bn. The industry has enjoyed growth of around 5% in recent years. ABHI's 280 members account for approximately 80% of the sector by value.

This paper is submitted in advance of our attendance to give oral evidence on 5th March 2019. We have supplied answers to the 10 questions posed ahead of that session, along with comments relating to the more general Terms of Reference of the Review.

1. We recognise that the majority of patients will not have any follow-up actions providing their implanted device functions well. For patients who experience adverse events, roughly what proportion are reported to clinicians and/or MHRA? What could we do to improve the adverse event reporting process?

It should be noted that all patients with implanted devices have a degree of follow-up, insomuch as a manufacturer's post market surveillance programme will include failure and event rates compared against the total number of devices used. Additionally, the process may also include follow-up on usability of the products which may result in changes to product functionality, thereby improving and reducing in-use risk.

It is impossible to estimate the proportion of adverse events reported to physicians and the MHRA.

A manufacturer is legally bound by both the existing Medical Device Directive and the new European Medical Device Regulation, which will be fully implemented in May 2020, to report any events and/or complaints that are highlighted. This activity, and any subsequent actions, are audited routinely by a third-party conformity assessment body (Notified Body) as part of a quality system review.

Some manufacturers have been involved in trialling the use of electronic data capture mechanisms which are significantly enhancing the gathering of data. Wider adoption of these practices is expected in the future as technologies improve.

2. Please could you provide a timeline outlining your understanding and recognition of risks for the use of pelvic mesh. This may include initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

These questions are not possible for an industry association to answer, as they are specific to product manufacturers.

ABHI is happy to discuss the implications of the current and future regulations as they relate to surgical meshes and devices in general.

3. Synthetic mesh can be made from a variety of materials. Is there a consensus on the differences in adverse events and success rates of procedures related to material type, and if so, can you describe the consensus reached.

These questions are not possible for an industry association to answer, as they are specific to product manufacturers.

ABHI is happy to discuss the implications of the current and future regulations as they relate to surgical meshes and devices in general.

4. How has the material used and design of synthetic mesh evolved? Going forward, what approaches or materials are looking most promising with regard to pelvic use?

These questions are not possible for a trade association to answer, as they are specific to product manufacturers.

ABHI is happy to discuss the implications of the current and future regulations as they relate to surgical meshes and devices in general.

5. When a device is marketed on the basis of equivalence on an existing device, should there be a notification if the originator device is withdrawn from the market? If so, should this be for any withdrawal, or for safety withdrawals?

It should be noted that the new European Medical Device Regulation, which will be fully implemented in May 2020, will make the use of equivalence data less relevant. As a result, and dependent on product risk classification, a manufacturer will have to demonstrate clinical performance and positive risk/benefit analysis as a consequence of clinical investigation, rather than clinical equivalence. Clinical equivalence will only be able to be claimed based on acknowledgement from the original

product manufacturer to which equivalence is being claimed, or by equivalence within an individual manufacturer's product portfolio.

6. How could device traceability be improved? What technology would need to be in place to enable this? What role, if any, would you think that Registries play in this?

The Unique Device Identification (UDI) is a system used to mark and identify medical devices within the healthcare supply chain.

The IMDRF (International Medical Device Regulator Forum), the United States Food and Drug Administration (FDA) and the European Commission are aiming for a globally harmonised and consistent approach to increase patient safety, and help optimise patient care, by proposing a harmonised legislation for UDI using global standards.

UDI applied to products will allow tracking to patient level provided that the necessary technology is available in the healthcare organisations using the products. This will enable far greater amounts of data to be collected on products across the board, whereas registries tend to apply only to single products. Therefore, the default should be tracking using UDI to patient level for large numbers of products depending on their risk categories, and Registries should be used where deeper analysis is required.

In practice, many manufacturers are already able to identify individual devices along with information about the origin of the product down to the shift on which it was manufactured.

7. In cases where device failure occurs across a class of devices, what measures would you recommend to enable this be detected more quickly, effectively monitored and resolved?

It should be recognised that devices are fundamentally different from pharmaceuticals, and that class effects are more difficult to establish than for drugs. Whilst assumptions may be made about the properties of drugs from the same therapeutic class, it is not possible to make the same read-across for devices. For example, all coronary artery stents do the same job, but there are marked differences in design, materials and delivery systems that make it very difficult to extrapolate the performance of one stent to another.

Post market surveillance currently includes, as part of the Medical Device Directive, a procedural and periodic assessment of a device's performance within its chosen clinical setting. This assessment will capture performance of both a manufacturer's specific product, along with how a 'class of products' is performing generally, noting the caveats described above. Capture of this data and the frequency of assessment will be determined by a combination of perceived risk of the product and its novelty to the market. The outputs of a post market surveillance programme are used to re-determine the overall risk/benefit ratio of the product and/or mitigation of any new risks that may become apparent with more frequent clinical use. In all cases, multiple stakeholders are used to determine this assessment, including;

- Physicians and other end-users
- Manufacturing personnel
- Quality engineers
- Safety and medical experts within the product class.

These post market surveillance activities are audited by the third-party conformity assessment groups (Notified Bodies), according to established European practices. A manufacturer would use such guidance to establish a specific programme which best suits the risk and classification of their product or product portfolio.

The Medical Device Regulation, which will be fully implemented from May 2020, will further enhance these post market activities, by introducing elements of clinical follow-up and transparency through publicly accessible databases. This will give the end-user greater visibility of the performance of a given device, again dependent on risk classification.

8. In your expert opinion, are the revised European Medical Device Regulations sufficient, or should more be done, particularly in relation to pre-market testing?

As detailed within the submission made to the Review by the MHRA, the Industry recognises that the new Medical Device Regulation provides a significant increase in the robustness of pre-market testing requirements prior to placing product on the market. The success of a regulatory system is generally measured by the public confidence in the products that it controls. Whilst the medical device industry in Europe welcomes the improvement of the regulation, there is a recognition that the new system is providing an increase in requirements that may lead to a finessing of product portfolios, which could restrict the range of products being supplied to patients.

9. What would you consider to be the defining features of an effective clinical registry? Who is best placed to host such a registry? How can healthcare professionals be encouraged to use the registry?

ABHI supports the principles outlined in the European trade association (MedTech Europe) position paper on registries (2017)[1]. This paper recommends the following principles;

- Definition of scope for the registry
- Governance structure of the registry
- Transparency of financing throughout
- Quality of data collection and protection
- Availability of data and transparency thereof
- Competency and education level of registry stakeholders.

[1] https://www.medtecheurope.org/resource-library/medical-technology-registries-six-key-principles

10. Part of the Review's remit is to consider wider systems of redress, and we would appreciate any input on redress mechanisms including the role of insurance.

ABHI can only answer questions related to the regulatory systems that cover medical devices.

Additional Comments Relating to the Terms of Reference of the Review

Compliance with professional standards, including adverse event reporting

ABHI has a Code of Business Practice, to which every member of the association adheres. The UK ABHI Code has been developed to align with the European-wide Code of Conduct issued by our umbrella organisation, MedTech Europe. It should also be remembered that companies are subject to laws such as the UK Bribery Act and the US Foreign Corrupt Practices Act.

Both the Code and adherence to international laws, establish the working relationships between industry and end-users, particularly healthcare professionals. As such, the industry believes that the balance in these interactions is maintained to ensure the continual development of devices, often done in conjunction with healthcare professionals, and the necessary and appropriate transparency of relationships.

Indeed, the relationship between the healthcare professional and those developing products within industry can be further enhanced by considering relationships built on mutual trust and no-blame cultures. The use of medical technologies is bound by continual training and communications between the users and the manufacturer to ensure that post-marketing effects are swiftly acknowledged and acted upon.

It should also be recognised that this Code is considered an industry standard and is therefore also followed by many non-ABHI members.

A manufacturer will have, as part of its compliance efforts, incorporated a quality management system (often aligned with international standards), that controls and makes consistent, the collection, processing and actioning of adverse events and complaints that are received from users of product. These records, which are audited by third-party compliance bodies (Notified Bodies), are used to further develop and mitigate risks that are presented by the product, as well as supporting manufacturers to seek continual improvements in their products.

Information sharing in the public and private sectors

The Code includes an element, unique to the UK, of advertising and marketing literature acceptance. This is aligned in the main with those requirements found within the pharmaceutical (ABPI) Code of

Practice, and ensures that nothing that is contrary or unsubstantiated, is claimed as part of the 'information sharing' activity.

Note that Article 7 in the new MDR, for the first time, includes a requirement for a manufacturer to fully justify the claims being made in marketing and advertising literature.

Complaints handling

A manufacturer's quality management system, employed as part of its compliance with CE Marking requirements, will include elements of adverse event and complaint handling. The third-party conformity assessment body (Notified Body) will audit these processes, to ensure that events and complaints are acted upon and resolved, but also that the outputs are fed into both risk and product development processes.

Such a system ensures that where possible, risks are mitigated, in the knowledge that not all risk can be designed out of a product, but minimised as far as possible. Requirements under the new Medical Device Regulation should further improve data collection and make early detection of issues more likely. It should be noted that no effective medical treatment is completely without risk.

Following the Oral Hearing, ABHI provided the following information:

Thank you for giving us the opportunity to present evidence to the Review during the oral hearings on Tuesday last. We committed to following up on a couple of items.

Firstly there was the question of manufacturers being able to “shop around” amongst Notified Bodies to obtain a CE Mark.

Article 53 of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1) states;

Involvement of notified bodies in conformity assessment procedures

1. Where the conformity assessment procedure requires the involvement of a notified body, the manufacturer may apply to a notified body of its choice, provided that the chosen notified body is designated for conformity assessment activities related to the types of devices concerned. The manufacturer may not lodge an application in parallel with another notified body for the same conformity assessment procedure.

2. The notified body concerned shall, by means of the electronic system referred to in Article 57, inform the other notified bodies of any manufacturer that withdraws its application prior to the notified body's decision regarding the conformity assessment.

3. When applying to a notified body under paragraph 1, manufacturers shall declare whether they have withdrawn an application with another notified body prior to the decision of that notified body and provide information about any previous application for the same conformity assessment that has been refused by another notified body.

4. The notified body may require any information or data from the manufacturer, which is necessary in order to properly conduct the chosen conformity assessment procedure.

5. Notified bodies and the personnel of notified bodies shall carry out their conformity assessment activities with the highest degree of professional integrity and the requisite technical and scientific competence in the specific field and shall be free from all pressures and inducements, particularly financial, which might influence their judgement or the results of their conformity assessment activities, especially as regards persons or groups with an interest in the results of those activities.

Furthermore in each of the conformity Annexes of the 3 Medical Device Directives (Directive 90/385/EEC regarding active implantable medical devices (AIMD), Directive 93/42/EEC regarding medical devices (MDD) and Directive 98/79/EC regarding in vitro diagnostic medical devices (IVDD)), it states a manufacturer must lodge an application for assessment of his quality system with a notified body which must include;

> “A written declaration that no application has been lodged with any other notified body for the same product-related quality system.”

We also referenced our “Code of Business Practice” which I have pleasure in attaching.

http://www.abhicodeofpractice.org.uk/multimedia/New%20Folder/ABHI%20Code%20of%20Business%20Practice%20(final)%20-%20July%202018.pdf

Association of British Neurologists (ABN)

Following the Oral Hearing, the Association of British Neurologists shared the following papers with the Review:

- Heather Angus-Leppan, Rebecca S N Liu. Weighing the risks of valproate in women who could become pregnant BMJ 2018; 361 :k1596 https://doi.org/10.1136/bmj.k1596
- Heather Angus-Leppan, Rohit Shankar, Hannah Cock. Valproate, women, and exceptional circumstances BMJ 2018; 362 :k3625 https://doi.org/10.1136/bmj.k3625
- Heather Angus-Leppan. Sodium Valproate: Valproate, women and patient empowerment. Epilepsy Professional. Winter 2018.
- SM Sisodiya and Epilepsy Advisory Group for the Association of British Neurologists Valproate and childbearing potential: new regulations Practical Neurology 2018;18:176-178. http://dx.doi.org/10.1136/practneurol-2018-001955
- Lance V Watkins, Hannah R Cock, Heather Angus-Leppan, Rohit Shankar. Valproate and the Pregnancy Prevention Programme-exceptional circumstances. http://openaccess.sgul.ac.uk/110273/
- Lance Watkins, Hannah Cock, Heather Angus-Leppan, Kim Morley, Mike Wilcock, Rohit Shankar. Valproate MHRA Guidance: Limitations and Opportunities. Front Neurol. 2019; 10: 139. Published online 2019 Feb 20. doi: 10.3389/fneur.2019.00139

British Association of Urological Surgeons

BAUS have brought the following articles to the Review's attention:

- Gurol-Urganci et al (2018) Long-term Rate of Mesh Sling Removal Following Midurethral Mesh Sling Insertion Among Women With Stress Urinary Incontinence. JAMA 320(16): 1659-1669. doi:10.1001/jama.2018.14997

- Song et al (2018) The efficacy and safety comparison of surgical treatments for stress urinary incontinence: A network meta-analysis. Neurology and Urodynamics. 37:1199–1211. doi:10.1002/nau.23468

BAUS shared the following on Database usage:
In 2018, 468 cases in total were inputted, of which 431 are from England.

BAUS also shared their response to the Specialised gynaecology surgery and complex urogynaecology conditions service specifications documents (following page).

Stakeholder Response to Specialised gynaecology surgery and complex urogynaecology conditions service specifications documents – BAUS FNUU subsection

BAUS subsection of Female, Neurological and Urodynamic Urology have considered the draft specialist commissioning service specifications for the management of recurrent incontinence and prolapse, mesh complications and genitourinary urinary fistulae. These documents seek to define these services and outline how the services will be delivered. BAUS recognises the need to encourage the development of specialist centres for these services and to restrict complex surgical practice to providers with sufficient expertise and resources to deliver them safely and effectively.

The 3 service specifications attempt to define how services are delivered and the necessary referral pathways. This is not yet clear. A number of different MDT types are discussed, including,

1. Mesh MDT (for assessment and treatment of vaginal mesh complications)
2. Specialised Urogynaecology/ Female Urology Conditions MDT (Uro-MDT)
3. Specialised Complex Urinary Incontinence and Prolapse MDT
4. Fistula MDT

It is important that these MDT types are clearly defined in all 3 documents. It is also important that the relationship between these MDTs is defined. There also needs to be a clear plan for delivering these services in networks, and how referrals from non-specialist providers will be managed.

Mesh-MDT

It is stated that centres treating Complex Mesh Complications must also be a fistula centre. There must therefore be a clear relationship defined between the Mesh-MDT and the Fistula MDT.

The specification makes reference to discussions between Mesh-MDT and Uro-MDT ("Appropriate management will be determined by the Mesh MDT and … Uro-MDT"). It should be made clearer how such discussions will take place. Communication between Mesh-MDT and Uro-MDT, as well as referral pathways and processes will only be possible if Mesh-MDTs have defined catchment areas that allow defined pathways with Uro-MDTs to be utilised. It is also not clear how providers that do not have a Uro-MDT will fit into the referral pathways and networks.

Recurrent incontinence and prolapse

The Specialised Complex Urinary Incontinence and Prolapse specification needs to be clear on its definition of recurrent incontinence. In the "Scope" section, it is implicit that this includes all patients who have incontinence after a previous surgical intervention. However, in section 3.2 (p6) it implies that the specification only applies to patients who have incontinence after 2 prior surgical interventions. It is not clear whether recurrence after bulking injections would be considered within the remit of this service. BAUS FNU feel strongly that the definition of recurrent incontinence is ongoing incontinence after any surgical intervention, but in the case of Bulking injections, a second injection with Bulking agent would be permitted as part of that primary treatment.

The “scope” section should also make clear that complex primary incontinence falls under the remit of the service specification, and the definition of complex primary incontinence should be strengthened to include radiotherapy, neuropathic bladder dysfunction, prior complex pelvic surgery etc.

Fistulae

The referral catchment areas for specialised services should be considered and defined for each centre. There needs to be a clear referral pathway, especially for acute fistulae, including methods for inpatient transfers where needed. Each trust must know which Fistula Centre it should refer patients to. A method of referring the patients urgently should be in place with consideration for what happens when the surgical team is not available due to leave etc.

General

None of the documents make clear how specialist centres will be identified or assessed. There is no framework for regular review of outcomes or peer-review. These are necessary to give assurance that specialist centres can deliver the services as specified and that any changes to personnel over time do not lead to a loss of services. BSUG accreditation is marker of process and not quality and does not necessarily cover all the elements of the commissioning standards specified, so cannot be used as a surrogate for compliance with these specialised commissioning standards.

Specialist commissioning in urogynaecology has joint working between urology and gynaecology at its core with certain specific operations being commissioned due to their complexity and uncommon nature. Some procedures are specific to urology whilst some are more common in gynaecology. Some are within the remit of both disciplines.

BSUG accreditation relates to the minimum requirements for general urogynaecology practice spanning a much broader range of procedures than specialist commissioning. In addition it addresses the whole make up of urogynaecology services many of which do not relate to specialist commissioning. The accreditation does not relate specifically to procedures contained within specialist commissioning.

To use an accreditation process that does not include urologists and is not related to specialist commissioning is inappropriate and could lead to disharmony and a lack of collaborative working. The breadth of BSUG accreditation could mean that specialist commissioning may be granted to units where clinicians have an inadequate level of experience and fail to work collaboratively with urologists. This may result in patient harm as they could be treated by clinicians with a lack of expertise. In addition, using a requirement to be a BSUG accredited unit may preclude units that are national referral centres for specialist urogynaecology.

BAUS therefore feels very strongly that BSUG accreditation should be removed from the specialist commissioning documents as a requirement for the reasons stated above. However we would endorse the development of a joint assessment (BAUS and BSUG) of specially commissioned units in line with the requirements defined in the specialist commissioning document.

Other minor suggestions and notes are included below.

NOTES

Specialised Complex Surgery for Urinary Incontinence and Vaginal and Uterine Prolapse

1. On p.1 "Scope" simply mentions recurrent POP and UI, but should also mention primary complex cases (DXT, neuropaths, prior complex pelvic surgery, EDS etc). This is mentioned later in section 1.2, but that list needs to include all the above.

2. Nomenclature. This specification says "Specialised Complex Urinary Incontinence and Prolapse MDT". Is this the "Uro-MDT" mentioned in the mesh specification – probably not. Need clear definitions of all these MDTs and how they inter-relate in a network.

3. Investigations list p 3 (section 2.1). Is this helpful? List is incomplete anyway.

4. Section 3.2 (p6) alludes to 1500 patients with recurrent UI, and 375 with 2nd recurrence. It appears to specify this smaller number as the target population. However, on p.1 (scope), it states the target population to include "Women with recurrent incontinence (stress predominant) usually following prior surgical procedures and who may require more surgery", which implies all first recurrences. This needs clarifying. We believe this should relate to all recurrences, not just second recurrences.

Fistula

1. Acute/early = 3 weeks. Need clear method to refer to centre for immediate treatment with inpatient transfers etc. Each trust must know which Fistula Centre it should refer patients to. A method of referring the patients urgently should be in place with consideration for what happens when the surgical team is not available due to leave etc.
2. If ileal conduit selected, can surely be done in non-specialist centre in many cases after discussion at MDT

Mesh complications

1. Why specify where the anaesthetic assessment is done? Not relevant and possibly unhelpful (individual providers to decide between themselves, surely)

2. P3 and elsewhere, seems to make assumption that referral will have come from a Uro-MDT, whereas it might have come from a DGH etc. Possible that Mesh MDT will receive referral from DGH, then will refer on again to Uro-MDT (who have never seen the patient or seen any results).

3. List of investigations p3 is varied but probably not comprehensive (colonoscopy, cystoscopy, poppy-seed test, IVU, retrograde pyelogram etc). Is a list of tests helpful as it does not appear to form part of the specification?

4. P.4 Outpatient Appointment. It says the Mesh-MDT will review the patient. All of them? Or just a single clinician – need to clarify. Also, will the Mesh-MDT see all patients in clinic, or will some be seen at the Uro-MDT centre. On p.2 it says "[patient] will be offered an outpatient appointment

to discuss their diagnosis and management options with the Mesh MDT or their care will take place at their Specialised Urogynaecology Conditions Centre."

5. P.4 Is a telephone call at >4 weeks from first OPA mandated in all cases? Is it necessary to specify this rather than leave to the centre to decide?

6. P.5 specifies post-op follow-up, then (2 lines below) face-to-face outpatient review at 4/12 and 12/12. Are these separate things? If not, would be better to mention once.

7. P.6 says to submit to database twice (two separate bullet points)

8. Interdependence of services. All mesh services to also be fistula services? Do we need more mesh centres than fistula centres?

9. Regional distribution and networks should be defined. This is important so that networks can establish care pathways, referral forms, protocols for investigations (and where they should be done, eg urodynamics, EAU, cystoscopy). Each Uro-MDT needs to know which Mesh-MDT it will be assigned to and patient travel must be taken into consideration.

Alignment of Mesh specification with NHSE Clinical Advisory group Document

Male urological sling incontinence procedures are not within the remit of this advice. However, these procedures should only be performed as part of a well-conducted randomised controlled trial, in line with existing NICE guidance. The first sentence says it is not within their remit. The second sentence says we cannot do it. In fact, the statement is more restricting than that for TVTs (which can still be done under certain circumstances, theoretically). The majority of experts in this field are of the opinion that male slings can safely be offered as they have been for several years. We recommend that the statement for slings is the same as that for hernia repair etc (ie excluded from the restriction).

A critical element of the high vigilance process must be assurance that the patient has been fully informed of the natural history of the condition, the risks and benefits of conservative, non-surgical and surgical treatment options and any consequence of postponing surgery until a later date. The process must demonstrate that the responsible clinicians have secured and documented the agreement and consent of the patient. The BAUS options leaflet may be used to support this. This is standard practice and should apply to all operations performed for any reason. This is not high vigilance.

Recommendation iv. is recording every procedure on the specialty database (BSUG, BAUS or TPFS - The Pelvic Floor Society) or any subsequently developed national recording system. If patients decline consent for their data to entered onto a database, this will not be possible. This should be acknowledged here. Also, BSUG and BAUS database access require surgeons to pay a subscription. It is not clear who is responsible for covering these costs if BAUS/BSUG membership becomes a prerequisite for being able to undertake this work.

Surgeons should collect summaries of audit data, both for their annual appraisal and at local level 3-monthly. This should correlate with records of activity to confirm 100% data entry compliance. 100%

compliance is not compatible with a requirement to obtain consent from patients to enter their data onto the database.

British Pain Society

Following the Oral Hearing, Dr Baranowski, President of the British Pain Society shared some additional information.

Thank you very much for the opportunity to feed into the review yesterday. As was suggested would be the case, there were a few thoughts that came to mind on reflection. I think there were several Themes:

1. Seeing the right person at the right time, local where possible. This is exactly the view of the BPS and the Faculty.

When I was Chair of NHS England's CRG Adult Pain, we strongly advocated a Highly Specialised Pain Service in each Region, that those services would support several local Speciality Services and those would support primary care, community and self management services. Much Pain can be managed by community services provided that they are adequately staffed with appropriately trained members. However, there has been a tendency for MSK services to predominate in the community and these provide a different type of approach.

Unfortunately, there are only 5 or 6 **Highly Specialised** services that meet NHS Englands Service Specification D08 (D07 in Draft form, out to consultation) and despite Pain being recognised as a primary condition and a corner stone service to other areas of specialised services, the number of centres has not increased. Also **Speciality services** inform us that they are being decommissioned as CCGs invest in community services. As a consequence gap in skilled service provision widens. The matter will deteriorate if NHS England's plans to close down the Adult Pain CRG goes ahead (this is now out for consultation), as building up a pathway of care needs to be supported from the top down.

2. Education

The BPS and the Faculty are promoting education in medical schools https://www.rcoa.ac.uk/faculty-of-pain-medicine/essential-pain-management/epm-uk and for all professionals https://www.rcoa.ac.uk/faculty-of-pain-medicine/e-pain The BPS has also under my Presidency published https://indd.adobe.com/view/175981e8-79ec-421c-933e-03c0c0e2e74f We would appreciate any further feedback on this.

Education for patients we provide through publications and events organised by our Patient Liaison Committee. https://www.britishpainsociety.org/people-with-pain/ The members and leaders / Chairs are those living with pain supported by The President of the BPS and other Council Members

3. Role of professional Bodies.

I can only give my opinion on this. I see the role of the BPS as supporting its members to give best patient care. The main funds come from membership fees and income from the Annual Scientific Meeting. I do not see that the Society (and for that matter am not convinced that any members Society with vested self interest) should be involved in regulation. The BPS has drawn up pathways of best patient care, with Maps of Medicine that where widely acknowledged as being based on NICE guidelines, but with the gaps being filled in with 'common sense' where the evidence did not fill the gaps.Maps of Medicine have withdrawn these pathways over lack of funding to update them. This is despite the pathways also being used by NHS England.

4. Evidence for pain management.

I don't feel that I answered this question well, partly because the answer is complex.

As I indicated there are multiple systematic reviews and Cochrane reports that demonstrate the efficacy of Pain Management Programmes in general patient groups. These demonstrate that the beneficial results are robust, significant and cost effective.

- Williams ACDC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2012, Issue 11. Art. No.: CD007407. DOI 10.1002/14651858.CD007407.pub3. Currently being updated

- Pike A, Hearn L , Williams ACdeC. Effectiveness of psychological interventions for chronic pain on health care use and work absence: systematic review and meta-analysis. *Pain* 2016;157(4):777-85. doi: 10.1097/j.pain.0000000000000434

- Williams, ACdeC. Corrigendum to: Effectiveness of psychological interventions for chronic pain on health care use and work absence systematic review and meta-analysis, by Pike et al. PAIN 2016;157:777–785. Pain 2017;158:1398-9. doi: 10.1097/j.pain.0000000000000925

Specific publications on pelvic pain are lacking summarised in https://uroweb.org/guideline/chronic-pelvic-pain/ , section 5.1.3., again by Amanda Williams.

I suspect specific pelvic pain data is lacking because of the relatively few centres that specifically specialise in pelvic pain. However, evidence of similar (but greater) distress in the pelvic pain group is widely published such as the work of Dean Tripp https://www.queensu.ca/psychology/sites/webpublish.queensu.ca.psycwww/file

s/files/Faculty/Dean%20Tripp/Dean_A_Tripp_May_2016_CV.pdf and at UCLH our audit data confirms that.

In our department, apart from [redacted] no one has formal academic sessions for research and [redacted] has a wide range of other commitments. UCL has only just appointed a Chair in Anaesthetics! There are several Chairs in Pain Medicine within the UK, but I suspect most are industry funded, non work with pelvic pain. As full time clinicians we do collect and audit data, this lends itself to data presentation in poster format rather than peer reviewed papers. The conclusions of the posters support that those with pelvic pain benefit through the group management approach.

To move the issue forward and as a part of facilitating data collection I commissioned a review of the outcome tools that are available. https://www.britishpainsociety.org/static/uploads/resources/files/Outcome_Measures_January_2019.pdf This supports that analysis needs to be multimodal, as those living with pain have different issues. Such complexity in its own right presents difficult issues for data analysis. The future analysis of data to support pathways of care would be positively aided if Baroness Cumberlege's suggestion of electronic data collection and analysis could be funded, in the past we failed because of lack of funds.

Should there be any other aspects of the discussion what you feel need further explanation, I would be happy to be contacted. Similarly, there will be others in the field that could provide more detailed summaries of their specific areas of interest and I can put you in contact.

Dr Baranowski also provided two further references around evidence base and service delivery:

https://www.britishpainsociety.org/static/uploads/resources/files/pmp2013_main_FINAL_v6.pdf

https://www.rcoa.ac.uk/system/files/FPM-CSPMS-UK2015.pdf

Chartered Society of Physiotherapists

The CSP shared the following with the Review:

- *The Pelvic Floor Muscles – a Guide for Women*. Produced by Pelvic Obstetric & Gynaecological Physiotherapy. 2018. https://pogp.csp.org.uk/system/files/publication_files/POGP-PelvicFloor.pdf

- Statement read to the panel (see next page)

In the Oral Hearing, the PROPEL study was also discussed. The project page can be found here: http://www.nmahp-ru.ac.uk/research/grant-awards/propel/.

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Physiotherapy management of women with stress urinary incontinence

Introduction

Up to 30% of women experience a problem with their pelvic floor muscles at some time during their lives. Pelvic Organ Prolapse (POP) is estimated to affect 41%-50% of women aged over 40.The most common problems experienced by women with pelvic floor disorders are unwanted leakage with physical activity, sneezing or coughing known as Stress Urinary Incontinence (SUI). As well as reducing women's activity levels, these disorders can cause secondary health conditions, such as urinary tract infections and skin ulceration, as well as depression. Bladder and pelvic floor muscle training (PFMT) are proven treatments to improve urinary continence, reduce symptoms of prolapse and improve women's quality of life, and should be the first line of treatment for this condition.

A third of women suffer from a pelvic floor disorder after childbirth, including Stress Urinary Incontinence and Pelvic Organ Prolapse. While childbirth is the biggest cause of pelvic disorders, they can also be common following a hysterectomy and as a menopause symptom.

Since the early 2000's, many women with pelvic floor disorders were offered transvaginal mesh implants. However, there is growing evidence that there is a risk of complications for women with a pelvic organ prolapse, and in the UK 1 in 15 women have later had to have their implant surgically removed. Whether or not mesh implants should continue, this controversy has put a spot light on the fact that many women asking for help from the NHS, are not being offered conservative treatment first, and are directed direct to surgery(1).

The role of physiotherapy

Physiotherapists, who have experience and or specialised in treating women with pelvic floor disorders, provide assessment and conservative (non-surgical) management. This comprises training and strengthening the pelvic floor muscles. Physiotherapists also provide advice to women with SUI and POP on key public health messages including weight loss, reduction in caffeine consumption and fluid intake, smoking cessation and increasing physical exercise.

The specialist women's health workforce

There are circa 800 physiotherapists in the UK who have specialist knowledge of women's health and expertise in assessment of pelvic floor disorders. The size of the specialist workforce is insufficient to provide pelvic floor muscle training to all those who require it. Current service provision is limited and variable across the NHS.

Evidence

The Cochrane Database Systematic review (2014) of Pelvic Floor muscle training versus no treatment, or active control treatments concluded (based on the data available), that pelvic floor muscle training (PFMT) can cure or improve symptoms of SUI and all other types of UI.

It may reduce the number of leakage episodes, and the quantity of leakage.

NICE are currently reviewing its guideline on Urinary incontinence and pelvic organ prolapse in women: management. Publication of the guideline is April 2019. This guideline will update NICE guideline published September 2013 and October 2006. Previous NICE guideline for UI advocates a trial of supervised pelvic floor muscle training of at least 3 months' duration as first-line treatment to women with stress or mixed UI and the continuation of an exercise programme if pelvic floor muscle training is beneficial.

There is growing evidence that PFMT can at least slow progression of POP and in some instances improve symptoms.

The PROPEL study (2018) funded by the National Institute for Health Research (NIHR) evaluated different models of delivering Pelvic Floor Muscle Training for Pelvic Organ Prolapse, to increase access for women to conservative management. The service models included some that trained different health care professionals at various levels to increase capacity to provide PFMT for some women.

Recommendations

- Women who have had a prolapse or stress urinary incontinence are referred for pelvic floor muscle training as first line of treatment
- Increase in the specialist physiotherapy workforce and non-specialists who are trained to provide pelvic floor muscle training.

References

1. Dumoulin C, Hay-Smith EJ, Mac Habee-Seguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014(5):CD005654.

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6th February 2

Royal College of General Practitioners

Following their attendance at the Oral Hearing session (23rd January 2019), the RCGP have provided the following documents and further information to the Review.

- BJGP article on sodium valproate scheduled for publication in April 2019. This is being drafted by Dr Judy Shakespeare with drafting groups. The IMMDS Review would appreciate a copy once it is published.

  We can let you know when this is available.

- HSL expressed a willingness to conduct member survey on compliance with standards set by RCGP, or re adverse event reporting should this help the Review. If you have conducted surveys like this before please could you let us have response rates. Do you get a reasonable response rate and do you feel it is reflective of your membership as a whole or not?

  We don't have any statistics unfortunately, but we can say that anecdotally when niche surveys are shared with members, we do not have high levels of engagement.

- Private research – we understand that practices can participate in this and that it would be paid. It would be helpful for the Review to have a broad understanding of the prevalence of this activity.

  We have discussed with our Clinical Research and Innovation Centre and unfortunately do not have any further information on this.

- Communication between specialist groups - we would welcome any information you have on this.
  We do not have any further information on this.

- GP awareness of foetal valproate syndrome (and sources of this information). We have heard from Sanofi that they surveyed medical practitioners and found high levels of awareness of the risk of valproate use during pregnancy. Do you have any information specifically related to GP awareness?

  We do not have any available figures on this.

- Taking (women's) concerns seriously. The IMMDS Review predominantly relates to treatments given to women. Do you have any guidance that focuses on taking patient concerns seriously, specifically women's concerns?

  Other than generic advice from NICE we know of no other, more specific, guidance.
  https://www.nice.org.uk/about/nice-communities/nice-and-the-public/making-decisions-about-your-care

- Limits on post-marketing surveillance studies. Any information you could provide on this would be helpful.

  We do not have any further information on this.

THE OUTCOME OF PREGNANCY STUDY (SCOTLAND)

This investigation was conceived and planned in 1965 by the Research Committee of the Royal College of General Practitioners, South East Scotland Faculty.

The primary purpose of the study was, by epidemiological methods, to investigate possible causes of congenital abnormality, especially with regard to factors operating during pregnancy, including illnesses and drugs, but also respecting mother's age and parity, previous pregnancies, regional distribution and other factors which might be relevant in this context. Hedberg et al[1] and many others have emphasised the value of prospective studies in this particular field. Information regarding the aetiology and perhaps incidance of abortions and stillbirths (other than those due to congenital abnormality) could reasonably be expected as by-products.

The basic data for the study was provided by a large number of general practitioners throughout Scotland from the beginning of 1966 to August 1968. Coordination was partly in the hands of the above-mentioned Research Committee and partly by a very small team from the Department of Social Medicine of the University of Edinburgh. Interpretation of the results were the responsibility of this last-mentioned team. The study broadly followed the lines of that already carried out in England (reference if the report of this has been published), but there were many differences in detail.

The intention was that as many general practitioners as possible who practice midwifery in Scotland should submit for analysis contemporary records of all their pregnant patients at 3 points of time; (a) first attendance of the pregnant woman; (b) first attendance after the 24th week; and (c) after the outcome, whether this was of birth of a normal child, an abnormality, an abortion or a stillbirth. In the case of abortions

only one or perhaps two recordings could be expected, otherwise three recordings were generally obtained.

Since the primary interest was that of Congenital Abnormalities, the study was largely financed by a grant from the Distillers Company Limited to the University of Edinburgh and we are therefore deeply indebted both to the Company and to the relevant University committee for the funds which enabled this study to be completed.

In order to minimise the extra work required from the participating practitioners, their ordinary "Maternity Service Record Cards" with only slight modification and one detachable added page, were used Fig. I.

The use of these cards had the advantages of saving in cost, and that undoubtedly a greater proportion of practitioners felt able to take part in the study since the added amount of work was comparatively small and the completed cards (see under) were returned to the practitioner. On the other hand there were some disadvantages inherent in this arrangement and these will be briefly discussed in the analysis section of this report.

Each card at the periods mentioned above was sent in a post-paid envelope to the Department of Social Medicine where it was Xerox-copied and returned to the practitioner within a few days. The Xerox copies were filed for record and subsequent analysis. The detachable first page of the card was filed in the original, since it had no further interest to the general practitioner.

All general practitioners practising midwifery in Scotland were circularised by the College towards the end of 1965 and their participation invited. 480 initially agreed to take part (out of a total of); 380 produced at least one complete record, and 272 remained participants from the beginning to the end of the study - viz, from January 1966 until August 1968. At the end of the study 15, 181 complete

records were available for analysis.

Theoretically it would have been desirable to analyse all of these 15,000 records in detail. Such an analysis might have provided much useful information on subjects disconnected with congenital malformations, but the staff was not available to undertake this enormous task. The records are however still extant should subsequent complete analysis be deemed desirable.

It was therefore decided initially that the analysis in detail should be confined to those pregnancies which resulted in an abnormal outcome, whether this was a congenital abnormality, an abortion, a stillbirth or a neonatal death, plus an appropriate number of randomly selected controls. The planned analysis included inter alia the investigation of all drugs prescribed, including for example, organic and inorganic iron, vitamins, antibiotics and antiemetics, in respect of their possible association with abnormality, abortion or stillbirth. (See appendix for complete list of drug groups).

However, at the suggestion of the Committee on the Safety of Drugs a less extensive analysis was made of records of all parturient women in the Study who had had any of a comparatively small group of drugs prescribed to them. These drugs included anti-emetics, hormones and a few others. It was hoped that this special study might be informative not only with regard to congenital abnormalities but also abortions.

The analysis of the Outcome of Pregnancy Study consists therefore of two parts: 1. General Analysis and 2. More limited analysis of those women to whom particular drugs had been prescribed.

General Analysis

Among the 15,181 outcomes there were 452 children with one or more abnormality, (2.98%); 513 abortions (3.38%); and 422 controls (2.78%) randomly selected without matching). Surgical terminations and doubtful outcomes were excluded.

Comparison between the total percentage of abnormalities and those of other studies is of no interest or assistance since criteria of diagnosis and many other factors differ so profoundly. The proportion of abortions recorded is however disappointingly low. This fact was noted early in the study. Scrutiny of the basic records showed that, while some doctors returned an "acceptable" figure of round about 10% or more, others with large numbers of full-term records returned no abortions at all. This was obviously due to a misunderstanding of the initial instructions and an attempt, only partially successful, was made to remedy this.

Since the abnormalities were recorded for the most part at birth by the general practitioners concerned, without subsequent confirmation from hospitals the large majority of cards, 396, recorded only one abnormality while 43 recorded two anomalies and 15 three or more. All but 12 of the additional abnormalities were either a) common associations with primary anomalies - e.g. congenital heart disease with mongolism, talipes equinovarus with spina bifida, and many other defects with anencephaly - or b) minor defects such as haemangiomata and pre-auricular tags. It was therefore decided that for analysis, only the primary abnormality should be considered.

Table I itemises the different "primary" anomalies reported.

Some Comparisons

Probably the first point which should be made is the difficulty of any comparison between different surveys on the grounds of criteria of diagnosis, classification of abnormalities, time of diagnosis, etc.

TABLE I

CNS anomalies		
	Anencephaly	23
	Anencephaly/Spina bifida	5
	Iniencephalus	2
	Hydrocephalus	14
	Hydrocephalus/Spina bifida	4
	Spina bifida & Cranium bifida	18
	Other CNS anomalies (1 each)	6
Eye defects		
	(No cataracts, 1 anophthalmic)	4
Head and Face deformaties		
	Micrognathia	1
Lips and Palate		
	Cleft lip alone	7
	Cleft palate alone	16
	Cleft lip and palate	7
Ear Defects		4
Skeletal Defects		
	Congenital Dislocation of Hip	59
	Talipes Equinovarus	29
	Talipes Calcanco Valgus	7

Polydactyly) Syndactyly)	(5 hands 2 feet)	7
Cervical ribs		2
Other deformaties	2 each	24

Gastro-Intestinal Defects

Pyloric Stenosis	8
Fibrocystic Pancreas	3
Oesophageal Atresia	5
Tracheooesophageal Fistula	2
Imperforate anus	2
Others	7

Deformities of Heart and Great Vessels

Congenital H.D. Not further specified	11
Interventricular Sptal Defect	4
Interatrial Septal Defect	2
Fallot's Tetralogy	3
Others	12

Deformities of Urinary Tract

Renal Agenesis	3
Others	3

Malformations of Genitalia

Hypospadias	17
Undescended/ectopic Testis	5
Others	1

Malformations of Respiratory System

Diaphragmatic Hernia	5
Hiatus Hernia	4
Eventration	2
Others	4

Endocrine Malformations	Goitre	1
Skin and Muscles		
	Capillary/Cavernous Hae	25
	Pigmented	20
	Pilonidal Sinus	8
	Epidemolysis bullosa	2
	Others	10
Chromosomal Abnormalities		
	Mongolism	24
	Others (unspecified)	1
Tumours etc.		
	Dermoid	1
	Cysts	3
Hernia excluding inguinal		
	Exomphalos	7
Unspecified Multiple Abnormalities		8

Some Comparisons

Probably the first point which should be made is the difficulty of any comparison between different surveys on the grounds of criteria of diagnosis, classification of abnormalities, time of diagnosis, etc. This difficulty has been emphasised by Knorr[2], Leck & Smithells[3] & Sievers[4] among many others.

Further, the number of births is small compared with many surveys of congenital abnormalities, e.g. that of Smithells[5], and the total population is unknown; the diagnosis of abnormality has been recorded by a large number of general practitioners and an unknown proportion of these diagnoses has been confirmed in hospital.

Inevitably major abnormalities, especially those resulting in stillbirth or neonatal death (e.g. anencephaly) are reported more consistently than minor abnormalities such as pilonidal sinus.

Therefore, while bearing in mind that it was not part of the aim of this study to determine incidence of congenital abnormalities in Scotland, it is possible to make some relevant comparisons in respect of some malformations.

TABLE II

	Incidence per 1000 births			
	Liverpool[5]	Dundee[6]	Birmingham[7,8]	Present Study
Anencephaly/unencephaly	3.14	2.3	2.58	1.98
Spina bifida/Cranium bifidum	3.36		2.73	1.45
Hydrocephalus alone	0.55			0.92
Cleft lip alone	0.42			0.46
Cleft palate alone	0.49		0.60	1.05
Cleft lip and palate	0.63			0.46
Syndactyly and polydactyly	1.37			1.12
Mongolism	1.43		1.09	1.51

Only conditions which occured sufficiently often and were readily diagnosable at birth have been included - Hydrocephalus is a doubtful inclusion on the second count. This comparison is probably useful insofar that it largely supports the reliability of the General Practitioner diagnoses, even though the figure for Anencephaly and Spina Bifida are low compared with the other studies. It is however, as has been stated, impossible to compare meaningfully precise figures since the total population in the present study is unknown.

The further results of this paper are concerned with possible aetiological factors in the production of congenital anomalies.

Marital Status

TABLE III

Outcome of Pregnancy/Marital Status

	CONTROL		ABNORMALITY		ABORTION	
	Obtained	Expected	Obtained	Expected	Obtained	Expect
Married	391	369.8	403	415.0	480	469.2
Single	26	27.2	41	29.0	22	32.8

Total : Married - 1274
Total : Single - 89

Notwithstanding the comparatively small numbers this table shows a significant difference in the number of single women with abnormalities and abortions ($X^2 = 9.17$ with 2 d.f. $0.05 > p < 0.01$). The number of abnormalities is significantly larger among single women than would be expected, and this finding is in agreement with those in many other studies. On the other hand, the number of abortions is significantly smaller in single women. A presumption which may be reasonably acceptable is that single women with threatened and then inevitable abortion are much less likely to consult their general practitioner than are married

married women in the same situation.

Area of Scotland (Regional Hospital Board Areas).

TABLE IV

Outcome / area of delivery

	CONTROL		ABNORMALITY		ABORTION	
	Observed	Expected	Observed	Expected	Observed	Expected
South-East	104	138	163	148	187	168
West	234	203	191	217	242	247
East	49	42	43	45	45	51
North-East	28	35	52	37	34	42
North	7	5	3	5	5	5

There are highly significant differences in the proportions in the areas South-east, West and North-east. Both abnormalities and abortions were significantly higher in the South-east; abnormalities were significantly lower in the West; while in the Northeast abnormalities were significantly higher and abortions significantly lower. (X^2 = 33.04 with 8 d.f. $p < 0.001$).

Interpretation of this table is somewhat hazardous. An intelligent guess might be that both abnormality and abortion figures are high in the South-east at least partly since this area was the hub of the investigation; general practitioners in the area perhaps recorded more faithfully, and also followup by the general practitioners themselves of doubtful cases was very much commoner than in the other areas. The increased proportion of abnormalities only in the Northeast may be partly explained by the very great interest in Congenital Abnormalities which has for long been the case in the Aberdeen area.

Social Class

Because of the extreme unreliability of interpretation of social class as recorded on the cards it was decided to group Social Classes I and II together and Social Classes IV and V. This grouping provided a much more reliable basis for statistical analysis.

TABLE V

Outcome / Grouped Social Classes

	CONTROLS		ABNORMALITIES		ABORTIONS	
	Observed	Expected	Observed	Expected	Observed	Expected
So. I. & II	60	69	75	71	84	79
III	259	234	206	243	283	270
IV & V	89	105	143	109	104	121

There is a significantly higher proportion of abnormalities in Social Classes IV and V (χ^2 = 25.89 with 2 d.f. p < 0.01). This agrees with, among many others, the finding of Coffey[9].

Toxaemia of Pregnancy (Analysis of this table (Table VI) showed no statistical difference between the various groups. It is recorded primarily for any interest there may be with the incidence of the Hypertension/Toxaemia.

TABLE VI.

Outcome/Toxaemia/Hypertension

	No.	%	No.	%	No.	%	No.	%
No Hypert/Toxaemia	303	72	314	69	13	3	630	45
Essential Hyper/No Toxaemia	4	1	6	1	9	2	19	1
Essential Hyper/with Toxaemia	3	1	9	2	–	–	11	1
Mild Toxaemia	50	14	51	11	11	2	113	8
Moderate Toxaemia	11	2	20	4	–	–	31	2
Severe Toxaemia	3	1	2	–	1	–	6	–
Not Known	38	9	51	12	488	95	577	42
Totals:	422	100	452	100	513	100	1387	100

The figures in relation to abortions are of course of little or no relevance.

The definitions of the terms used were as follows:

No Hypertension or Toxaemia : No diastolic reading over 90 mm Hg if at least 4 B.P. readings were taken. If fewer than 4 readings were taken this item was recorded as "not known" if none of the readings was above 90 mm.

Essential Hypertension without Toxaemia : Diastolic B.P. over 90 mm Hg. before the 20th week without subsequent rise.

Essential Hypertension with Toxaemia : Diastolic B.P. over 90 mm. Hg before the 20th week and a subsequent rise of at least 10 mm.

Mild Toxaemia: B.P. between 90 and 99 after 20th week.

Moderate " B.P. between 100 and 109 after 20th week.

Severe " B.P. 110 and over after 20th week.

Place of Booking and Delivery

TABLE VII

Outcome/Place of Booking and Delivery

	Controls		Abnormalities		Abortions		Totals	
	No.	%	No.	%	No.	%	No.	%
Home/Home	83	20	48	11	26	5	157	11
Home/Hospital	12	3	36	8	42	8	90	6
Hospital/Home	4	1	5	1	38	7	47	3
Hospital/Hospital	256	61	282	62	151	29	689	50
Nursing Home/N.H.	18	4	19	4	3	1	40	3
Home/Nursing Home	–	–	–	–	1	–	1	–
Nursing Home/Home	–	–	2	1	6	1	8	1
Home/Not Specified	13	2	5	2	32	6	50	4
Hospital/Not Specified	31	7	38	8	98	19	167	12
Others	4	1	10	2	22	4	36	3
N.S./N.K.	1	–	7	2	94	18	102	7
Totals:	422	100	452	100	513	100	1387	100

There were predictably significant differences between Home/Home and Home/Hospital, and between Hospital/Home and Hospital/Hospital groups, in respect of both Abnormalities and Abortions.

TABLE VIIa

	Controls		Abnormalities		Abortions	
	Observed	Expected	Observed	Expected	Observed	Exp
Hospital/Home	4	17	5	18	38	1
Hospital/Hospital	256	243	282	269	151	17

(X^2 = 80.08 with 2 d.f. p < 0.01)

TABLE VII b

	Controls		Abnormalities		Abortions	
	Observed	Expected	Observed	Expected	Observ.	Exp
Hospital/Home	4	17	5	18	38	1
Hospital/Hospital	256	243	282	269	151	17

(X^2 = 80.08 with 2 d.f. p = 0.01)

From Table VIIa it is seen that a significantly higher proportion of abnormalities and abortions who were intended for home delivery were in fact delivered in hospital. This finding is supported by Table VIIb showing the eventual delivery places of those booked for hospital.

The clinical explanation is almost too obvious to be stated : that any prenatal signs of abnormality or abortion led to these cases being admitted as un-booked cases to hospital, on the other hand a significant proportion of gravid women booked for hospital aborted at home before it was possible for them to be admitted.

Parity

TABLE VIII

Outcome / Parity

	Controls		Abnormalities		Abortions	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
Primipara	113	118	140	125	122	131
Para 1.	129	111	119	117	103	123
Para 2.	83	80	76	84	93	88
Para 3.	51	55	51	58	72	61
Para 4.	24	23	20	25	30	26
Para 4	13	26	31	27	38	29

(X^2 = 24.70 with 10 d.f. p. 0.01)

Abnormalities were significantly more frequent in primipara but the results of this analysis are otherwise inconsistent and difficult to interpret as far as abnormalities are concerned. Perhaps minor abnormalities such as naevi were more lively to be missed in pregnancies 2 - 4 since the general practitioner was more likely to be present at 1st and 5th or subsequent births? This is merely a guess. Abortions show a consistent increase in all pregnancies after the second.

It might have been rewarding here to break down the anomalies and analyse them vis-a-vis parity and maternal age but a preliminary scrutiny of the results showed that the numbers of each abnormality were so small that, with the exception of mongolism, no significant results would be obtained. And with regard to mongolism, these relationships have been so well documented in comparably larger surveys - e.g.Collmann and Stoller (10) with 780,000 births - that it was not considered that this comparatively small survey would add appreciably to our sum of knowledge in this respect.

Previous Abortions

Unlike the report of Coffey (9) quoted above, and some others, there as in this study no suggestion of an increased frequency of previous abortions in mothers bearing abnormal children. On the other hand there is a very significantly higher rate of previous abortions in those whose outcome here was also an abortion.

TABLE IX

	Controls		Abortions	
	Obs.	Exp.	Obs.	Exp.
Previous abortions				
0	357	336	356	386
1 or more	52	72	114	83

(X^2 = 222.5 with 2 d.f. p 0.001).

This not unexpected result may be of interest vis-a-vis other abortion studies.

Similar results were recorded with regard to previous stillbirths and/or neonatal deaths. There was a significantly higher proportion of these only in patients in the present study where the outcome was an abortion.

TABLE X

Outcome/Previous stillbirths and or N.N.D's.

Previous stillbirths or neonatal deaths	Controls Obs.	Controls Exp.	Abortions Obs.	Abortions Exp.
0	396	386	432	446
1 or more	13	23	39	26

(X^2 = 11.18 with 2 d.f. p 0.01).

Abnormalities in previous children and in parents

TABLE XI

Outcome / Anomalies in previous children etc.

	Controls No.	Controls %	Abnormalities No.	Abnormalities %	Abortions No.	Abortions %	Total No.	Total %
Negative history	407	96	420	93	475	93	1302	94
1 similar anom in previous child	0	0	6	1	0	0	6	0
1 similar anom. in previous children	0	0	1	0	0	0	1	0
1 Dissimilar anomaly in previous child	0	0	4	1	0	0	4	1
Dissimilar anom. in previous children	0	0	2	0	0	0	2	0
Anomalies in controls	3	1	0	0	0	0	3	0

TABLE XI CONTINUED

	Controls		Abnormalities		Abortions		Total	
	No.	%	No.	%	No.	%	No.	%
Presumed abnormalities in abortion sib	0	0	11	2	0	0	11	1
Anomalies in parents	0	0	8	1	4	1	12	1
Not known	12	3	11	2	34	6	46	3
Total	422	100	452*	100	513	100	1387	100

(* The totals in the abnormalities column and in the overall totals do not tally because of plurality of sib/parent abnormalities in abnormal outcomes)

This table was not analysed statistically since the numbers were so small. It is of interest however to note that 3 of the 6 previous similar anomalies, and the one occurrence of 2 previous similar anomalies, were all congenital dislocation of the hip. Two points about this condition have been frequently noted :
a) familial incidence which is well recognised (Rubin[13]) and
b) the unreliability of unequivocal diagnosis of C.D.H. within a few days of birth. Especially when there has been a previous C.D.H. among the sibs, the tendency will inevitably be to treat any subsequent "doubtful" child as a definite positive. From all points of view except that of the epidemiological investigator this view is more than justifiable; preventive measures are atraumatic to the infant, while the consequences of missing the diagnosis are little short of disastrous.

The loss of "epidemiological material" is an insignificant price to pay for the value of early prevention in such cases even if only 5-10% of the cases diagnosed at birth would eventually without prophylaxis have developed into true dislocations. It is in fact not the least important facet of a study such as this that general practitioners can be alerted to the possibility of diagnosis within a few days of birth by Palmeris manoeuvre[12].

Of the other 3 "similar anomalies", two were haemangionata and one was an anencephalus. All the dissimilar anomalies belonged to the minor category. Anomalies in control sibs were 1 syndactyly (fingers) and two other minor anomalies. The data recorded with regard to "presumed anomalies in abortion sibs" were not precise enough for analysis. The numbers of anomalies in parents were very small due to inadequate recording, and there was no significant pattern.

Gestation Time

TABLE XII

Outcome / weeks gestation

Gestation period in weeks	Control		Abnormalities		Abortions		Total	
	No.	%	No.	%	No.	%	No.	%
<4	-	-	-	-	4	1	4	-
5<9	-	-	-	-	98	19	98	7
10<14	-	-	-	-	244	48	244	18
15<19	-	-	-	-	64	12	64	5
20<24	-	-	1	-	57	11	58	4
25<29	-	-	4	1	22	4	26	2
30<34	2	-	37	8	-	-	39	3
35<39	161	38	146	32	-	-	307	22
40<44	247	59	235	52	-	-	482	35
>44	5	1	2	-	-	-	7	1
N.K.	7	1	27	3	24	4	58	4
TOTALS:	422		452		513		1387	

Ignoring the abortions, the abnormalities are significantly shorter in gestation time (X = 7.437 with 2 d.f. Sig. at 5%). This is in agreement with other similar studies and is to be expected on clinical grounds.

Weight of Baby

TABLE XIII

Outcome/Weight of Baby

Weight in oz.	Controls		Abnormalities	
	No.	%	No.	%
24	-	-	1	-
32	-	-	1	-
40	-	-	3	1
48	-	-	7	2
56	-	-	7	2
64	1	-	8	2
72	3	1	9	2
80	9	2	8	2
88	5	1	12	3
96	28	7	33	7
104	28	7	40	9
112	46	11	62	14
120	55	13	66	15
128	67	16	57	13
136	71	17	33	7
144	26	6	19	4
152	20	5	9	2
160	9	2	4	1
168	2	-	-	-
176	3	1	2	-
176	1	-	-	-
N.K.	38	9	56	12
TOTALS:	412		437	

Using a "two tailed test" indicating a difference between the time distributions of two groups, there is a significant difference between the controls and the abnormalities at a 1% level. The average weight of the abnormalities is significantly lower than that of the controls ($X^2 = 31.2$ with 2 d.f. $p < 0.01$). This finding, while not perhaps intrinsically of much interest, does correspond with the finding of a shorter gestation period in the abnormalities.

It will be noted that the totals in this table are slightly smaller (-10 Controls and -15 Abnormalities), than in other tables. The weights of these 25 babies were recorded in grams, and the grouped weights in grams could not be fitted in with the grouped weight in ounces. The number involved however is so small that it is of no significance and is of interest only perhaps as an indication of the rate of progress towards decimilisation at that time!

Sex Differences

TABLE XIV

Outcome/Sex

	Controls		Abnormalities		Total	
	No.	%	No.	%	No.	%
Male	208	49.3	195	43.1	403	100
Female	203	48.1	228	50.5	431	100
N.K.	11	2.6	29	6.4	40	100
TOTAL:	422	100	452	200	874	100

There is no significant difference between the proportions ($\chi^2 = 1.521$ with 1 d.f.)

Ideally the sex differences of each separate abnormality should have been analysed. Though no doubt there would for example have been a significant preponderance of females with Congenital Dislocation of the Hip, it was felt as with "age of mother" and "parity" mentioned above, that the amount of work entailed in performing such an analysis would not be justified by the results obtained.

Type of Delivery

TABLE XV

Outcome/Type of Delivery

	Controls		Abnormalities	
	Obs.	Exp.	Obs.	Exp.
Spontaneous	345	320	307	332
Induced	7	19	31	19
Forceps	27	35	45	37
Caesarean S.	15	20	25	20

There was a significant increase in the proportions of abnormalities having a "non-spontaneous" delivery: (X^2 = 24.13 with 3 d.f. P <0.001) - a note unexpected result, perhaps just worth recording.

Conditions of Baby

TABLE XVI

Outcome/ Condition of Baby

Condition	Controls		Abnormalities	
	Obs.	Exp.	Obs.	Exp.
Normal	372	316	263	319
Mild Asphyxia	7	11	16	12
Severe Asphyxia/Poor	5	11	17	11
Stillbirth	-	24	49	35
Death within 1 month	1	22	44	23

There is a highly significantly greater proportion of babies with abnormalities whose condition was not normal at birth - (X^2 = 118.35 with 4 d.f. P< 0.001). It should be noted however that by definition "controls" excluded stillbirths and this fact therefore reduces the significance of these figures. The difference in proportions nevertheless remains significant and is of course predictable.

The following other analysis were produced in the general study:

1. Outcome/illness within the 6 weeks prior to pregnancy and Outcome/Chronic Illness (e.g. tuberculosis, thyrotoxicosis etc.) No significant differences were found.

2. Outcome/illness in the first trimester. The outcomes of those suffering from one specific illness only - not combinations of illnesses - were tested against those with no illness. No significant results were recorded in regard to abnormalities, but the following results were significant vis-a-vis abortions.

TABLE XVII

Outcome/Illness in 1st trimester

(a) Upper Respiratory Tract

	Controls		Abnormalities		Abortions	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
None	139	138.2	164	153.3	50	61.5
U.R.T.I.	16	16.8	8	18.7	19	7.5

(No significant difference controls ve. abnormalities. Controls/abortions $X^2 = 26,72$ with 2 d.f. $p < 0.001$)

(b) Urinary Infection

None	139	138.9	164	150.7	50	54.5
Urinary Infection	10	9.1	5	10.3	8	3.5

(Controls/abortions $X^2 = 8.98$ with 2 d.f. $0.05 > p < 0.01$).

(c) Morning Sickness

None	139	126.2	164	161.5	50	65.3
Morning Sickness	29	41.8	51	53.5	37	21.7

(Controls/abortions $X^2 = 19.86$ with 2 d.f. $p < 0.01$)

It should be noted that this diagnosis was recorded only when it was so recorded on the Maternity Services Card. A considerable number of patients were given anti-enetic drugs without such diagnosis being recorded. For example,

one practitioner prescribed such drugs for nearly half of his patients, while another, with approximately the same number of gravid patients, prescribed none at all. The results recorded are therefore equivocal, to say the least.

d) Other diseases only

	Controls		Abnormalities		Abortions	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
None	139	133.5	164	157.3	50	62.2
Others only	7	12.5	8	14.7	18	5.8

Controls/Abortions $X^2 = 33,91$ with 2 d.f. $p < 0.01$)

All these showed a statistically significantly higher proportion of abortions in mothers suffering from the enumerated complaints. The difficulty here is to separate the possible effect of the diseases from that of their treatment. In the meantime all that can be done is to record these results, perhaps as a basis for future analysis of the possible abortefacient effects of a number of illnesses and/or drugs.

3. Illnesses later in pregnancy. No significant results were obtained from analysis of this table.

4. No specific chronic diseases - e.g. tuberculosis, mental disorders, thyreotoxicosis, epilepsy - produced any significant result. The remaining conglomerate of "other diseases" did produce a result significant at a 5% level, but it was so heterogeneous and the numbers involved were so small that no conclusions could be drawn from the figures.

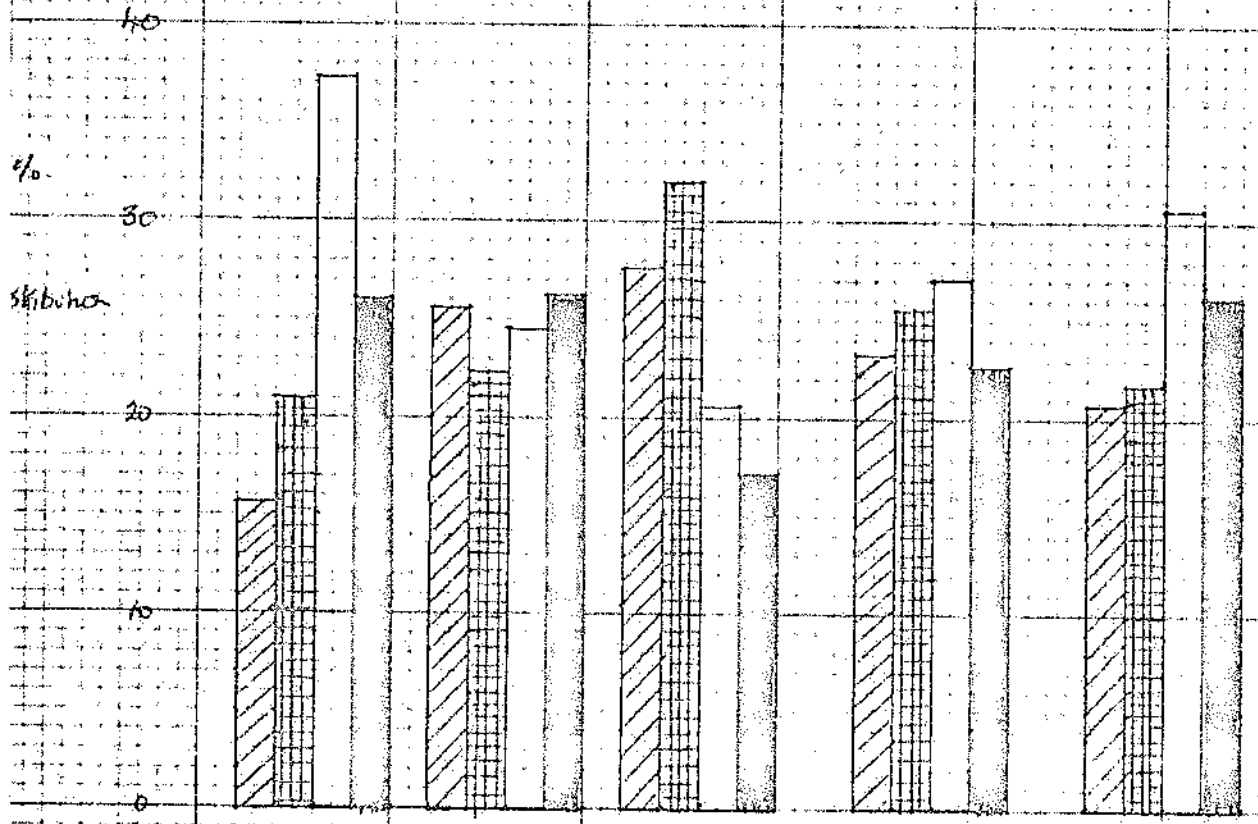
5. Drugs. All the drugs listed in the appendix were investigated for possible association with abnormalities. In view of the fact that a separate study was made of particular drugs - see the second part of this report - particular attention was focussed in the general study on drugs which did not feature in the special one - e.g. tetracycline, bearing in mind Carter's report[13]. No significant association was found in regard to any of the drugs.

6. Similar negative results were recorded in respect of; x-rays, threatened abortion, contact with illnesses and preventive inoculations.

7. An attempt was made to determine any significant seasonal variation in the occurrence of abnormalities. In the absence of a breakdown into particular abnormalities the findings recorded in Figs. I and II under, may have little significance, but the data accumulated are available should further analysis be desired. It is relevant however in this context to underline the reservations which Sillberg et al[14] expressed regarding the interpretation of such variations.

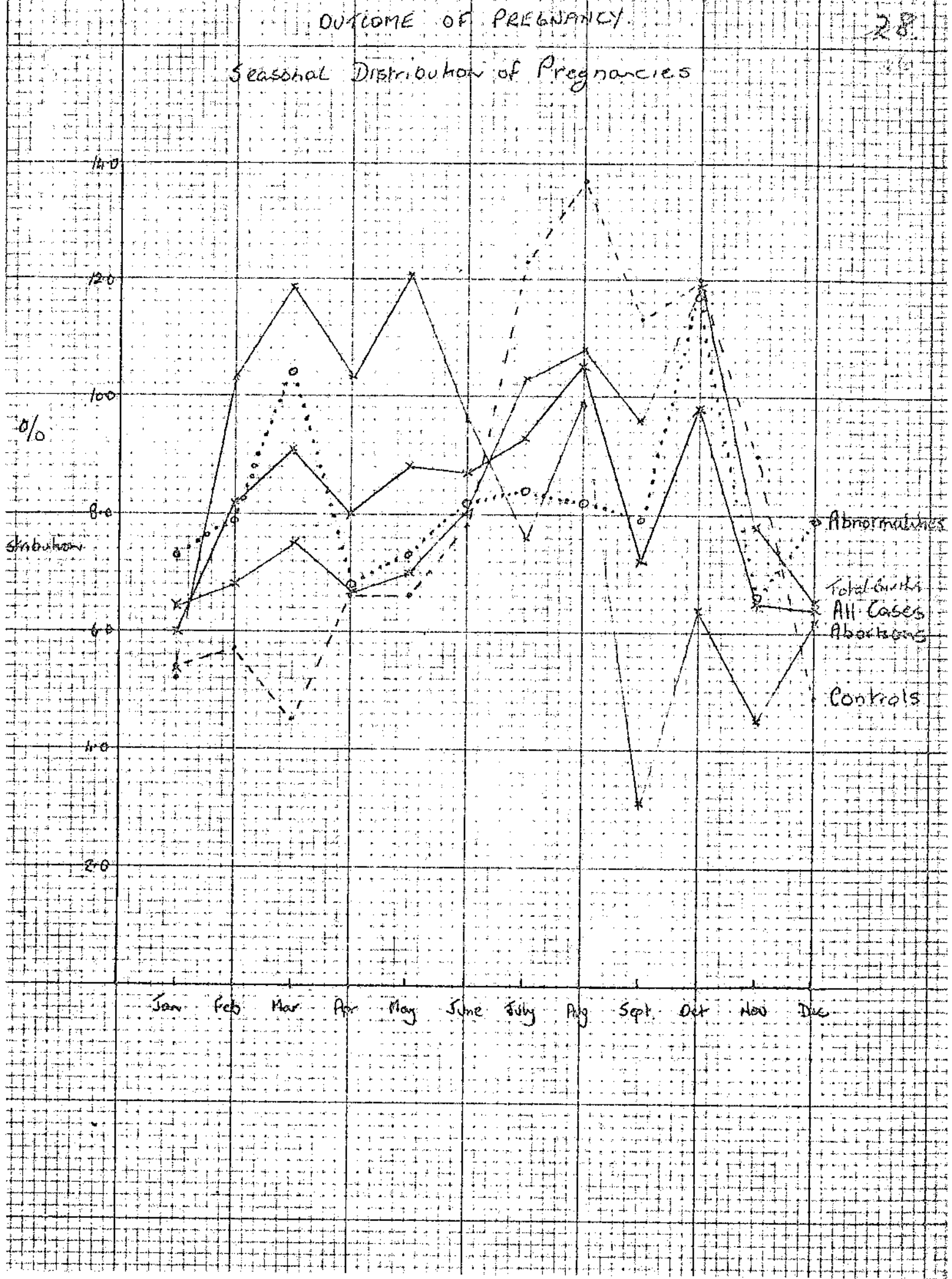
OUTCOME OF PREGNANCY

% Quarterly Distribution



OUTCOME OF PREGNANCY

Seasonal Distribution of Pregnancies



Special Drugs Study

In the opinion of the Committee on the Safety of Drugs it would have been desirable to analyse in detail the records of all women who had been give medication of any sort. While in theory we agreed with this, in practice it was impossible with limited resources to analyse in detail over 10,000 records. Moreover it was exceedingly doubtful whether any positive results would be obtained. In the end it was agreed to perform a limited analysis of the records of all women who had been given one or more of certain groups of drugs in which the Committee was particularly interested from the point of view of possible teratogenic or abortefacient effects.

This decision meant that all 15,381 records had to be rescrutinised, and a separate analysis designed for all those who had been prescribed the relevant drugs. Table XXI enumerates the drugs concerned.

TABLE XXI

Code No.	Pharmacological Classification	Examples
42	Carbamates	Meprobamate (Equanil)
43	Glutamide Derivatives	Doriden
44	Clopoxide and combinations	44.1 librium 44.2 hibrax
45		45.2 Nysoline 45.? Oblivon
70	Ethylene-diamines	70.1 Triominic 70.2 Antistin 70.3 Anthisan 70.4 Hystadyl 70.9 others
71	Ethers	71.2 Benadryl, 71.3 Benyl 71.4 Debendox 71.5 Dramamine 71.6 71.7 Others
72	Phenothiazines	72.1 Aromine 72.3 Largactil 72.4 Mandrax 72.5 Phenergan 72.6 Sparine 72.7 Stelazine

TABLE XXI (Cont.)

Code No.	Pharmacological Classification	Examples
		&72.8 Stemetil 72.9 Pentazine Nomidine etc.
73	Piperazine	73.1 Ancoloxin 73.2 Ancolan 73.4 Vibazine 73.5 Cyclizine and Valoid 73.6 Marzine 73.9 Others
74	Propyl- and Allylamines	74.1 Capriton 74.2 Pinton 74.3 Histyl 74.5 Actidil 74.6 B 74.7 Others
76		Thephrin
77		Lobak
78	Miscellaneous anti-emetics etc.	78.1 Valium/Sorenid 78.2 Fabalistin 78.3 Periactin 78.4 Tryptizol/ Tryptofen 78.5 Allegral/Aventyl 78.6 Vallergan 78.9 Others
82	Amphetamines etc.	82.1 Durophet 82.2 Methedine 82.3 Edinal Dexedine Adetate 82.4 Femate 82.5 Drinamyl 82.6 Preludin 82.7 Ponderx 82.8 Dexten 82.9 Apisate + Others
85	Imipramine	Tofranil
93	Pregnancy test hormones	93.1 Orasecron 93.2 Primodos 93.4 Norlestrin 93.5 Amenorve F 93.6 Lyndiol 93.7 Secrodyl 93.9 Others
94	Other hormones	94.1 94.2 Duphaston, 94.3 Primolut Depot Progesterone

In addition the same analysis was made for those women given Phenobarbitone (Code 40), and other Barbiturates (Code 41). The rationale of this decision was that this group should serve as controls. They were prescribed commonly, but not, like Iron and Vitamines, too commonly, and had no teratogenic or abortifacient stain on their characters.

The period at which each drug was given was recorded:

1. During the 6 weeks prior to conception;
2. from conception to the end of the 4th week;
3. 5th - 6th week;
4. 7th - 8th week;
5. 9th - 10th week;
6. 11th - 12th week
7. after 12th week;
8. repeated in first trimester.

Prior to Pregnancy

TABLE VIII

Outcome/Drugs within 6 weeks prior to conception

Drugs	Abnormalities	No Abnormalities	Totals
No drugs in period	123	3,461	3,5??
Phenobarbitone/Barbiturates	12	187	19?
Carbamates	3	31	3?
Clopoxide	0	65	6?
Ethers	3	37	4?
Phenothiazines	4	73	7?
Propyl-allyl-amines	1	33	3?
Amphetamines	4	65	6?
Totals in each category	164	4138	4,3?

This table includes only those drugs given in numbers capable of producing statistically significant results. The category "No drugs in period" comprises records in which there was no note of relevent drugs prescribed prior to pregnancy, but with one or more of these drugs prescribed during pregnancy. Each drug was tested individually against the controls (Phenobarbitone and other Barbiturates) and against the "No drugs", but there was no statistically significant difference in any of the results

During Pregnancy

For each of the periods of pregnancy mentioned above the "no drugs" group was first tested against the control group. The only period which showed a significant difference was the 11th - 12th weeks of pregnancy.

TABLE XXII

No drugs/controls at 11th-12th Week

	Abnormality		No Abnormality	
	Obs.	Exp.	Obs.	Exp.
No Drugs	12	16.3	[illegible]	[illegible]
Control drugs	8	3.7	60	54.3

(χ^2 = [illegible] with 1 d.f. 0.05 > p > 0.01)

There is a significantly higher number of abnormalities among the control groups than in the "no drugs" group.

Had this result occurred at a period earlier in pregnancy one would have been tempted to ascribe medical as well as statistical significance of it. However, occurring so comperatively late, one must assume that this is one of these results which can occur wholly by chance in between

1% and 5% of such comparisons.

When each drug group was compared, for each period separately, with the "no drugs" group and with the controls. The only group which produced significant figures both with the "no drugs" group and with the controls was group 94 (Other Hormones) in the "repeated during"the first trimester" time-span.

TABLE XXIV a and b

Outcome / Other hormones repeated in 1st trimester

a) vs. "No Drugs"

	Abnormality		No Abnormality	
	Obs.	Exp.	Obs.	Exp.
No Drugs	40.0	47.0	720	913.0
Other Hormones		1.0	13	20.0

(χ^2 = 43.31 with 1 d.f. p < 0.001)

b) vs. Controls

	Abnormality		No Abnormality	
	Obs.	Exp.	Obs.	Exp.
Controls	5	11.2	106	119.8
Other Hormones	8	1.8	13	19.2

(χ^2 = 22.[illegible] with 1 d.f. p < 0.01).

This polyglob group was therefore broken down into its constituent parts as follows:

TABLE XXV

Outcome/Specified Other Hormones repeated in 1st Trimester

		Abnormality	No Abnormality
941	Enavid 2 etc.	1	1
942	Duphaston "	0	11
943	Primolut "	4	44
944	Prerinon "	0	1
945	Anovlar "	0	1
946	Cortisone "	0	5
947	Conovid "	0	0
948	Ovulen "	0	2
949	Insulin	2	15
940	Thyreoid	1	6
40.41	Controls	10	198
0	No drugs	40	920

Despite the fact that a superficial glance at this table gave rise to some suspicion that groups 943 (Primolut and Progesterone) of Dillon[15] and 949 (Insulin) might be implicated, this was not in fact confirmed by statistical analysis.

Briefly therefore none of the drugs investigated produced figures indicating any significant increase in the proportion of abnormalities compared with either the "no drugs" group or with the controls. Indeed drug group 73 (Piperazines - Ancoloxin etc) gave figures indicating a significantly lower proportion of abnormalities compared with controls, when given in the 11th - 12th week period!

TABLE XXII

Piperazines/Controls at 11-12 weeks.

	Abnormality		No Abnormality	
	Obs.	Exp.	Obs.	Exp.
Controls	8	4.5	60	63.5
Piperazines	2	5.5	82	78.5

(X^2 = 3.965 with 1 d.f. 0.05 > p > 0.02)

The same remarks apply as to Table III in the general study, namely that though the result is statistically significant at [illegible] level, it is almost certainly coincidental and unlikely to have any medical significance.

Though the failure to incriminate any drug or groups of drugs may seem unsatisfactory to those who wished to see positive results from such a study, it is at least as important to produce such "negative" results. This has been pointed out by many, including Dorling[16].

The size of this study is too small to allow one to be absolutely confident in declaring any of the drugs investigated to be teratogenically harmless, but there is at least no indication of teratogenecitity in any of these commonly prescribed drugs. Moreover, the results here produced can be compared with those of other studies, notably the English one referred to above, and one would hope that our findings would thereby be reinforced.

Three additional points:

1. Early in the study a random sample was drawn of 50 antenatal patients, solely in order to investigate the range of drugs prescribed, so that a reasonable pharmacological/therapeutic classification could be provisionally drawn up with the help of the Pharmacology Department of the University of Edinburgh. Then as soon as a sufficient number

of complete pregnancy records had been received, a random sample of 406 completed records was drawn. This was necessary in the absence of a pilot study, which would have been much more desirable and which one would recommend strongly for any subsequent similar investigations.

This sample of 406 cases enabled coding procedure to be determined, based upon reliable knowledge of, for example, illnesses during pregnancy, the percentage of abnormalities and abortions expected, the frequency of recording of such items as contact with illness and poliomyelitis immunisation, and a more detailed knowledge of drugs prescribed. The fact that the procedure then determined required very little alteration as the study progressed was an indication of the value of drawing this sample.

2. When the study was nearing completion an urgent request was received for information regarding the possible abortefacient risk of one particular hormone pregnancy test. (Primodos named if necessary). This information was rapidly produced and supported other investigations to such an extent that it is understood that the drug concerned was withdrawn from the market.

3. It was hoped that a follow-up could be carried out at age of between 1 and 2 years of all children who were classified at birth as normal or with a doubtful abnormality. In fact this was not possible for a variety of reasons. However, a total of 5033 of such babies (33.15% of <u>total</u> births), were followed up with the following results:

TABLE XXVII

Babies followed up at age 1 - 2 years

		%
Total followed up	5033	100
Normal	4353	86.5
Congenital abnormality not recorded at birth or recorded then as doubtful	79	1.57
Deaths not from congenital abnormality	26	0.5
Still doubtful	11	0.2
No record available (mostly patients left district)	564	11.2

Since these results were not obtained for the most part until those from the main study had been sent in for analysis they were not included in the analysis.

Table XXVIII however lists the abnormalities uncovered by this follow up. No multiple abnormalities were reported, and this is not surprising.

TABLE XXVIII

Breakdown of abnormalities reported after 1 – 2 years. Compare with Table I

		Totals
C.N.S. Anomalies	: Microcephaly 2; Hydrocephalus 1; Spin. Bif. Occult. 1	4
Eye Defects	: Congen. Obstruction Tear Ducts 4; Macular dystrophy 1.	5
Lip and Palate	: Cleft Palate 3	3
Ear Defects	: Nerve Deafness 3; Preauricular sinus 1	4
Skeletal Defects	: C.D.H. 7; Talipes Equinic Varus, 4; Genu Valgum 3	14
Gastro-Intestinal Defects	: Pyloric Stenosis 1; Atresia Bile ducts 1	2
Heart and Great Vessels	: Ventricular Septal Defect 5; C.H.D. unspecified 1	6
Urinary Tract	: Hypoplastic Kidney 1	1
Genitalia	: Hypospadias 2; Undescended Testicle 4; Cyst of Spermatic Cord 1	7
Respiratory System	: Hiatus Hernia 2	2
Skin and Muscles	: Haemangioma 22; Pilonidal sinus 1	23
Chromosomal	: Mongolism 1	1
Tumours, Cysts etc	: Dermoids 2; Cyst 1	3
Others and insufficiently specified		4
		79

It will be seen that the great majority of these cases were either minor abnormalities – Haemangioma, undescended testis, pilonidal sinus etc., 37 of the 79 recorded – or were conditions not necessarily diagnosable in the neonatal period – Nerve deafness, congenital heart disease, hiatus hernia, microcephaly, hypoplastic kidney, all 4 of the "others, atresia of the bile ducts, etc. 30 cases in all. The remaining 12 cases composed 7 congenital dislocations of the hip, 3 cleft palates and 2 cases of hypospadias, all of which ought ideally to have been recorded at birth. Milham[17] has, for example noted under-reporting of cleft lip and palate at birth.

GENERAL COMMENTS

1. These notes are no more than a broad outline of the results achieved following analysis of some 15,000 pregnancy records from all over Scotland, with particular reference to congenital abnormalities. It may be that others will be anxious to investigate specific details of this study, and if so, the complete records, both the basic Maternity Service Record Cards, and the Cards are available for further analysis. We appreciate that the Study is not as complete as we, and doubtless many of the other participants, would have wished. Geographical separation from not only erstwhile colleagues but library facilities has curtailed, for example comments an comparisons with other investigations in the same field, and pressure of other work has added to the difficulties.

2. Nevertheless it is hoped that the results of this Study as noted here are perhaps of intrinsic value in providing at least a small piece of mosaic in the complicated pattern of the aetiology of congenital malformations, and, as a by-product, that of abortions. Most of the major findings, for example those connected with social class, parity and age of mother, confirm findings from larger studies in Britain and in other parts of the world; this is in itself of value as an indication of the reliability of the present study.

With regard to the possible, teratogenic effect of drugs the findings here support those which for example have been recorded by Leck [18] in regard to meclozine where no teratogenic association was found. On the other hand, as has been noted, the suspicion of teratogenicity attributed by Carter [13] to tetracycline is not supported. These are indications perhaps of the very large number of pregnancies which require investigation before any statistically significant incriminating evidence can be produced in conditions of such comparatively low incidence as specific types or

groups of anomalies.

Even the 15,000 pregnancies in this study was too small a number as has been pointed out, for investigation in detail of many combinations of circumstances; e.g. illness during pregnancy in a specific region, set against occurence of a specific abnormality.

3. It may be that the darkness of our profound ignorance of the aetiology of congenital abnormalities may be lightened in the cytogenetic or biochemical laboratory rather than by epidemiological means. At the moment however epidemiological studies must remain one of the most important methods of investigation in this sphere, both as ends in themselves and as indicators of areas in which laboratory research would be of most value. (W.H.O. Techn. Report[19]).

This being so, prospective studies like the present one ought to play an important part. It is inappropriate here to discuss the relative advantages of prospective vis-a-vis retrospective studies. It is however both appropriate and relevant to emphasise that prospective investigations of congenital abnormalities would, in North Western Europe at any rate, be quite impossible if general practitioners were not involved to a major degree. With all its disadvantages and drawbacks, of which we are fully aware and from which we have learned many lessons for the future, this study had the inestimable advantage that all the basic records were contemporary, and such records could have been provided only by general practitioners.

4. Looking at this study then from the point of view of a general practitioner investigation, there are a number of worthwhile points to be made or lessons to be learned.

a) A study such as this has great value in promoting interest in research among general practitioners and in demonstrating that whether they work alone in comparatively isolated places like Ballindalloch or Dalbeattie or in a group practice in Glasgow or Edinburgh, each individual can make a

a valuable contribution to medical knowledge - pace McMichael who recently at a meeting of the British Association is reported to have suggested that it is only within a University and its associated city that advances in medicine can be expected to take place.

b) General practitioner research can provide especially epidemiological data at comparatively little cost and with a comparatively small co-ordinating staff; and it has already been emphasised that in some spheres only general practitioners are in a position to provide such data. The assistance however of a medical statistical department is however essential if the results produced are to bear examination in this modern, perhaps hyper-critical, age. In this context however it is perhaps worthy of passing note that the results produced by for example, Jenner, or in our time by Burkett[26] in Africa and A.T. Wilson[21] in Scotland, would not initially have been accepted as statistically significant. Only subsequent more detailed analyses have proved the truth of their original essentially general practitioner observations.

c) Out of the 480 general practitioners who originally agreed to participate, 272 (56.6%) continued from beginning to end of the study, over a period of 2½ years. This is a very encouragingly high proportion especially considering the length of time and the additional amount of work involved. There was a wide spread in the number of cases per practitioner; disregarding in this context practitioners who obviously did not send in all their records or who stopped before the end, the range was from to , the latter total comprising admirably complete and legible cards from a single-handed practitioner in West Lothian (T.H.) to whom we are very grateful. Legibility of the basic records makes a very great difference to the time spent in deriving the necessary information from them; this may seem a trivial point but it is not, especially when it is necessary to decipher and record names of proprietary drugs.

d) Before mounting a comparatively large-scale general practitioner project such as this was, a pilot study, if not absolutely essential, would certainly have made the subsequent full-scale investigation much simpler, more informative and more reliable. For example, a simple insert on the cards of "Threatened Abortion" Yes/No" and a similar minor modification requiring a specific statement - again of the "Yes/No" variety - of drugs prescribed, would have eliminated a large proportion of the "unknowns" in these fields and thereby provided much additional information at little extra cost or trouble. These omissions would, or should, have been discovered in the course of the pilot study.

It is appreciated that, in order to obtain maximum participation the forms, and the investigation as a whole, had to be kept as simple as possible. Nevertheless for many reasons, some of which have earlier been mentioned, a pilot study in any future investigation of this scale is most strongly recommended.

5. Finally, these notes cannot be considered as the last word on this study, still less as the last word on prospective studies of congenital abnormalities. One would hope rather that they will serve as a jumping off point for deeper investigation, and furthermore, be an encouragement for other similar research projects involving general practitioners.

It cannot be stressed too strongly that the fact that this study produced no "positive" results - if by "positive" one means results incriminating one or more factors as teratogenic agents - was not unexpected. But negative results are as valuable as positive ones, and for this reason it may be considered that the study has fulfilled its purpose. Moreover, the study cannot but have assisted in stimulating general practitioners' interest in the early diagnosis and indeed treatment of some congenital abnormalities. "Progress Reports" sent round to participating general practitioners from time to time during the study should have assisted in this object, and were indeed a necessary part of a study lasting for as long as 2½ years.

The role of the general practitioner in research was stressed at the 24th World Medical Assembly in Oslo in August 1970, and it was there evident that Britain, through the Royal College of General Practitioners, is playing probably the leading part in such organised research in Europe. A study such as the present one and its English counterpart should do much to maintain this reputation; practically no other research projects reported at this Assembly involved general practitioners working outside large health centres in the neighbourhood of universities.

SUMMARY

This study consists of an analysis of 15, 161 pregnancy records compiled contemporaneously by some 400 general practitioners throughout Scotland. The object was to shed some light on possible factors in the aetiology of congenital abnormalities.

452 children (2.98%) were recorded as having one or more anatomical abnormality, and the records of these, together with those of abortions, neonatal deaths, still births and 422 unmatched controls, were analysed.

No significant aetiological factors were discovered among these groups.

A further analysis was made of the records of all women who had had any of a small group of drugs prescribed to them. These drugs included anti-emetics and hormones. No significant association was revealed between prescription of these drugs and the occurrence of congenital abnormality, though some had a significant association with abortion.

The value of such prospective studies, in which general practitioners can play a significant part, is discussed, and it is stressed that even such negative results as have been produced are valuable in the study of the obscure aetiology of congenital abnormalities.

ACKNOWLEDGEMENTS I must first express my thanks to Dr. E.V. Kuenssberg for persuading me, very much against my better judgement to undertake this task; many times I have regretted my rashness, but in the end I am grateful and only hope that the results will be considered to have justified the amount of work expended on the study by some 400 participants.

Without the support and encouragement of Professor S.L. Morrison of the Department of Social Medicine, the University of Edinburgh I could not have devoted the time necessary for the coordination of the study while Mr. Walker Lutz and several of his staff of the Statistics Section of the same Department have been my strength and stay in giving willing and immediate advice regarding coding procedures, in arranging all the computer work and finally performing the statistical analysis of all the tables.

Mr. John MacPherson, Deputy Secretary of the University of Edinburgh and Professor Montgomery of the Department of Pathology were primarily responsible for making additional funds available from the Distillers Company Grant.

My wife not only was deeply concerned in the co-ordination of the Study and the coding of the results, but in the past 18 months in difficult circumstances she has helped and encouraged me when often I would fain have given up, and these notes, such as they are, would never haveebeen produced.

Mrs. Anne Littlejohn has been, in the midst of many other duties, an invaluable liaison officer in the unsatisfactory situation of trying to produce an acceptable report at some 600 miles distance from sources of information. Many others assisted in the day-to-day working of the survey; I hope I may be forgiven if they are not mentioned by name.

Finally and most important, this study was a General Practitioner research project and we are most grateful to all those who took part, especially to those, from Stornoway to Whifhom, who were patient enough to continue from beginning to end. It is hoped that they will believe that their perseverance, without which no such study would have been possible, has been worthwhile.

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Hormone Pregnancy Tests

As part of the "Outcome of Pregnancy Study" organised by the Royal College of General Practitioners (Scotland) we have, at the suggestion of Sir Derrick Dunlop and Professor Emery, investigated particularly the outcome of pregnancy (not only in regard to congenital abnormality which is the primary purpose of the study), when certain specific drugs were given. These drugs included hormona pregnancy tests.

At Dr. Kuenssberg's request we have, as a matter of urgency, looked at this latter group before the rest of the data has been analysed. The results of this analysis are summarised in the following table.

Drug	No. of cases in which prescribed	No. with normal outcome	No. of abortions	No. of stillbirths	No. of neonatal & infant deaths	No. of abnormalities
PRIMODOS	79	66	8	1	1	3
AMENORONE FORTE	28	28	-	-	-	-
ORASECRON	15	15	-	-	-	-
NORLESTRIN	5	5	-	-	-	-
SECRODYL	3	1	1	-	-	1
OTHERS & UNSPECIFIED	5	5				
TOTAL	135	~~119~~ 120	9	1	1	4
TOTAL NO. IN STUDY	15209	13707	777	115	124	486

It should be emphasised: a) that these are preliminary figures only; and b) that no statistical analysis has been performed, because of lack of time, on the figures for Primodos.

On the face of it, however, it does appear that, compared with the other drugs, even though these are closely similar in pharmacological content (Norlestr being of the same constitution apart from dosage), the figure of 10% abortions recorded after Primodos is unlikely to be due to chance. With regard to the 4 abnormalities recorded, two (one after Primodos and one after Secrodyl) were of cleft palate. Since we have not available the total cleft palate incidence figures it is not possible to draw any conclusions from this finding and it may

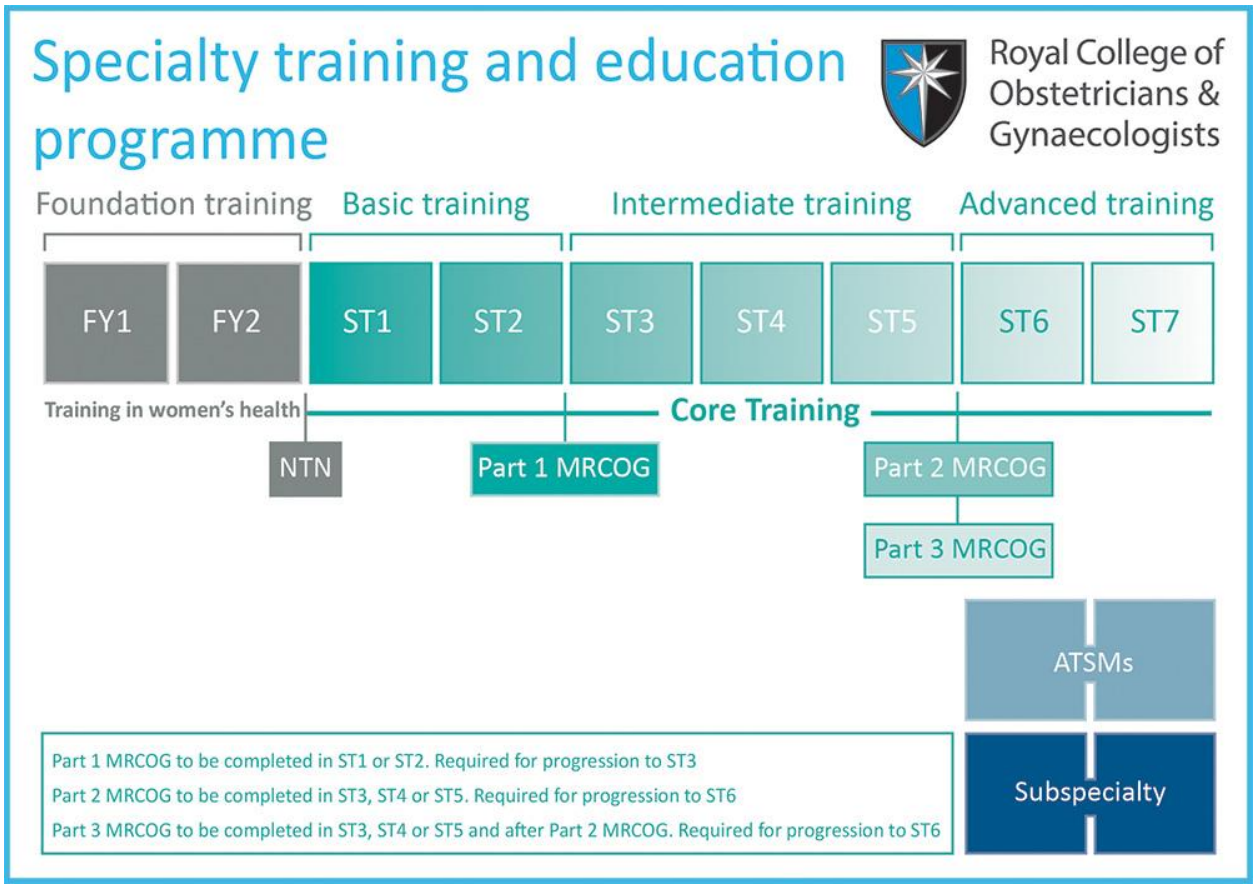
be coincidental. The other two abnormalities, both after Primodos, were 1 Congenital Dislocation of the Hip and 1 Mongol.

In view of these findings, tentative though they are, it would be my own view that, since there is in any event no very sound medical reason (in my opinion) for the use of such hormonal preparations, Primodos should be withdrawn from use. I would hesitate to offer any opinion regarding any of the other preparations in view of the small numbers.

N.M.B. DEAN

Royal College of Obstetricians & Gynaecologists

Professor Regan shared the following specialty training and education programme diagram in the Oral Hearing session. This can be found on the [RCOG website](#).



Public bodies

Department of Health and Social Care (DHSC)

DHSC have provided the following documents and further information to the Review:

DHSC Briefing for Independent Medicines and Medical Devices Safety Review – Autumn 2018

Background

In February 2018, Jeremy Hunt announced the Independent Medicines and Medical Devices Safety Review, chaired by Baroness Cumberlege. The Review will be looking at the lessons we can learn from the issues raised by mesh, Sodium Valproate and Primodos. DHSC is the commissioner of the Review and will be the recipient of the Review's recommendations.

In the same announcement Jeremy Hunt also committed to specific actions on the three issues covered in this paper, namely:

- On Primodos, asking Lord O'Shaughnessy to drive forward – and where possible accelerate – the recommendations of the Expert Working Group, further strengthening our systems for monitoring the safety of medicines in pregnancy.
- On valproate, implementing the strengthened regulatory position through actions such as introducing a new warning symbol on valproate packaging, updating NICE guidance on valproate and introducing a contraindication for valproate in women of childbearing potential not using effective contraception.
- On vaginal mesh, publishing a retrospective audit to investigate the links between patient-level data to explore outcomes; and invest £1.1m to develop a comprehensive database for vaginal mesh to improve clinical practice and identify issues

This paper sets out key events and timelines that led to this point.

DHSC does not currently have a settled policy on the issues the Review is exploring – indeed that is the reason the Review has been asked to look at them. DHSC intends that the outcomes of the review will help to develop that policy.

Mesh

Background

Short Summary

1. Surgical mesh has been used for a number of years in the treatment of Stress Urinary Incontinence (SUI) and Pelvic Organ Prolapse (POP) to provide further artificial support when repairing weakened or damaged tissues.

2. For many women suffering the distressing effects of SUI and POP, surgical procedures using mesh devices have provided an effective form of treatment which can be far less invasive than alternative surgical procedures. There is published evidence to suggest improved outcomes for procedures using mesh, over the periods studied, but complications are also recognised.

3. Although some published research suggested the risk of complications from surgery using mesh falls within accepted limits, an increasing number of women have reported complications, sometimes many years after their surgery. The shared personal experience from patients told us that complications can, for some, be very severe and life-altering. Patient groups questioned the safety and efficacy of surgery for SUI and POP using mesh devices. They considered the evidence cited to justify use of mesh to be flawed and incomplete. Women felt that medical professionals were insufficiently aware of the potential complications following surgery and that insufficient information was provided for women.

4. Following reports of a number of adverse consequences, the Mesh Oversight Group (which included members from professional bodies and patient groups and was chaired by Keith Willet) set out a number of actions to address the issues that had been raised. They did not recommend banning or suspending the use of mesh, as it remains a device that can lead to positive outcomes for many women. Their recommendations focused on improving consent and patient information; improving data collection to allow clinicians and regulators to better understand outcomes and consequences; and putting in place remedial services for women suffering from complications.

Full Timeline

5. Surgical meshes have been used since the 1950s to repair abdominal hernias and were then used in the 1990s for the treatment of male and female stress

urinary incontinence (SUI), female pelvic organ prolapse (POP) and colorectal functional disorders (CFD).

6. Synthetic meshes were originally introduced as options for urogynaecological surgery due to the complexity and the high failure rate of other surgical procedures used in treating the distressing and often life changing conditions of stress urinary incontinence and pelvic organ prolapse, which are common conditions among women, particularly after childbirth and with increasing age.

7. In common with other medical devices these have undergone a number of iterations over time as lessons have been learned regarding configuration, fixation and their overall place in urogynaecological surgery, as determined by the surgical community. There have been no recalls of urogynaecological meshes in the UK for safety reasons, but a number of devices have been withdrawn from the market over time for other reasons.

8. MHRA hosted a workshop in 2011 to better understand the use of these devices and complications associated with their use. With representatives including Royal College of Gynaecologists and National Institute of Clinical Excellence, a summary of that discussion and recommendations were published in the European Urology Journal.

9. In 2012, the issue surrounding meshes was brought to the attention of ministers and DHSC via an advice note from MHRA. Guidance and support for NHS surgeons on mesh implants was then issued and Sir Bruce Keogh wrote directly to NHS surgeons and Medical Directors to ensure they were aware of the guidance when carrying out these surgical procedures.

10. The former Scottish Cabinet Secretary for Health and Wellbeing, Alex Neil MSP, first met with a group of women adversely affected by the use of mesh to treat these conditions in May 2013. Following this meeting, a Working Group was set-up to address the issues affecting women who have undergone transvaginal mesh surgery. This group Transvaginal Meshes Working Group (TMWG) was initiated to develop a clearer understanding of the issues affecting women who had suffered complications from mesh surgery. A review of the remit of this working group led to greater clinical representation to review current clinical practice and make recommendations for change. The Expert Group was formed in December 2013 as a development of the TMWG.

11. On 1 May 2014, a public petition was lodged on behalf of the Scottish Mesh Survivors (SMS) Group. Amongst other points, the petition called on the Scottish Parliament to urge the Scottish Government to suspend use of polypropylene transvaginal mesh procedures and Initiate a Public Inquiry. In

the light of growing public concern, the Scottish Government considered that an Independent review of transvaginal mesh surgery was necessary to establish the facts.

12. In 2014, NHS England and DHSC recognised the need to take action to better understand these issues and what should be done to tackle them. This led to the formation of the Mesh Working Group which contained membership drawn from MHRA, DHSC, professional societies (BSUG and BAUS and RCOG) along with patient interest groups.

13. MHRA reviewed this area in 2014 and determined that there was no justification for the Agency to undertake any additional regulatory action at that time.

14. In 2015, the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published its review which echoes the findings of the Scottish and English reviews that these devices remain acceptably safe when used as intended, as part of an appropriate treatment pathway.

15. In England, the Mesh Oversight Group published its early findings and recommendations in an Interim Report in December 2015, which aimed to address the 3 major concerns expressed by the patient interest groups – the clinical quality, data and information and informed consent. The interim nature of the report reflected the insufficiency of evidence available at the time. It also gave an opportunity for patients, clinicians and stakeholder organisations to work together and understand each other's experiences.

16. In 2016, the MHRA had a peer reviewed paper published in the International Urogynaecology Journal titled "In vivo response to polypropylene following implantation in animal models: a review of biocompatibility". The evidence showed that polypropylene evoked a less inflammatory or similar host response when compared with other materials used in mesh devices.

17. The final report of the Scottish Independent Review of Transvaginal Mesh Implants was published on 27 March 2017.

18. In England, the final Mesh Oversight Group Report was published in July 2017.

19. An All Party Parliamentary Group on Surgical Mesh Implants was established in September 2017, chaired by Owen Smith MP.

20. In April 2018, NHS Digital published experimental statistics on patients that have had a procedure for urogynaecological prolapse or stress urinary

incontinence including those where mesh, tape or their equivalents have been used. The report, *Retrospective Review of Surgery for Vaginal Prolapse and Stress Urinary Incontinence using Tape or Mesh, England April 2008 - March 2017* also investigates these patients' subsequent interactions with NHS Hospital outpatient services. The statistics are experimental and provide a count of individuals, rather than a count of episodes as is the norm when publishing standard Hospital Episode Statistics (HES). Professor Nick Black offered an independent view of the data: http://piru.lshtm.ac.uk/assets/files/Commentary%20on%20NHS%20Digital's%20Retrospective%20Review%20of%20Surgery%20for%20Urogynaecological%20Prolapse%20%20Stress%20Incontinence%20using%20Tape%20or%20Mesh%20April%202018%20(Black)%2018%20June%2018.pdf

21. On Thursday 19 April 2018, MPs held a debate in the House of Commons on a motion on surgical mesh. https://hansard.parliament.uk/commons/2018-04-19/debates/C5B94EB2-2398-4F0E-BE9E-D502ACEBFA62/SurgicalMesh

22. On 2 July 2018, Ministers received a letter from Baroness Cumberlege and Sir Cyril Chantler asking for a pause on mesh insertions. On 10 July, a Written Ministerial Statement gave details of the pause. https://hansard.parliament.uk/commons/2018-07-10/debates/18071039000008/IndependentMedicinesAndMedicalDevicesSafetyReviewUpdate

23. On 20 July 2018, NHSE and NHSI wrote to Regional Directors, Trust Medical Directors, and clinicians involved in the care of patients with stress urinary incontinence and pelvic organ prolapse, announcing a pause to be operationalised as a 'RESTRICTION OF USE', and a 'HIGH VIGILANCE RESTRICTION PERIOD'.

24. Baroness Cumberlege set out the following conditions that should be met before the pause can be ended:
    - Surgeons should only undertake operations for stress urinary incontinence if they are appropriately trained, and undertake such operations regularly;
    - Surgeons report every procedure to a national database;
    - A register of operations is maintained to ensure every procedure is notified and the woman who has undergone the surgery is identified;
    - Reporting of complications via MHRA is linked to the register;
    - Identification and accreditation of specialist centres for stress urinary incontinence mesh procedures, for removal procedures and other aspects of care for those adversely affected by surgical mesh; and
    - NICE guidelines on the use of mesh for stress urinary incontinence are published.

25. Given the urgency of responding to the recommendations on data, the Healthcare Quality Improvement Partnership (HQIP) has been commissioned to explore the potential of existing databases to service immediate information needs.

26. Currently there are three existing databases ran by professional societies (BAUS, BSUG and The Pelvic Floor Society) that record data on urogynaecological procedures using mesh. We have commissioned Healthcare Quality Improvement Partnership (HQIP) to undertake preliminary work with the professional societies to identify how effective each of the existing databases are in capturing sufficient data.

27. To identify how these databases can be enhanced HQIP has held two workshops:
    a. The first workshop, was held on 13 November. Chaired by Keith Willet (NHS England) focused on a technical discussion of the existing databases.
    b. The second workshop, on 28 November, was Chaired by Annie Laverty (Chief Experience Officer at Northumbria Healthcare with significant experience in leading quality improvement and patient experience programmes). The Chair has not previously been involved in the surgical mesh debate. Patient groups, MPs and members of the IMMDS Review Team were invited.

28. Subsequently, HQIP will work with the three societies to implement the workshop recommendations. Through this work immediate data needs should be met. It will also provide underpinning exploratory work for the development of a prospective registry at a later stage.

Key Reports

<u>The Scottish Independent Review of Transvaginal Mesh Implants</u>

29. The final report was published on 27 March 2017. The recommendations were accepted by Scottish Government.

30. The report set out a number of conclusions to improve the safeguards available including:
    - Mesh must not be offered routinely to women with pelvic organ prolapse.
    - Reporting of all procedures and adverse events to be mandatory, in line with the guidance from the General Medical Council.

- Extra steps to ensure that patients have access to clear, understandable advice to help them make informed choices.
- In the case of surgical treatment for stress-urinary incontinence, all appropriate treatments should be available, subject to informed choice and assessment.
- Improved training for clinical teams involved in transvaginal mesh.
- Improved research into the safety and effectiveness of the products.

NHS England's Mesh Oversight Group Report

31. The final report was published in was published in July 2017. It held the bodies responsible for the delivery of the recommendations set out in the interim report to account and set out the progress made to date against each:

Clinical Quality

- After considering all the new evidence, views of topic experts and the NHS England Mesh Working Group Interim Report, NICE agreed to an update and extension of the scope of the existing clinical guideline for Urinary Incontinence to include Pelvic Organ Prolapse. NICE has further updated all Interventional Procedures Guidance relating to SUI and POP.
- In order to deliver improved support to women with post-operative problems 18 hospital trusts in England (and one in Scotland) have now self-declared to act as centres for women with mesh complications to be referred to for advice. A formal service specification for commissioning of these services is now being undertaken by NHSE Specialised commissioning reference group. A list of these centres has been published and can be found at: http://www.baus.org.uk/patients/sui_mesh_complications.aspx
- In addition, awareness has been raised among hospital clinical and GPs and an e-learning tool has been developed for GPs and patients.

Data and Information

- Surgeons' compliance with reporting procedures on the current national specialty mesh databases (BSUG and BAUS) and their reporting adverse incidents (AIs) to MHRA will be checked during their annual appraisals.
- MHRA are continuing to enhance awareness of the Yellow Card reporting system for adverse outcomes to increase reporting rates among both clinicians and patients.
- Surgical procedure codes (OPCS codes) have been updated to include the type of procedure and implant and the type of secondary surgery carried out including total and partial removal of mesh.
- Funding has now been announced for a prospective registry that will capture accurate data on the use of mesh and mesh complications and will track

individual devices over a long period of time to see if there patterns in any complications that do arise.

- NHS Digital, under the direction of Secretary of State, has undertaken a retrospective review of potential cases of adult female patients in England who have had mesh procedures for stress urinary incontinence and urogynaecological prolapse between 2008 and 2017.

Informed Consent

- Comprehensive patient information leaflets have been produced in collaboration with the Independent Review of Transvaginal Mesh Implants working group for Scotland. The leaflets provide detail about SUI and POP, alternatives to surgery and the success rates, risk and complications of procedures.

NICE Guidelines

32. Following the recommendations set out in NHS England's final Mesh Oversight Report, NICE identified a need to update its clinical guideline on urinary incontinence and 8 pieces of interventional procedures (IP) guidance relating to vaginal meshes.

33. Clinical guidelines and interventional procedures guidance both provide robust, evidence-based guidance for clinicians, but they are different products with different functions. NICE clinical guidelines provide detailed guidance for the NHS on the most effective ways to treat patients, whereas IP guidance makes recommendations on whether a specific procedure is sufficiently safe and efficacious for routine use in clinical practice. All recommendations in NICE IP guidance are intended to address the practical steps that clinicians should take to carry out the procedure safely in relation to their hospital's clinical governance arrangements, the patient consent process and the collection of data.

34. NICE have updated and published all 8 pieces of interventional procedures guidance. The final piece, published 15th December 2017 and titled Surgical Repair of Vaginal Wall Prolapse Using Mesh, recommended that this procedure only be used for research purposes due to the evidence for long term efficacy is currently inadequate.

35. The update of NICE's clinical guideline on urinary incontinence is underway. A draft was made available in late 2018 as part of NICE's consultation process and guidance is expected to be published in April 2019.

Primodos

Full Timeline

36. Hormone Pregnancy Tests (HPTs), such as Primodos, were used to diagnose pregnancy between the 1950s-70s. They have not been available in the UK since the late 1970s. Primodos, specifically, has not been available in the UK since 1978.

37. There have been claims of a link to birth defects since the 1960s. The then medicines regulator kept the issue under close review following the publication of the first study in 1967 which suggested that HPTs may cause malformations. Precautionary action was taken over the years to inform doctors of possible risks despite the evidence being inconsistent.

38. *The following lines are taken directly from the EWG report (page vii):* Between the 1950s and 1978, when Primodos was withdrawn from the market in the UK, a number of studies were published which investigated a possible link between women being given an HPT to diagnose pregnancy and the occurrence of a range of congenital anomalies in the offspring. Although there was never any reliable evidence that HPTs were unsafe, concern about this issue, coupled with the development of better pregnancy tests meant that a series of precautionary actions were taken to restrict the use of HPTs to treating disorders of menstruation and to prevent their use in women who were pregnant. However, evidence suggested that these restrictions were not always being adhered to, and because the alternative non-hormonal pregnancy tests were becoming more widely available, the products were withdrawn from the market by the manufacturers. Whether these precautionary actions were sufficiently timely became a subject of controversy.

39. In 2014, at the request of ministers, the UK's Commission on Human Medicines (CHM) set up an Expert Working Group (EWG) to review all the available evidence on the possible association between the use of HPTs and adverse outcomes of pregnancy.

40. This EWG was established in October 2015 to review this issue with the benefit of up to date scientific expertise. The purpose of the review was to rigorously review the totality of the available scientific evidence on the possible association between exposure in pregnancy to HPTs, such as

Primodos, taken by the mother and adverse pregnancy outcomes in pregnancy, such as a miscarriage, stillbirth or birth defects.

41. The EWG published their report on 15 November 2017. Following an extensive and rigorous review the overall conclusion, based on the totality of the data, is that the scientific evidence does not support a causal association between the use of HPTs, such as Primodos, and birth defects or miscarriage.

42. The relevant health minister accepted the CHM's advice that the available scientific evidence, taking all aspects into consideration, does not support a causal association between the use of HPTs and adverse outcomes of pregnancy; and agreed to the report's recommendations. A Written Ministerial Statement (WMS) was made on 15 November 2017 with a copy of the report.

43. The review produced several recommendations to further strengthen the systems in place for detecting, evaluating and communicating safety concerns with use of medicines in pregnancy. These are being taken forward by the MHRA in collaboration with others in the healthcare system.

44. The Chairs of the EWG and CHM had a private meeting with the patient group before the report was published. The Chair of the EWG met with All-Party Parliamentary Group[1] (APPG) members the same day. The patient group is understandably not happy with the conclusion of the report and has also criticised the review process itself.

45. The relevant health minister continues to have regular contact with the APPG on HPTs and attended a meeting with them in December 2017 to discuss the publication of the report, as promised at the previous meeting in August 2017.

46. Lord O'Shaughnessy wrote to Yasmin Qureshi, Chair of the APPG on HPTs, on 24 October 2018 to update her regarding the two reviews of the Vargesson paper on zebrafish. In this letter the minister also made reference to the work of the Cross Sector Group, that he chairs, and referred to an announcement on progress in the New Year (2019).

47. Legal proceedings are not currently underway.

Next Steps

[1] All-Party Parliamentary Groups are informal cross-party groups that have no official status within Parliament. They are run by and for Members of the Commons and Lords, though many choose to involve individuals and organisations from outside Parliament in their administration and activities.

48. The findings of the EWG of the CHM were published in November 2017. The group concluded that the available scientific evidence does not support a causal association between HPTs and adverse outcomes of pregnancy. This view was endorsed by the CHM but concerns remain among campaigners. Since then ministers have met with the APPG on HPTs and have committed to respond to any further questions the group have.

49. Even though the HPT patient group (and APPG) were not satisfied with the EWG's conclusions, there was broad consensus on the need to implement the actions that were recommended.

50. The EWG's recommendations include strengthening basic science and use of non-clinical data, how data on adverse effects are better collected and integrated, clarifying roles and responsibilities of all stakeholders, and strengthening communications and transparency.

51. The Cross Sector Group on the Safety of Medicines in Pregnancy, chaired by Lord O'Shaughnessy, was established in mid-2018. The Group meets on a quarterly basis, with two meetings having taken place so far in July and October. The membership of the group consists of representatives from the Royal College of Obstetrics and Gynaecology, the Royal College of Midwives, the NHS and NHS Digital, the MHRA and others.

52. The MHRA are generally responsible for progressing all of the actions arising from this Group, which so far have predominantly related to better data collection and analysis. At the October meeting, MHRA took away an action to consider a "one year on" statement to inform Parliament of overall progress against the actions to improve the safety of medicines used in pregnancy; this would be delivered in February 2019.

Key Reports

<u>Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests</u>

53. An EWG of the UK's CHM published their report in October 2017 on the use of HPTs and adverse effects relating to pregnancy, including possible birth defects.

54. An extract of the report is below:

8.2 Recommendations of the EWG

- The EWG noted that substantial changes have taken place within the field of pharmacovigilance and pharmacoepidemiology since HPTs were available in

the UK but felt that more could be done to safeguard future generations. The EWG considered that a number of steps could be taken to strengthen the systems in place for detecting, evaluating, managing and communicating risk with exposure to medicines in early pregnancy.

For the families

- A full up-to-date genetic clinical evaluation, in line with current best practice, should be offered to families of the Association for Children Damaged by HPTs, whose lives have been impacted by adverse pregnancy outcomes and who were given HPTs to diagnose pregnancy.

Optimising collection of, access to and use of data on medicines in pregnancy

- A new Working Group should be set up to advise on better ways to collect and monitor data on the safety of medicines during pregnancy. The Working Group's remit should, in particular, explore the potential for:

    - better capturing and linking of existing data on adverse outcomes of pregnancy, including congenital anomalies identified prenatally and neonatally, and developmental disorders that take longer to become apparent, to facilitate regular surveillance
    - other ways to capture relevant information from, amongst others, midwives and pregnant women on exposure to all medicines, including prescription and over-the-counter, during a pregnancy
    - improving access to all relevant data on medicines taken during pregnancy to enable studies to be conducted to support pharmacovigilance
    - improving the analytic design of studies examining drug safety in pregnancy
    - a system for the early sharing and expert review of possible signals or concerns regarding teratogenicity of a drug
    - systematic, detailed clinical and genetic evaluation of patients in whom a teratogenic effect is being queried

- Electronic Yellow Card reporting should be made available at point of care, including at scanning in early pregnancy, to all those who suspect an adverse outcome of pregnancy in association with exposure to any medicine in pregnancy. In particular, Yellow Card reporting should be included in relevant clinical systems and promoted in a dedicated campaign to raise awareness of this possibility.

- There should be regular, independent review by experts of all suspected adverse drug reactions in pregnancy that are reported by healthcare

professionals and women in the UK to the MHRA. The CHM should publish the findings and conclusions in their annual report.

- A scientific workshop should be held to bring together different disciplines to consider:

a) how results from studies in pregnant animals, with individual medicines or the chemical class, can be made more accessible in order to help predict and assess the potential effects of medicines in pregnancy
b) the feasibility of using computer modelling and molecular structure alerts to generate safety signals from animal and in vitro data and to prioritise drugs for further study.

- A strategy to co-ordinate and promote research on the following should be taken forward with appropriate experts in the field:

a) mechanisms of teratogenicity in early embryonic development and how the actions of and reactions to drugs vary with the individual's genes
b) drug transporter expression in the placenta, particularly in early pregnancy; how it differs between individuals; and how it is affected by maternal disease.

Safeguarding future generations

- For medicines used commonly in pregnancy, particularly the first trimester, pharmacokinetics and pharmacodynamics studies in pregnant women should be performed, where possible, to understand better how pregnancy affects the levels of drug to which the mother and fetus are exposed and to develop evidence-based dosing and frequency of administration for use in pregnancy.

- In support of the above recommendation opportunities should be provided for obstetricians to receive training in pharmacology.

- Regulators should develop specific guidance for regulators and the pharmaceutical industry to i) strengthen the capture and evaluation of data on possible safety concerns with medicines used in pregnancy, and ii) support the more systematic use of measures to reduce harm from identified risks of medicines in pregnancy.

- MHRA should systematically monitor outcomes after taking important regulatory action to protect patients from harm from medicines, and use this information to inform further action where necessary.

Informing and engaging healthcare professionals, patients and the public

- MHRA should work with the key information providers to ensure healthcare professionals and patients receive the best available information, and are empowered to make informed decisions and ask questions about any medicines they may be prescribed in pregnancy.

- MHRA should do more to encourage and make it easier for women, and health professionals who work with women, to report any adverse reaction they experience while taking a medicine during pregnancy through the Yellow Card Scheme.

- MHRA should build a partnership with other bodies within the healthcare system to improve the impact of safety messages relating to medicines, to support the objectives above.

Summary of Research on Zebrafish Embryos

Title:	The Primodos components Norethisterone acetate and Ethinyl estradiol induce developmental abnormalities in zebrafish embryos
Authors:	Samantha Brown, Lucas Rosa Fraga, Gary Cameron, Lynda Erskine & Neil Vargesson
Date of publication online:	13 February 2018

PLEASE NOTE: The following paragraphs are taken directly from the report

- Primodos was a hormone pregnancy test used between 1958–1978 that has been implicated with causing a range of birth defects ever since. Though Primodos is no longer used, it's components, Norethisterone acetate and Ethinyl estradiol, are used in other medications today including treatments for endometriosis and contraceptives. However, whether Primodos caused birth defects or not remains controversial, and has been little investigated.

- Here we used the developing zebrafish embryo, a human cell-line and mouse retinal explants to investigate the actions of the components of Primodos upon embryonic and tissue development. We show that Norethisterone acetate and Ethinyl estradiol cause embryonic damage in a dose and time responsive manner. The damage occurs rapidly after drug exposure, affecting multiple organ systems. Moreover, we found that the Norethisterone acetate and Ethinyl estradiol mixture can affect nerve outgrowth and blood vessel patterning directly and accumulates in the forming embryo for at least 24 hrs.

- These data demonstrate that Norethisterone acetate and Ethinyl estradiol are potentially teratogenic, depending on dose and embryonic stage of development in the zebrafish.

- Further work in mammalian model species are now required to build on these findings and determine if placental embryos also are affected by synthetic sex hormones and their mechanisms of action.

Background

- The lead researcher Dr Neil Vargesson presented his preliminary work on chick and zebrafish embryos to the EWG on HPTs in October 2016. As the work was unpublished he was unwilling to leave a copy of his slides or a draft manuscript for more detailed review. A further telecon was held in August 2017 when the researcher provided a verbal update on the zebrafish findings that had by then been submitted for publication.

- The preliminary zebrafish research formed part of the non-clinical scientific evidence reviewed by the EWG and is highlighted on page 39 in the final EWG report. In addition to the zebrafish research, the EWG evaluated data from studies in mice, rats, guinea pigs, rabbits and non-human primates. Altogether over 80 animal studies were considered as part of the review process and a decision was made on the totality of the evidence including the preliminary zebrafish research.

- The Vargesson paper was published on 13 February 2018 and was accompanied by a press release from the University of Aberdeen. The paper concludes that the components of Primodos, norethisterone acetate and ethinylestradiol, induce developmental abnormalities in zebrafish embryos. This conclusion is based on developmental defects that were observed in zebrafish embryos following exposure to a norethisterone acetate/ ethinylestradiol mixture. The paper does not mention two preliminary findings that were raised when the work was originally presented to the EWG: that the effects were reversible in zebrafish and there was no effect when chick embryos were tested.

Outcome of Review(s)

- An ad hoc EWG of the CHM (composed of entirely different experts to the first Group) reviewed the paper and agreed with the conclusions of the previous

EWG report, that is the scientific evidence does not support a causal association between the use of HPTs, such as Primodos, and birth defects or miscarriage.

- The European Medicines Agency (EMA) review concluded: “Overall due to the multiple limitations of the study described in the manuscript (Brown et al., 2018) the results of this study do not add to the current knowledge regarding adverse events in early pregnancy in human. The CHMP concluded that there are no new clinical implications based on the results of the presented zebrafish study.”

New Publications on Primodos

- Two papers on HPTs were published in late October 2018, one of which concludes that an analysis of observational studies indicates an association with an increased risk of birth defects, contradicting the conclusions of the CHM EWG on HPTs’ report published in November 2017, on which the government’s position is based.
- The other paper, published online, presents “a historical argument for regulatory failure in the case of Primodos and other hormone pregnancy tests” and suggests that MHRA would have much to learn about how the regulatory process can be improved in the future.
- MHRA has begun work to set up a new ad hoc group of independent, expert, epidemiologists and estimate this could be convened in mid-late February, due to the time needed to find suitable experts and navigate their availability. They will provide a progress update in due course.
- MHRA is also writing to the EMA to request another EU-level review, and will notify the minister as soon as they receive a response.
- The new study, which contradicts the conclusions of the original Expert Working Group, has attracted media interest from Sky News.

Sodium Valproate

Full Timeline

55. Sodium valproate , also known as valproic acid, valproate, and divalproex sodium, is a medication primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches. It is useful for the prevention of seizures in those with absence seizures, partial seizures, and generalized seizures.

56. The Association of British Neurologists advises that valproate is the most effective treatment for generalised epilepsy and this is reflected in NICE

guidelines. For some women with epilepsy it may be the only effective treatment for preventing life-threatening seizures.

57. From the time valproate was first marketed in 1974, the information provided to healthcare professionals included a warning about the possible risk of birth defects. Over the years, and in response to new data, the medicine's warnings have been updated and strengthened. The MHRA (and its predecessors) has kept the product information updated and has issued regular warnings to healthcare professionals in 1983, 1993, 2003, 2013 and 2015.

58. In 2013, following publication of new data showing the full magnitude of risk of developmental disorders, and due to concerns that some women had not received information on the risks, the MHRA took the step to refer this issue to the EMA for a formal scientific review.

59. The MHRA led a European review in 2014. The review concluded that the balance of benefits and risks of valproate in epilepsy and bipolar disorder remains favourable in women of childbearing potential where other drugs are ineffective or not tolerated. This is within the context of the new risk minimisation measures, including the need for effective contraception during treatment. In addition, the review concluded that the risk of congenital malformations is ~10% while studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems.

60. In January 2015, MHRA lead an extensive communications exercise informing healthcare professionals of the strengthened warnings and actions to take. Because of its risks, valproate should only be used to treat women of childbearing age if other drugs are ineffective or not tolerated.

61. MHRA has continued these efforts by working with stakeholders to develop a valproate "toolkit". This consists of a patient card, a healthcare professional booklet, a patient guide, checklist for prescribers to support patient discussions, and a prominent warning on the outer packaging highlighting the risks.

62. In early February 2016, the toolkit was launched and promoted via this network of 39 national groups and organisations. There have been ongoing efforts to disseminate and promote the toolkit since.

63. Although the usage of valproate is declining, survey results relating to patient awareness of the risk clearly indicate that more needs to be done.

64. This prompted an EU review, which concluded in March 2018 and resulted in the implementation of a strengthened regulatory position in the UK from April 2018 (full details below).

Current Position

65. The EU review into sodium valproate concluded in March 2018. Following this, in April 2018 the UK launched an enhanced regulatory position, the goal of which is to rapidly reduce, and eventually eliminate, pregnancies exposed to valproate.

66. Valproate has been contraindicated in women of childbearing potential, unless they meet the conditions of a Pregnancy Prevention Programme (PPP). The PPP aims to ensure that every relevant individual knows about the risks of valproate in pregnancy, that where appropriate is on effective contraception, and that a review by a specialist prescriber takes place at a minimum once a year, when a risk acknowledgment form will be discussed and signed by both prescriber and the individual concerned.

67. Specialist prescribers will assess whether treatment with valproate is necessary for any woman of childbearing potential referred to them, namely that there is no suitable alternative treatment.

68. Pharmacists will ensure the medicine is dispensed in packs which will include the new pictogram and the warning statement.

69. The MHRA has worked in partnership with professional bodies and the healthcare system to bring together a package of measures to support healthcare professionals in implementing these important changes. Educational materials for healthcare professionals and patients are currently being sent to GPs and specialist prescribers.

70. NICE has updated its guidance which mentions valproate to reflect the new regulatory measures.

71. GP electronic system providers have provided a search and audit function to facilitate the identification of women of childbearing age on valproate and have updated the alerts for valproate.

72. There is ongoing communication to raise awareness among professionals and patients of the new regulatory position and other measures being taken across the system to support and embed the changes needed in prescribing practice.

73. MHRA are aware that there has been some evidence of non-compliance amongst healthcare professionals with the valproate PPP. This has included issues such as women being given valproate in plain, white pharmacy boxes rather than the original manufacturer's box, which displays a warning, and women being given valproate without a Patient Information Leaflet (PIL) included.

74. It is the responsibility of every healthcare professional involved in the prescribing and dispensing of valproate to ensure women are aware of the risks, and are on the PPP.

75. MHRA have taken action to address these issues, including raising with the General Pharmaceutical Council (GPhC). On 15th November 2018, the GPhC published an article on their website reiterating the MHRA's guidance, in particular for dispensing valproate.

Title: New measures to avoid valproate exposure in pregnancy

Dr June Raine, Director of MHRA's Vigilance and Risk Management of Medicines Division said:

"We welcome the CMDh[2] endorsement of the strengthened regulatory position on valproate medicines which we have been championing through the Europe-wide review.

"Valproate (Epilim, Depakote and other generic brands) is associated with a risk of birth defects and developmental disorders in children born to women who take valproate during pregnancy. If valproate is taken during pregnancy, up to 4 in 10 babies are at risk of developmental disorders, and approximately 1 in 10 are at risk of birth defects.

"Valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

[2] Coordination Group for Mutual Recognition and Centralised Procedures (CMDh) is a committee of the European Medicines Agency (EMA).

“These new regulatory measures also include a ban on the use of valproate for migraine or bipolar disorder during pregnancy, and a ban on the use of valproate to treat epilepsy during pregnancy unless there is no other effective treatment available.

“Patient safety is our highest priority. We are committed to making sure women and girls are aware of the very real risks of taking valproate during pregnancy. However, we also know it is important women don’t stop taking valproate without first discussing it with their doctor.

“This regulatory position has been developed through close collaboration with professional bodies, health system organisations, and patient and campaign groups.

“I would like to particularly thank the families of the Valproate Stakeholder Network who have shared their experiences and expertise with us. Their support will help keep future generations of children safe.”

Annex A – Commission on Human Medicines (CHM)

About the CHM

- The Commission on Human Medicines (CHM) was established in October 2005 and advises ministers on the safety, efficacy and quality of medicinal products. Its functions are set out in regulation 10 of the Human Medicines Regulations 2012 (SI 2012/1916).
- The CHM is an advisory non-departmental public body, sponsored by the Department of Health and Social Care.

Responsibilities

The CHM is responsible for:

- advising on applications for both national and European marketing authorisations
- considering further representation against our provisional advice in respect of national applications
- advising on the need for, and content of, risk management plans for new medicines
- advising on the impact of new safety issues on the balance of risks and benefits of licensed medicines – e.g. adding warnings, restricting or suspending use of a medicine
- advising the licensing authority on changes to legal status of marketing authorisations

Appointments

The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to Public Bodies, issued by the Commissioner for Public Appointments. The Chair and Commissioners follow a code of practice, in which they are precluded from holding personal interests. Their interests in the pharmaceutical industry are published in the Commission's annual report each year.

Meetings

The Commission meets monthly in London. The Commission is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine. In addition, the Commission calls on experts not readily available through its membership.

Terms of Reference

The Commission on Human Medicines was established in October 2005. Its functions are set out in regulation 10 of the Human Medicines Regulations 2012 (SI 2012/1916).

The functions of the Commission on Human Medicines are:

- to advise the Health Ministers and the Licensing Authority (LA) on matters relating to human medicinal products including giving advice on the safety, quality and efficacy of human medicinal products where either the Commission thinks it appropriate or where it is asked to do so
- to consider those applications that lead to LA action as appropriate (eg where the LA has a statutory duty to refer or chooses to do so)
- to consider representations made (either in writing or at a hearing) by an applicant or by a licence or marketing authorisation holder in certain circumstances
- to promote the collection and investigation of information about adverse reactions to human medicines so advice can be given

The Commission is similarly involved in respect of medicinal products to which relevant EC legislation applies.

Members and Chair

- Professor Stuart Ralston MB ChB MD FRCP FMedSci FRSE FFPM (Hon): Arthritis Research UK Professor of Rheumatology, University of Edinburgh, Western General Hospital, Edinburgh (Chair)
- Dr J Colin Forfar BSc (Hons) MBChB PhD MD MA FRCP FRCP (Edin): Consultant Physician and Cardiologist, John Radcliffe Hospital, Oxford
- Dr Jamie Fraser BSc MB ChB MRCGP GP Partner, Southside Surgery, Inverness
- Professor Jonathan S Friedland MA PhD FRCP FRCPE FRCPI FMedSci: Hammersmith Campus Director and Head of Section of Infectious Diseases and Immunity, Imperial College London; Hon Consultant in Infectious Diseases ICHT
- Dr Richard Gilson MD FRCP: Director, Centre for Sexual Health & HIV Research and Head, Research Department of Infection and Population Health, University College London

- Professor Martin Gore CBE MBBS PhD FRCP: Medical Director and Consultant Medical Oncologist, The Royal Marsden NHS Foundation Trust and Professor of Cancer Medicine Institute of Cancer Research
- Professor Malcolm R Macleod BSc MBChB MRCP PhD FRCP (Edin): Professor of Neurology and Translational Neurosciences, University of Edinburgh and Honorary Consultant Neurologist, NHS Forth Valley
- Dr Rebecca Mann BM BS FRCPCH: Consultant Paediatrician, Taunton and Somerset NHS Foundation Trust
- Dr Sarah Meredith: Deputy Director, MRC Clinical Trials Unit and Honorary Senior Lecturer, Department of Primary Care and Population Sciences, University College London
- Dr Siraj Misbah MBBS (Hons) MSc FRCP FRCPath: Consultant Clinical Immunologist, Lead for Clinical Immunology, Oxford University Hospitals
- Professor David G C Owens MD (Hons) FRCP FRCPsych Professor of Clinical Psychiatry, Edinburgh University
- Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FMedSci David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Associate Executive Pro Vice Chancellor, Director of the Wolfson Centre for Personalised Medicine, Director of the MRC Centre for Drug Safety Science
- Professor Shirley Price MSc, PhD, FBTS, FRSB, ERT, FHEA, FRSC, MBPharmacolSoc Professor of Toxicology, Academic Director, Student Progression and Learning Gain
- Professor Kevin M G Taylor BPharm PhD MRPharmS Chair of the British Pharmacopoeia Commission and Professor of Clinical Pharmaceutics, UCL School of Pharmacy, London
- Professor Angela E Thomas OBE MB BS PhD FRCPE FRCPath FRCPCH (Vice-Chair) Consultant Paediatric Haematologist, Royal Hospital for Sick Children, Edinburgh
- Mrs Helen M Ward MSc, BSc (Hons), Senior Fellow HEA, RGN, RCN Nurse Practitioner, PGCEA, PG Cert NMP, Queens Nurse, Advanced Nurse Practitioner
- Professor Christopher Weir BSc (Hons) PhD MSc FRSS C.Stat C. Sci Personal Chair in Medical Statistics and Clinical Trials, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh
- Dr Martin Wilson MRCP (UK) MPhil (Glasgow), FRCP(Edin) Consultant Physician in Care of the Elderly, Raigmore Hospital, Inverness

Further information on the CHM can be found here:
https://www.gov.uk/government/organisations/commission-on-human-medicines

Expert Working Group on Hormone Pregnancy Tests

Following their attendance at the Oral Hearing session (5th March 2019), HQIP have provided the following documents and further information as requested by the Review.

Following the Oral Hearing, the EWG shared the following information with the Review:

References to meeting in the US

- Symposium "Meta-analysis of Observational Studies " at the 26th Annual Meeting of the Society for Epidemiologic Research, Keystone, Colorado, June 16-18, 1993. The following commentaries are based on presentations made at this symposium.
    - Shapiro, S (1994) Meta-analysis/Shmeta-analysis. *American Journal of Epidemiology* 140(9) :771–778 doi: 10.1093/oxfordjournals.aje.a117324
    - Petitti, DB (1994) Of Babies and Bathwater. *American Journal of Epidemiology* 140(9):779–782 doi: 10.1093/oxfordjournals.aje.a117325
    - Greenland, S (1994) Can Meta-analysis Be Salvaged? *American Journal of Epidemiology* 140(9): 783–787 doi: 10.1093/oxfordjournals.aje.a117326
    - Shapiro, S (1994) Is There Is or Is There Ain"t No Baby?: Dr. Shapiro Replies to Drs. Petitti and Greenland. *American Journal of Epidemiology* 140(9): 788–791 doi: 10.1093/oxfordjournals.aje.a117327

  FDA meeting related to preparation of guidance "Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry". The draft guidance was made available in November 2018 for comment: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM625241.pdf

Further supporting materials:

- CIOMS (2016) Evidence Synthesis and Meta-Analysis for Drug Safety. Report of CIOMS working Group X. Geneva. https://cioms.ch/shop/product/evidence-synthesis-and-meta-analysis-report-of-cioms-working-group-x/

- Kobyasheva, A (2014) Using epidemiological evidence in tort law: a practical guide. Professional Negligence 30(3):125-134 https://www.gibsondunn.com/wp-content/uploads/2018/10/Kobyasheva-Using-epidemiological-evidence-in-tort-law-a-practical-guide-Journal-of-Professional-Negligence-Bloomsbury-10-2014-.pdf

Further information was shared by the MHRA.

In response to a question about whether a meta-analysis was conducted by the EWG, Dr Ailsa Gebbie provided the following response:

The Expert Working Group did not carry out a statistical meta-analysis of epidemiological studies as part of its review into the possible association between HPTs and congenital malformations. There is a distinction between reviewing all the evidence systematically and calculating a single statistical summary ("meta-analysis"), which requires a large number of assumptions, especially for observational studies. This is covered in the minutes: (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf).

At our meeting of 18th October 2016, a preliminary review of the epidemiological evidence was considered, with the strengths and limitations of each study summarised individually in a report. While this was helpful, the epidemiologists and statisticians on the Group requested that the data instead be presented using forest plots and where possible odds ratios should be calculated from the available data with absolute rates and numbers of events provided in addition.

The Group considered this re-analysis at its meeting of 27th March 2017, with the data from the epidemiological studies presented using forest plots as we had requested. As stated in the report, the forest plots were intended solely as a graphical representation of the results of the studies. During our consideration of the re-analysis, in response to a question the Group openly discussed whether the data were amenable to a meta-analysis. The expert epidemiologists were very clear that because the studies were so different such an analysis would not be informative. The EWG recognised the difficulties in summarising a large number of studies, especially when comparing studies with different designs. A meta-analysis was not considered appropriate or helpful because the studies were not sufficiently robust, were too heterogeneous in design and because the weighting system is usually based on study size which given the extensive limitations of many of the studies would not have been appropriate. The rationale of the Expert Working Group is clearly documented in the published minutes of the meetings and in the final report.

To generate the forest plots a statistical software package was used which, if required, can also be used to meta-analyse data from individual studies. However, as this was not the request from the EWG no such analysis was carried out and only the forest plots were generated. A footnote is present on one of the plots that states 'Weights are from random effects analysis'. This footnote is an artefact of the coding used to generate the plots and does not have any relevance to the plot itself. The presence of the footnote should also not be interpreted that a meta-analysis was

conducted as this was not the case. An identical footnote was deleted from all the other plots. I appreciate this may have caused some confusion.

I do hope that this will give reassurance that the issue of a meta-analysis was carefully considered by the EWG and not undertaken for sound epidemiological reasons following expert scientific advice.

Healthcare Quality Improvement Partnership (HQIP)

Following their attendance at the Oral Hearing session (5th March 2019), HQIP have provided the following documents and further information as requested by the Review.

Independent Medicines and Medical Devices Safety Review

Professor Danny Keenan – HQIP Medical Director

Contents

1.0 Background

This review is submitted by the Healthcare Quality Improvement Partnership (HQIP) to the Independent Medicine and Medical Devices Safety Review (IMMDSR) in relation to the use and positioning of "Medical Registries" in healthcare in the United Kingdom.

Clinicians have long kept registers of patients, events and procedures and many interventionists maintained a log of their individual activity. With the advent of inexpensive computers and useable software, such logs have been moved into computers which have the ability to hold data in a way and volume that was unimaginable even 25 years ago.

The oldest more formal registries date back probably to the mid 70's when the registry of cardiac pacemakers was started. The reasons for wanting this data, have not really changed in the years since, although they have been added to.

These reasons were:

1. To log patients who have such a device implanted so that they were not lost in the system
2. To keep track of the device and leads that had been implanted, initially to follow battery life (post marketing surveillance)
3. To look at the outcomes for the patients who had the device implanted.

In more recent years these registries have been added to multiple times so that there is now a wide spectrum of metrics record and analysed by the registries.

2.0 Operational definitions

At the Review Panel hearing there was a discussion about definitions, particularly related to databases and registries.

We were all agreed that a dataset is what it says it is; a spreadsheet with multiple data points which, if left as it stands, confers little useful information.

A registry is considerably more than a database. It takes the data from the dataset and produces useful information in the various different areas where there is need and interest. These areas vary depending on the audience and sophisticated registries will cater for many audiences.

Registries may include:

1. Device information:
    a. Serial numbers for tracking and purchasing
    b. Demographics concerning the device:
        i. Date, place of manufacture, person manufacturing; expected device life expectancy (battery, material, durability), storage
        ii. Components included in the device
    c. Explant information including reason and any post explant review
    d. Off-label use of devices
2. Procedure information:
    a. Patient demographic information
    b. Specific metrics related to the particular condition
    c. General disease status not related to the condition in question, including previous medical history and therapeutic history (allowing risk algorithms to be developed)
    d. Procedure performed including the site and team, including the medical practitioners
    e. Variants of the specific procedure
    f. Patient outcomes (see section 5).
3. Disease or condition information:
    a. Patient demographic information
    b. Specific metrics related to the particular condition
    c. General disease status not related to the condition in question, including previous medical history and therapeutic history (allowing risk algorithms to be developed)
    d. Information on complications, progress and outcomes.
4. Input information:
    a. Institution and team, including medical practitioner, managing a condition and/or implanting devices
    b. Date of entry to register and all-important events such as an implant, admission to hospital, start of new therapy, complications and survival.

There are important differences to consider when devising a registry, primarily a device or procedure, versus looking at a condition. So with female urinary incontinence, the condition could have the registry built round it or the register could be purely related to the implant device or material. These registries will look quite different and will have vastly different numbers of

information fields. We have seen this variation in fields required to look at specific conditions (for example knee ligament repair) compared with the more general National Joint Registry (NJR).

3.0 Audiences

There are multiple audiences and stakeholders involved including:

1. Patients
2. The public
3. News media
4. Law makers.
5. Providers of healthcare
6. Commissioners of healthcare
7. Healthcare industry
8. Public health professionals
9. Researchers.

4.0 Patient information

As seen above there is a host of different patient, condition and device information that can be recorded. These have already been specified but include:

1. Demographics of patients
2. Patient symptomatology and presentation
3. Status; elective and urgent and many grades in between.
4. Medical characteristics
5. Medical, family and social history including medicines
6. Outcomes which can be over a short period (e.g. 30 days) or life long (joint being followed up for 25 years). The latter is especially important in children.
7. Tracking over time and geographically.

5.0 Standards of care

In the midst of the different types of registries, standards of care can be incorporated.

These could be quite explicit (for example time from ambulance call to primary angioplasty) or more general, incorporating several process measures (for example patient discharged following an episode of heart failure and whether they are prescribed evidenced based medicines).

6.0 Clinical outcomes

This crosses over to the world of measuring clinical outcomes, encompassing, as it does, outcome measures, process measures and patient reported outcomes. The sophisticated registries have the ability to encompass such complexity and give all concerned a much more comprehensive picture of care pathways, institutional and individual clinician performance and clinical effectiveness. This opens the door to the use of such registries as comprehensive performance management tools with the ability to assure and improve services.

7.0 Patient outcomes

Whilst the earliest of registries might have been devised to look at outcomes for patients and devices in the short term, the ability to track both of these has conferred a major advantage in term of looking at the different treatment options available for patients and, using this real world data, to define, much better, what procedures are most appropriate in different categories of patients. Similarly watching the performance of devices over years has added an extra dimension to the patient safety agenda. Indeed combining data from different registries (NJR and heart failure) has allowed late non-device complications to be explored and managed.

Registries have allowed the introduction of new techniques to be quickly transferred from the research world to the everyday world with a much quicker application of the new technique (for example coronary artery stenting versus coronary artery bypass grafting and percutaneous aortic valve replacement versus open replacement).

HQIP has built up a portfolio of National Clinical Audits (NCA) over many years and remains host to the NJR. Nomenclature here can be confusing. Professor Sir Bruce Keogh regarded these national audits as registries and looking at the world wide definition of clinical registry, these audits are registries. Incorporated in the portfolio there are specific device registries, (for example cardiac implantable devices and heart valves), but overall, the HQIP portfolio is one of the most comprehensive set of registries in the world and internationally aspired to.

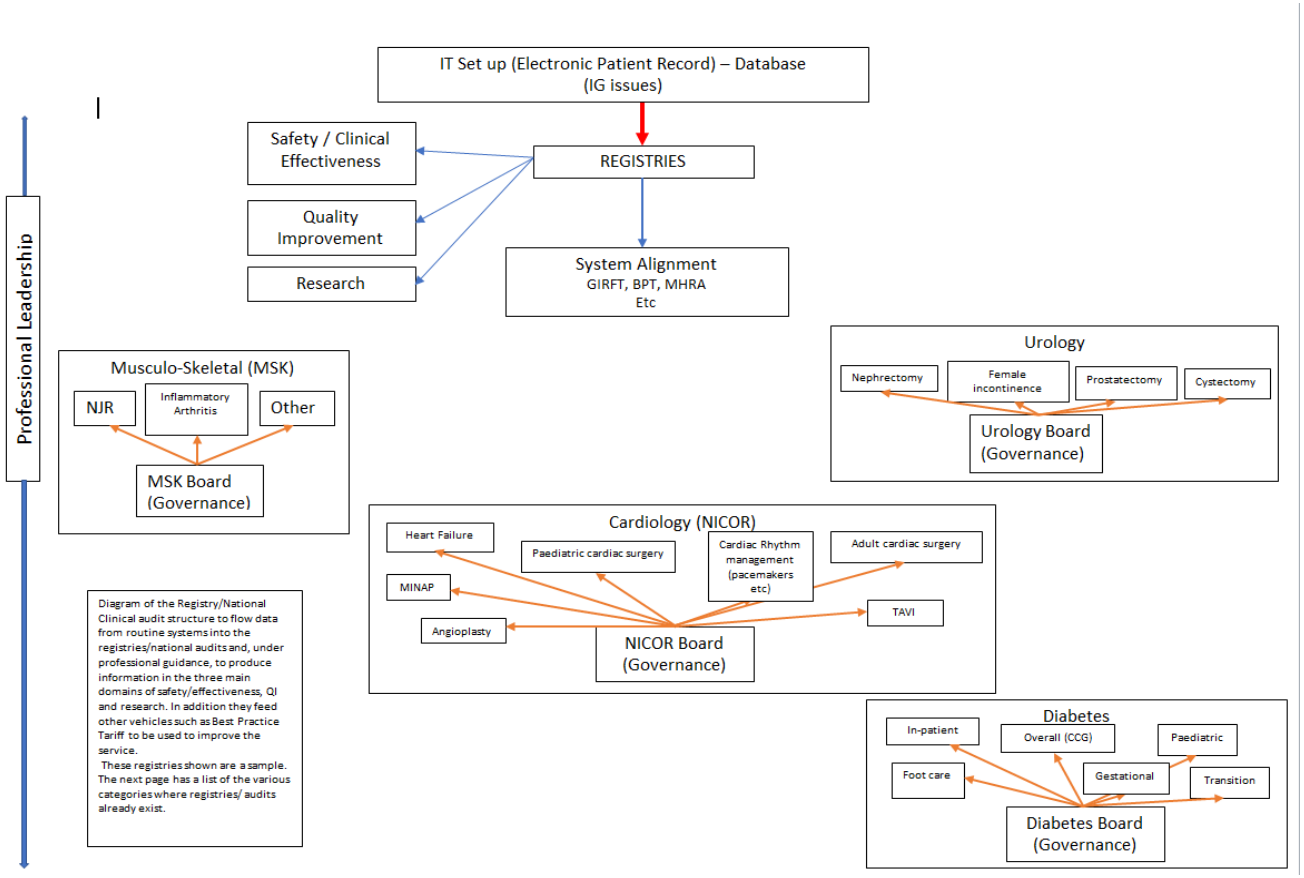
This claim is backed up by one of the most important criteria concerning registries, which is that they collect i) a high percentage of the relevant data and; ii) that the case ascertainment is high. HQIP has always concentrated on these two attributes so that the messages emanating from the programme

is based on sound numbers. Given the size of the population served and our adherence to these two fundamentals, we believe that we can make this claim.

8.0 Data linkage

Data linkage; see appendix one, this is an area where there will be much additional benefit to be gained. Linkages between the cardiac and cancer registries have already yielded benefit. Linking these registries with primary care data will yield much additional benefit. Obviously, such linkage needs to be done with recognition and within the legal boundaries of information governance and the political climate that prevails.

9.0 Appendix one



National Clinical Audit Programme

30+ national audits covering:

- Acute
- Cancer
- Children and Women's Health
- Heart
- Long-term Conditions
- Mental Health
- Older People

Mortality Review Programmes

HQIP currently manages four programmes here:

- National Child Mortality Database
- Learning Disability Mortality Review Programme (LeDeR)
- National Mortality Case Record Review programme
- Perinatal Mortality Review programme

National Joint Registry

Collects joint replacement information, monitoring implant, hospital and surgeon performance:

- Holds 2m+ records
- Includes hips, knees, ankles, elbows and shoulders
- Covers England, Wales and Northern Ireland
- Mandatory for NHS since 2011

Medicines and Healthcare products Regulation Agency (MHRA)

Following their attendance at the Oral Hearing sessions (10th January 2019, 27th February 2019), MHRA have provided the following documents and further information as requested by the Review.

- Follow up information request
- Minutes of the Valproate Stakeholder Network meeting November 2018 and February 2019
- Medicines Commission 'Note on Epilim – Sodium Valproate' 1976
- Committee on Safety of Medicines – Sub Committee on Adverse Reactions
- Follow up on the Yellow Card oral hearing session [medicines]
- Follow up on the Yellow Card oral hearing session [devices]
- MHRA paper on medical device registries
- Medication and Medical Device Safety Officers

Expert Working Group on Hormone Pregnancy Tests

MHRA also provided the following documents related to the Expert Working Group:

- Hormonal Pregnancy Tests Working Group minutes 18th October 2018
- Hormonal Pregnancy Tests Working Group minutes 27th March 2017
- Papers: Evaluation of systematic review and meta-analysis of studies on oral hormone pregnancy tests, including Primodos - proposal for an ad hoc expert group
- Participants of the EWG to review Heneghan et al.
- CHM's Expert Working Group on Hormone Pregnancy Tests - Clarification points arising during the oral hearing on 28th January 2019

Follow-up points arising from the MHRA Oral Hearing sessions

1. Provide further information on operating a voluntary scheme for transparency of manufacturer data

The MHRA aims to be as transparent as legally possible and we have worked hard towards greater transparency from a Medical Devices perspective. This has included leading the way - aiming to deliver a UK transparency scheme by 2020, when the new Manufacturer Incident Report (MIR) form (see below) is due to enter into use across Europe so the public can see a range of fields from the final MIR report.

The MHRA believed that a change in the Medical Device Regulations, and the medical device Manufacturer Incident Report (MIR) form in particular, was necessary to improve surveillance, and that a vigilance transparency scheme should be introduced which was informative and interrogatable.

We argued strongly for increased transparency under the new Medical Device Regulations. Some improvements were included, such as the requirement for manufacturers to place a summary of safety and clinical performance (SSCP) into the public domain. Whilst the Regulations are not explicit about publishing information about all reportable adverse incidents associated with medical devices, the MHRA and other EU regulators, together with the Commission and manufacturers aim to deliver an EU vigilance transparency scheme. The MHRA is participating in a new task force set up to improve transparency across the Medical Device Regulation.

Some notable actions we have taken to increase transparency in relation to medical devices are as follows: We can provide greater detail in relevant documents upon request.

- In 2011, as part of an EU wide consideration of what the new Medical Device Regulations (MDR) should contain, we argued for a centralised EU system that included making final reports of incidents public. We were also recommending the introduction of Unique Device Identifiers (UDI), actor (competent authorities, manufacturers and their representatives) registration, and the use of standard medical device terminology, all essential for signal detection and essential for a transparency scheme.
- In 2014, we influenced DG-SANCO (the EU Directorate General for Medical Devices at the time) to develop and pilot a centralised medical device vigilance repository. We led the development of a supplementary manufacturer incident report form, which incorporated adverse incident terms and Unique Device Identifiers (UDI).
- This centralised repository was successfully trialled in 2015/16 and we proposed that this could provide the means for the launch of a voluntary vigilance transparency scheme. The Joint Research Council (JRC, the European Commission's science and knowledge service) published a policy research paper in 2016 which concluded that the pilot was extremely useful for three reasons:
    - It confirmed the general feasibility of categorised reporting of incidents by manufacturers.
    - It identified inadequacies of the existing nomenclature suggesting the need for the development of freely available, scientifically and technically satisfying and adequate nomenclature for adverse event reporting of incidents and events also in the pre-market space.
    - It led to the proposal of several potentially useful terms in view of future developments of nomenclature for incident / adverse event reporting.
- Following the centralised repository pilot, for the next 2 years the MHRA and JRC strongly contributed to the development of new adverse event terminology, which was

significantly better than the previous version, and has now been adopted by the US FDA, Canada, and Europe. This work has been incorporated into the new Manufacturer Incident Report form (MIR), which now provides the platform for future medical device vigilance in the UK and rest of Europe.

- We also contributed significantly to the development of EUDAMED (EU database), including the vigilance module that will provide the platform for future EU medical device vigilance transparency.
- At the November 2018 meeting of the pan-EU Vigilance Medical Device Expert Group, the first implementation of the EU vigilance transparency scheme, using a subset of the MIR form fields was agreed.

With regards to mesh and linking the future mesh registry with case reports of adverse incidents, the planned voluntary transparency scheme will include mesh related adverse incidents. In the longer term, it might be possible to create a linkage from the registry at the UDI-DI (device identifier) level when available, or otherwise via the combined details of manufacturer, model, catalogue number, and lot number, so that future safety signals can be more reliably identified and managed in a transparent way, in the same way as the National Joint Registry.

Furthermore, it is important to note that we use a range of communications to provide data and alert healthcare professionals and the public to actual and potential safety issues such as Medical Device Alerts, device-specific information on our webpage, One-Liners, Field Safety Notices and Dear Healthcare Professional letters (as detailed in our written response to Q7, Q10 and Q12).

2. Provide briefing on the valproate registry and continue to invite the Review Team to future meetings to discuss the registry

Following two 'brainstorm' meetings on the proposed valproate registry in November 18 and February 19 with key stakeholders from clinical bodies, academic researchers including those experienced in the antiepileptic registry, together with patient representation we have reached agreement on the key principles underpinning the registry as proposed (please see attached working document) [Annex 1]. These principles are to:

1. *Track the implementation of all aspects of the valproate Pregnancy Prevention Programme and facilitate early identification and investigation of any potential non-compliance and any resulting exposed pregnancies in order to indicate where additional action is required*

2. *Help understand changes in the use of valproate in the UK and the impact of these changes on the health of women with epilepsy and bipolar disorder and their children*

3. *Facilitate further research into valproate-exposed pregnancies and childhood outcomes and enable monitoring and follow-up of any identified children born to women taking valproate during pregnancy*

Importantly, the meeting considered that the lead for development of the Valproate Registry would appropriately be with the clinical professional bodies and Royal Colleges representing neurology and paediatric. The next step is to bring together all the key organisations to lead on development of the registry including establishment of a steering group to draw up a full study proposal and progress discussions on funding. Patient representatives have made clear their opposition to obtaining funding from the pharmaceutical industry and other sources for public funding are being explored.

3. **Look at the oral contraceptive PIL/SmPC with pregnancy contraindication and congenital abnormalities listed: The SmPc for Brevinor (unnamed Oral Contraceptive pill from the session) includes a special warning about reports of congenital abnormalities in pregnancy. As far as we have found, this is the only OC which includes the constituents of Primodos together, albeit in different dosage and with different posology (NE and EE). I have included the url below: https://www.medicines.org.uk/emc/product/1145/smpc**

We have reviewed the product information for all norethisterone-containing products that are authorised in the UK. We were concerned to find that a warning about a reported increased risk of congenital anomalies, including heart and limb defects, was present in the marketing authorisations for Brevinor, Noriday, Norimin, Synphase and Norinyl-1. This warning appears to have been included in these marketing authorisations as a result of a company-led change of ownership which does not require a scientific assessment.

We have written to the Company concerned to highlight the inconsistency between their warnings and those in similar norethisterone-containing products authorised in the UK and with the current scientific position. The Company has committed to vary its product licences promptly and is preparing to submit applications to complete these corrections by 11th May. We have confirmed that other sources of information for healthcare professionals such as the British National Formulary do not contain this information.

4. **I'd be grateful if you could send us details of the discrepancies between the valproate PIL and SmPC that you highlighted in the session please: A key concern of patient groups is the historical timings of warnings to clinicians and patients, and their relation to available research at the time. I have attached a copy of the changes over time to the valproate SmPCs and PILs and any key studies which have been raised to us as being of concern, to assist you. Do let me know if you have any further questions.**

When new studies are published which raise a potential new safety issue for a medicine, the study is reviewed in the context of all available data, including previously published studies, spontaneous reporting data and any relevant unpublished data. Decisions on the need to take regulatory action (eg changes to the summary of product characteristics and Patient Information Leaflet) are taken on the basis of all the available data and usually on the advice of our expert committees. The need for the regulator to take action quickly is balanced against the requirement for robust decision making taking into account the therapeutic context.

We have reviewed the information we have available on the historical timings of warnings to clinicians and patients on valproate in relation to the available research at the time. We provide below further information on the regulatory response to the research highlighted in your table 'Comparison of information provided to healthcare professionals (Datasheets/SmPCs) and patients (Patient Information Leaflets)'. The Marketing Authorisation Holder (MAH) has provided details of the regulatory interactions in their response to the IMMDS Review. and we have focussed on information that we have that is additional to that provided by the MAH.

1982 Bierkdal et al. Valproic Acid and Spina Bifida

The CSM considered the study by Bierkdal et al in December 1982, and the implications for the valproate product information. The minutes of that meeting state that '*Although the*

current warning in the data sheet was adequate the Committee would not object to the amendment proposed by the company along the lines that pregnancy should be carefully monitored in women receiving Epilim'.

The Committee concurred with the Sub Committee on Efficacy and Adverse Reactions (SEAR) recommendation that there was a need for specific research into the role of anti-convulsant therapy in epileptic mothers in increasing the risks of congenital malformation of the foetus.

The Committee advised the publication of an article in the bulletin sent to healthcare professionals at that time 'Current Problems in Pharmacovigilance', which was published in January 1983. This bulletin article references the publication by Bierkdal et al.

1985 DiLiberti et al, 1986 Lindhout and Schmidt, 1987 Winter et al.
We have not been able to find any record of discussions in response to these publications of case series, although the submission to the review by the MAH outlines ongoing interaction between the MAH and DHSS during this period. The next record of regulatory action is the update to the product information in 1989 to include warnings about foetal abnormalities including neural tube defects. Previous warnings were that '*Sodium valproate, like other anticonvulsants, has been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.*' An article was published in Current Problems in Pharmacovigilance in 1993. Warnings in product information were subsequently expanded as outlined in your table.

Signals regarding developmental delay were the subject of CSM review in November 2000 triggered by a pre-publication copy of a study by Adab et al (the Professor Chadwick research team) 'Additional educational needs in children born to mothers with epilepsy.' The assessment presented to the CHM considered a range of data sources including a number of other published studies. The CSM minutes (attached) state that '*The Committee concluded that the evidence currently available did not clearly support a causal association between sodium valproate exposure in utero and developmental delay, however there was a signal of a safety issue which should be kept under close review. It was recommended that the existing warning that sodium valproate was for second line use only in women of childbearing potential should be more prominent in the product information and that this issue should be referred to the Committee's paediatric medicines working group.*'

In March 2001, a warning in product information that sodium valproate should only be used in women of childbearing potential in severe cases or in those resistant to other treatments was expanded to reflect the available evidence on the risk of birth defects and to state that women should be informed of the risks and benefits of continuing treatment.

The CSM Working Group on paediatric medicines considered the issue of developmental delay in November 2002 and advised that there was now evidence from a number of studies suggesting an increased risk of developmental delay following in utero exposure. The Working Group advised that the product information for valproate should be updated to include a warning. In April 2003, warnings were added that *'Women of childbearing potential should not be started on Epilim without specialist neurological advice.'* The Pregnancy section of the SmPC (section 4.6) was changed to include malformation rates associated with epilepsy and anti-epileptics, an expanded list of malformations associated with valproate and the frequency of spina bifida. Detailed advice was added on reviewing treatment, dosing advice if treatment continued and folate supplementation. Warnings about developmental delay were added: *"Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal antiepileptic treatment. Notwithstanding*

those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus."

An article on 'Sodium valproate and prescribing in pregnancy' was published in the September 2003 issue of Current Problems in Pharmacovigilance. This warned of an increased risk of congenital malformations in infants born to mothers with epilepsy taking sodium valproate and highlighted studies which suggested an association between in utero exposure to valproate and the risk of developmental delay. The article gave the following advice to healthcare professionals:

- 'Women of childbearing potential should not be started on sodium valproate without specialist neurological advice
- Women taking sodium valproate who are likely to become pregnant should receive specialist advice because of the potential teratogenic risk to the fetus
- If taken during pregnancy sodium valproate should be prescribed as monotherapy at the lowest effective dose, in divided doses and if possible, as a prolonged release preparation
- Folate supplementation prior to pregnancy may reduce the incidence of neural tube defects in infants born to women at high risk. Women should take 5mg folic acid **as soon as contraception is discontinued.'**

2004 Meta-analysis by Fried et al, Cochrane review, Chadwick study (Adab et al. 2004)
In response to the findings of the Adab et al study showing the effect of valproate on verbal IQ, the statement on developmental delay in the Summary of Product Characteristics was updated in 2005 to read '*Some data from studies, of women with epilepsy, have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ". This was translated in the PIL as 'some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal and may require additional educational support*.'

2005 First findings of the NEAD study
Preliminary analysis of the NEAD study showed an increase in adverse neurodevelopmental effects for valproate (24%), phenytoin (12%), carbamazepine (10%) and lamotrigine (2%). Updates to product information approved in 2005 included addition of the following statements in addition to the update to the statement on neurodevelopmental disorders above: *'Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus.*' *'Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks. If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate'.* In relation to counselling, the PIL was updated to say that if planning a pregnancy women should consult their doctor '*in order to receive appropriate counselling and to allow your doctor to adapt your treatment and/or dosage and to adequately monitor your pregnancy.*'

Morrow et al 2006
This paper by Morrow included data from the UK Epilepsy and Pregnancy Register and reported an increase risk of major congenital malformations with valproate (6.2%) compared with carbamazepine (2.2%) and lamotrigine (3.2%). No changes were made to the product information on the basis of these data. Warnings about major congenital malformations were already included The PIL stated '*It is known that women receiving Epilim during pregnancy*

have a higher risk than other women of giving birth to a child with an abnormality.' and included a list of reported abnormalities.

Bromley et al, 2008 Autism spectrum disorders following in utero exposure to antiepileptic drugs

A review of the available data prompted by this publication led to updates to the product information in 2010 which included a statement that *'Autistic spectrum disorders have also been reported in children exposed in utero'.* This was based on case reports and retrospective studies.

5. Patient groups have also raised concern about the process by which valproate was licensed in the UK. I would appreciate if you could set out your understanding of the evidence base and conditions of the original limited license (1972), and the full product license (granted 1974, commencing 1973).

The assessment report on the licensing of valproate (at that time called Labazene) which was considered by the Committee on Safety of Medicines and its subcommittees in 1972 is attached at Annex 2 and summarises the evidence base for the decision at that time.

The CSM minutes of January 1972 state that the main committee '*agreed that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since the evidence of efficacy and safety in the clinical studies is inadequate. Subject to the applicant being willing to undertake a clinical trial on the lines indicated, then issue of a certificate could be recommended without further reference to the Committee.'*

A further paper attached at Annex 3 was considered at the May 1972 meeting of the CSM and states that the deficiencies in the data had been discussed with the company and the company had submitted a '*substantial amount of further information, mainly clinical, to support the licence application.*' The CSM recommended that '*consideration of this application should be deferred pending further discussion with the applicant regarding the possibility of a clinical trial being undertaken in an epileptic centre in the United Kingdom*.'

In June 1972, the CSM '*advised the grant of a product licence for one year …..provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy.*' . We have not been able to locate the paper discussed at that meeting. This decision may have been on the basis of the papers considered in the January and May meetings rather than a separate further paper.

In March 1974, the CSM advised on a variation of the product licence for Epilim to delete the requirement regarding the monitoring (the requirement to limit promotion to hospitals and other centres specialising in the treatment of epilepsy) on condition that the indication for use reads 'f*or use in generalised, focal or other epilepsy. In women of child bearing age, it should only be used in severe cases or those resistant to other treatment*.' and that the following warning was included in all literature: *'<u>Women of childbearing age</u> This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.'* We have not been able to locate the assessment report that was considered at this meeting, although the extract from the minutes of the meeting of the Sub-Committee on Toxicity and Clinical Trials, which advised the CSM on this issue, say that their recommendation to remove the requirement to limit promotion to hospitals and other centres specialising in the treatment of epilepsy was based on 'the results presented, and in particular the further data on teratology..'.

Questions that we did not have time to cover in full in the session:

6. **In your evidence, you state one of your main aims is to identify and communicate effectively and quickly problems associated with medicines and medical devices. Do you think you have succeeded with regard to the interventions under Review?**

The MHRA has communicated extensively over the years in relation to the risks of mesh and of valproate in pregnancy as new information became available in clinical practice and from research. However, we remain very concerned when we hear that, for example, some women on valproate are not aware of the serious risks in pregnancy. We want and intend to improve how we communicate problems associated with medicines and medical devices to the public, patients and healthcare professionals. We are keen to learn from others and build on experience, and we have been and are taking action to improve our effectiveness and timeliness in identifying and communicating on safety issues.

The MHRA is seen a leader amongst other regulators in identifying and evaluating signals and communicating the benefits and risks of medicines and medical devices, and we have continually strengthened the methods we use to evaluate and communicate benefits and risks over time (see below for examples). We nonetheless appreciate that we need to invest further in this area and work more effectively with others in the healthcare system in order to meet patient needs and public expectations. We have researched new developments in detecting signals of emerging or changing harms using new tools and methodologies and have explored an increasingly diverse range of communication tools including social media.

In order to strengthen our ability to identify signals, we use statistical software, to carry out signal detection a weekly basis, for all reports committed to the database the week prior, to identify issues which require further evaluation and to prioritise these according to potential public health impact. The statistical methods used are reviewed on a regular basis to assess their effectiveness. A multidisciplinary team of scientists and healthcare professionals assesses the Yellow Card signals each week alongside additional sources of data including clinical trials, medical literature and information from other international regulators to investigate the possible causal relationship between the suspected medicine or vaccine and the adverse reaction. The MHRA may also ask the marketing authorisation holder for further information and data in relation to a particular drug and event.

We have led EU device initiatives to:

- developed international terminology for medical device adverse events
- overhaul the current manufacturer reporting form to include: adverse event terminology, similar incident data statistics along with denominator data, and Unique device identifiers and
- explore techniques for safety signal detection as part of our patient safety and vigilance strategy.

Please see response to Q2 and Q32 of MHRAs written evidence for more details.

In order to strengthen our communications, we instituted a Health Summit in January 2017 bringing together leaders in healthcare organisations across the UK. This was addressed by the Chief Medical Officers and other leaders and delivered recommendations which led directly to establishing the NAPSAC committee under the leadership of NHS Improvement.

Turning to the interventions under Review, regulatory systems and the approach to communicating safety concerns have changed substantially over time, particularly since the time before the introduction of the formal regulatory licensing regime that Hormone Pregnancy Tests were first available.

With regard to Hormone Pregnancy Tests, the government of the day was the only one to initiate its own case-control study of maternal drug histories and congenital anomalies and to take action when early results suggested that a relatively greater proportion of mothers of children with anomalies had used HPTs. Further communications were issued to healthcare professionals when evidence suggested HPTs were continuing to be used for the diagnosis of pregnancy despite earlier warnings they should not be used for this purpose.] In the UK Primodos was never authorised for the diagnosis of pregnancy.

With regard to valproate, we are one of the first regulators worldwide to take stringent action in relation to the growing evidence of harms of valproate, and to communicate the serious risks in pregnancy. In 2013 we initiated the European safety review of valproate, in 2016 we developed the valproate toolkit and package warnings which were subsequently rolled out by the brand leader company worldwide, and in 2018 we pressed for a PPP to be implemented to further minimise the risks. Despite sending clear Drug Safety Update messages to healthcare professionals on 5 occasions since the launch of the PPP, and communications from the Chief Medical and Chief Pharmaceutical Officers, we remain extremely concerned that there are still women receiving valproate who could become pregnant and who are not on the PPP. We continue to work intensively with patient groups, healthcare professional organisations and other regulatory and guidance bodies in the MHRA's Valproate Stakeholder Network to ensure that all those who prescribe valproate are in compliance with the strengthened statutory position. We have committed to continue to do so until there is sound evidence that pregnancies exposed to valproate have been rapidly reduced and ultimately eliminated.

With regard to mesh, we were also one of the first regulators to identify a signal and take a number of significant actions to investigate and address increasing numbers of reports relating to the use of surgical mesh, as well as highlighting the issues and working with others to consider their place in appropriate treatment pathways. The actions and communications are outlined in our written evidence timeline and include the outcomes of the 2011 and 2012 workshops for SUI and POP which resulted in several actions by MHRA and all parties concerned to reduce risk such as informed consent and increasing patient information. Over time, these were further enhanced by actions taken by the wider healthcare system, supported by the MHRA such as our participation in the NHS E mesh working group report.

7. Your review of the historic literature in 2014 indicated that there was not enough evidence to support a causal link between HPT use and congenital malformations. What did the Expert Working Group add to your 2014 Review?

The terms of reference for the Expert Working Group review were broader than the MHRA's historical review enabling the scope of the review to be far wider and undertaken in much greater scientific detail. This is explained below. The Terms of Reference also enabled the group to give detailed consideration as to whether any lessons could be drawn for how drug safety issues in pregnancy are identified, evaluated and communicated in the present regulatory system and how the effectiveness of risk management is monitored.

The background is that in January 2014, Dr Dan Poulter (who was then the relevant minister) further to a meeting with Yasmin Qureshi MP, Chair of the All Party Parliamentary Group (APPG) on HPTs, asked the MHRA to provide a summary of findings from the historical evidence on HPTs. The historical review included the key published epidemiological studies, but no other forms of evidence were considered and, at that stage, the MHRA did not have access to any other evidence. In October 2014, the then Minister for Life Sciences, George Freeman MP, in response to requests by the APPG for a public inquiry, asked for an independent review of all the evidence on HPTs and congenital anomalies and stated that he would instruct that all relevant documents held by the Department of Health be released.

To ensure that all relevant data were included, the MHRA conducted an extensive search for evidence including: a thorough review of the published literature; a search of the UK National Archives by a professional researcher; a public call for information from anyone who considered they might have relevant knowledge and a request for relevant data from companies, other regulatory bodies worldwide and from professional bodies. In addition, all documents from the Landesarchiv Berlin were reviewed, including thousands of German language documents that were professionally translated to English. The Expert Working Group also listened carefully to the evidence from 13 families of the Association for Children Damaged by HPTs.

Careful consideration was given by the Commission on Human Medicines to the membership of the EWG to make sure the panel had the expertise needed to evaluate all aspects of the questions before the Group and the types of data that would need to be assessed to conduct a rigorous scientific review. The EWG comprised a total of 23 experts from a wide range of relevant scientific disciplines including gynaecology, obstetrics, human prenatal and clinical genetics, embryology, neonatology, reproductive endocrinology, perinatal health, toxicology, epidemiology, statistics and medicinal chemistry. The EWG heard presentations from 8 experts (3 at the request of the Chair of the Association for Children Damaged by HPTs, Mrs Marie Lyon) and from Mrs Lyon herself.

The EWG met 7 times over a period of 18 months in order to ensure all available evidence had been comprehensively evaluated, including through:

- theoretical considerations for transfer of the components of Primodos to the developing fetus and subsequent action on the fetus, based on the known actions of the hormones in the body and transfer across the placenta;
- evaluation of all available animal studies (over 80);
- expert scrutiny of reports of birth defects in women given an HPT during pregnancy, and comparison of the range and pattern of the birth defects reported in association with HPTs with those reported to a national and a European birth defect database;
- review of nearly 100 published and unpublished studies in women given an HPT during pregnancy; and
- review of evidence on the ability of the components of Primodos indirectly to cause birth defects through disruption or interruption of the intra-uterine blood supply.

The minutes of the meetings reflect clearly the Group's desire to undertake the best possible review which led to fresh approaches to analysing the data, asking for additional information and re-evaluations on several occasions until they were satisfied every avenue had been explored. The EWG therefore added a wealth of expertise and a much more comprehensive evidence base to a review that was not restricted to the published epidemiology but included all available data relevant to the questions in hand. This was also the first time that an Expert Group included the Chair of a patient association throughout and, at their request, invited three researchers in the area to present their work to the Group.

Importantly the Review by the Expert Working Group on HPTs has provided a set of clear recommendations for a programme of work to improve the safety of medicines in pregnancy, and to ensure that information on medicines safety is available to support decisions by women and their healthcare providers. Work is well in hand under the direction of a Cross-Sector Group chaired by the minister and is being progressed by MHRA in liaison with EU and international regulators. Information on one aspect of this work is provided in question 13, however we can provide further information to the Review if this would be helpful.

8. The EMA referral stated that further research was needed on potential transgenerational effects of valproate. We understand that you have been advising

the marketing authorisation holders on appropriate research plans. If you can share any details of this with the Review that would be very helpful.

The work on the research on potential transgenerational effects of valproate was a regulatory commitment of the second EU safety review which was completed in May 2018. This commitment arose from new studies. One showed that a change in gene expression (one gene) in male mice after exposure to a histone deacetylase (HDAC) inhibitor (not valproate but a substance with a similar mechanism of action) was observed also in the offspring of these mice (Jia et al, 2015)[1]. Another study in mice showed that administration of valproate during pregnancy (day 10) produced autism-like symptoms and increased expression of several proteins in the brains up to the third-generation offspring. This increase was not shown for teratogenic effects as malformations in the first-generation offspring were not observed in the second and third-generation offspring (Choi et al, 2016)[2]. The Pharmacovigilance Risk Assessment Committee considered that several limitations existed in these studies and that more research was necessary.

The work to progress this commitment is being coordinated by the EMA. A protocol for the study on transgenerational effects of valproate is under development and our comments on the draft protocol will be via the rapporteur country (the Netherlands). So far we have not had any interactions directly with the Marketing Authorisation Holders on the study.

We anticipate that there will be further consideration of draft study protocols at European level in the next few months.

9. We have heard that the evidence for mesh safety is flawed because it lacks appropriate patient outcome measures. Do you agree?

There is a wide range of evidence in the scientific literature of outcome measures reported by patients and outcome measures not reported by patients. Most are good short-term data (typically 1 or 2 years) and performance is demonstrated when the CE mark is obtained and maintained during the re-certification process. Clinical data for implants typically does not include an evaluation of long-term safety and performance prior to the CE marking process but forms part of the manufacturers post market surveillance obligations once the CE mark is obtained.

We recognise the need for long-term systematic assessment of the ongoing safety and performance in relation to different surgical procedures using mesh. Therefore, we welcome the systematic capture of outcome measures (with validated PROMS questionnaires as can be seen from the success of the NJR registry), as an essential part of a future system that can monitor safety and performance over time, and inform patients, clinicians, commissioners of healthcare, and regulators. All parties concerned can also better understand those patients who have benefitted from these procedures.

This can feed into the benefit-risk evaluation undertaken by manufacturers and competent authorities, ensuring the continued acceptability of identified risks and of detecting emerging risks, and supporting the informed consent process so that up-to-date understanding of benefits and risks can be communicated to patients.

Patient outcome measures complemented by current activities such as reporting adverse events, market surveillance, vigilance, post-market surveillance including PMCF (post-market clinical follow-up; a continuous process that updates the pre-market clinical evaluation and requires manufacturers to proactively collect and evaluate clinical data from

[1] Jia H, Morris CD, Williams RM, Loring JF, Thomas EA. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. Proc Natl Acad Sci U S A. 2015 Jan 6;112(1):E56-64.

[2] Choi CS, Gonzales EL, Kim KC, Yang SM, Kim JW, Mabunga DF, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. Sci Rep. 2016 Nov 7;6:36250

the use in or on humans of the CE marked device) and a mature dataset from a registry (using UDI and Scan4 Safety methodologies) will help us to gain, analyse and act upon safety signals but, perhaps more importantly, they will enable outcomes analysis at local level which can feed into quality improvement initiatives and, in so doing, reduce the likelihood of performance outliers becoming a wider issue. They may also facilitate a more effective interaction between regulators and the providers when issues are identified.

10. Patients are very concerned about biocompatibility. Please can you explain the process by which device materials are selected and tested?

- **a. A biological evaluation of the final device is required under the new MDR. Please explain the roles of the manufacturer and the notified body in this process.**
- **b. MHRA has previously conducted explant studies (PIP breast implants) are there any plans to carry out similar studies on mesh?**
- **c. Mesh has multiple variables (porosity, mechanical properties). At the design stage how are these variable characteristics matched to the indication being treated, and who has oversight of this process?**

Biological evaluation and mesh variable characteristics/properties (a. and c.):

The current EU Medical Device Directive and the new EU Medical Device Regulations require the device (including the chosen material) to be evaluated for its safety, quality and performance. This includes sterility, physical and mechanical testing, and a biological evaluation (usually to BS EN ISO 10993 series of international standards) to be carried out as appropriate and documented. This is the responsibility of the manufacturer who must ensure that the chosen design including material, construction and its properties achieves the performances/claims intended for the indication of use by the manufacturer and compliance to Directive/Regulations.

For surgical mesh, this will also include following an appropriate assessment by an independent certification body, called a Notified Body, which will issue relevant certification, providing the device meets the requirements set out in the legislation. This allows manufacturers to then put CE marks on their products and sell them anywhere in the EU if they meet the requirements. The MHRA audits notified bodies within the UK to ensure they are undertaking their assessments properly.

See Q20 and Q35 of the MHRA's written response to the call for evidence on design selection, verification and validation by the manufacturer of the device and role of Notified Body. Q35 in the MHRA written evidence which includes reference to the SCENIHR's Opinion on the safety of surgical meshes used in urogynecological surgery and factors which affect the outcome of surgical procedures, including the type classification of mesh properties concluded to be the most appropriate synthetic mesh – see Table 10 and devices that come under that type at the time of publication.

Explant studies (b.)

The MHRA has not conducted any explant studies on mesh per se and has no current plans to undertake such studies. We are not aware of any mesh specialist review centres undertaking any studies on the device which may be similar to that being carried out by 'retrieval centres' for orthopaedic implants and run mostly by academic organisations. However, the MHRA commissioned a literature study of mesh as described in *Summaries of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence*

and Prolapse (see Annex D of the MHRA written evidence). The MHRA may commission further studies in future.

As part of the vigilance requirements placed on medical device manufacturers, they should have access to a medical device implicated in an adverse event to undertake an investigation. We would welcome the opportunity to discuss with groups such as the mesh review centres to establish the feasibility of an analysis of mesh that has been removed (full or partial). However, as above we are not aware of any academic body or review centre with an interest or capability in examining removed mesh devices.

The advice we have from clinical and materials experts is that studies on the mesh removed may be of limited value. This is partly because the devices are usually removed in many small pieces so any analysis would be either impossible to do or impossible to interpret. Further, the patient's body's natural inflammatory response to the device is very variable and unpredictable and is just as important a factor as the chosen material as a predictor of the outcome of the procedure.

It could be more useful to direct resources to basic science research on human immune responses to implants so that surgeons would be better able to predict the response of an individual before surgery and incorporate this into the choice of treatment.

11. Will forum shopping for CE marking be able to continue under the new EU Directive? – if yes will this be transparent? Will manufacturers be required to say if their application has previously been turned down by another notified body? How will this be monitored? What information if any does MHRA currently receive on the CE marking application process? For example, would you know if a product had been rejected or had been considered by multiple notified bodies?

Will forum shopping for CE marking be able to continue under the new EU Directive? – if yes will this be transparent

Whilst there is little evidence that 'forum shopping' is a widespread problem, anecdotal evidence suggests that this can sometimes take place. The new Medical Device Regulations, which the MHRA has actively championed, will go a long way in tackling this issue. This will largely be through the increased levels of transparency and accountability that the Regulations require. As such, manufacturers will no longer be allowed to submit applications for conformity assessment to more than one notified body in parallel. Furthermore, the Joint Action Plan placed greater scrutiny on notified bodies performance and raised standards, and the introduction of EUDAMED will improve the transparency and accountability of the application process. See below for more information.

Will manufacturers be required to say if their application has previously been turned down by another notified body? How will this be monitored?

No, but the notified body is expected to upload information regarding any application refusal onto EUDAMED – see below.

What information if any does MHRA currently receive on the CE marking application process? For example, would you know if a product had been rejected or had been considered by multiple notified bodies?

Under the current Directives, we would know if a product had been rejected by a UK notified body. UK notified bodies upload information onto EUDAMED which is available to the MHRA and all EU competent/designating authorities. Furthermore, we receive information from UK notified bodies relating to refusal applications when the refusal was based on safety issues.

The MHRA disseminates this to all competent/designating authorities and other UK notified bodies for their information and consideration. New legislation was introduced in 2013

whereby a notified body must inform its designating authority and other notified bodies about all certificates issued, suspended, withdrawn or refused.

There is currently no harmonised approach across Europe for refusal of CE applications. However, while the new EU regulatory framework will continue to allow manufacturers to choose notified bodies, it places significantly stricter obligations on all economic operators and notified bodies during the conformity assessment process and consistency across member states.

Under the new Regulations, we would know if a product had been rejected by a notified body (UK and non-UK). The requirements for EUDAMED will be strengthened and notified bodies will be required to upload information onto EUDAMED to inform other notified bodies when a manufacturer withdraws its application or when the notified body decides to refuse the application. In addition, when the manufacturer lodges a new application with a notified body it will need to provide a written declaration that no application has been lodged with any other notified body for the same device or information about any previous application for the same device. MHRA expectation is that the reasons for the refusal will be included in the information provided about any previous applications for the same device.

For background, please see the MHRAs written evidence on the strengthening of pre-market assessments conducted by notified bodies, through the EU Joint Action Plan. The Action Plan focused on 4 key areas: the functioning of notified bodies, market surveillance, coordination of vigilance and communication and transparency.

The joint assessments are performed by the Designating Authority of the country where the notified body is based plus a Joint Assessment Team. This includes at least one member from the European Commission and two national experts from Member States other than the one in which the notified body is established. This has led to greater visibility of their activities across Europe and the status of the certificates they issue. This is currently a paper-based approach, however, the introduction of a revised version of the electronic database for medical devices, EUDAMED, in the new EU Regulations for medical devices and *in vitro* diagnostic devices will provide a more uniform and consistent approach to monitoring notified body activities.

12. 95% of the funding for device regulation comes from the SLA with DHSC. How has the level of funding changed in real terms over the last 10 years.

Medical Devices regulation is primarily funded through a service level agreement with the DHSC with approximately 10% of its revenue from fees charged to recover costs incurred by the Agency. Devices annual funding this year is 39% lower than it was in 2008/09 in real terms. We are currently in discussion with the DHSC regarding a sustainable funding model that meets public health requirements and the demands of the new Medical Device Regulations.

13. Is there a clear way to identify or raise awareness of gaps in research? Does MHRA identify research priorities and where do these go? What proportion get funded?

There a several approaches available to us for identifying research gaps and raising them with those whom we regulate, and the healthcare network and associated funding bodies. We are not able to provide a reliable estimate of what proportion of the gaps we identify in research actually get funded. Our approach is generally scenario-specific, often stimulated by discussions at our independent scientific advisory committees but there is currently no established route or systematic way to raise awareness of gaps in research. Over the last year we have worked with the European Medicines Agency on its Regulatory Science

Strategy which has made some progress relevant to this issue. If there are any aspects where you would like additional information, then please let us know.

We have an internal Horizon Scanning Work Group that monitors new areas of research, as well as new technologies, drugs and devices in the healthcare pipeline. This group scans relevant scientific and regulatory medicine journals, as well as many other sources of information (including other medicine regulators, pharmaceutical companies, and health-related charities, as well as UK and global public bodies including the World Health Organisation), also assessing whether there are gaps in the coverage of new research. There is also a review of funding opportunities in the health/science-related fields.

We have conducted some studies in collaboration with other government bodies, such as with Public Health England to monitor the safety and effectiveness of vaccines; and aerosol generation risk in heater-coolers used in cardio-pulmonary bypass as another example. We also stimulated research by a clinical academic department into the burden of adverse drug reactions in UK, and research into the association of antidepressants with suicidal behaviours in children and young people.

A current example of a research gap which we have identified and aim to address is the pharmacokinetic profile of medicines used in pregnancy. We are working with the Medical Research Council to undertake a call for proposals and to locate funding. This strategy has the support of key clinical leaders in obstetric medicine and the Royal College. Examples of previous research studies conducted by MHRA to fill gaps, some in conjunction with external researchers, are annexed here: [Annex 4]

For medicines, if there are specific knowledge gaps about a product at the time of licensing or significant new safety concerns arise post-marketing, then further investigation or follow up by the marketing authorisation holder (MAH) can be requested through the Risk Management Plan. We can request the MAH to conduct a post-authorisation safety study (PASS) and for centrally authorised medicines or where the study is included as a condition of the marketing authorisation, this will be coordinated through the Pharmacovigilance Risk Assessment Committee (PRAC). There are 575 ongoing studies and 684 finalised studies on the PASS register. Details can be found at http://www.encepp.eu/encepp/viewResource.htm?id=29160

For medical devices, it is the manufacturer's responsibility to resolve any gaps in research through further pre or post market surveillance studies/research, involving its notified body as appropriate. This can be in response to requests by a competent authority as part of its market surveillance role (e.g. review of data as part of clinical investigation application identifies gaps and raises it with the manufacturer to address).

We previously ran a Targeted Research Programme, where areas of research need were identified by external parties and bids for funding were received. The proposals submitted were then reviewed and funding was granted for specific vigilance related areas of research. Since then, we have contributed actively to the selection of the EMA's priorities for funded research, and a number of studies included UK patient data. There is also the possibility to address gaps in research through the EMA, and the attached EMA document '*European Medicines Agency process for engaging in externally funded regulatory sciences and process improvement research activities for public and animal health'* sets out criteria that should be followed when considering EMA engagement in externally funded regulatory science activities to support regulatory decision-making for the benefit of public and animal health.

As well as the regulatory centre, the Clinical Practice Research Datalink (CPRD) and the National Institute for Biological Standards and Control (NIBSC) have an active role in

research. We routinely use the data in the Clinical Practice Research Datalink (CPRD) for medicines and vaccines to conduct in-house studies. When conducting these studies, we consult the Commission on Human Medicines Pharmacovigilance Expert Advisory Group, which consists of epidemiologists, clinicians and healthcare professionals, who make recommendations on the study design, subsequent study results and any need for regulatory action. Study protocols are then approved by the Independent Scientific Advisory Committee (ISAC) for the MHRA Database Research prior to the study being conducted. The CPRD data have been used to assess safety signals, assess primary care prescribing patterns, prospectively monitor and assess issues around benefit risk and to monitor the impact of regulatory actions and the effectiveness of risk minimisation measures. The data are also used to support decision-making within regulatory medicines vigilance and for supporting external communications, including the Drug Safety Update publication for example.

Research priorities for NIBSC are identified in line the public health priorities of the Department of Heath which align with the UK Life Science Industrial Strategy. These are overseen by the internal NIBSC Research Oversight Committee and our external Science Advisory Committee to ensure we are researching in the right areas, and to identify possible gaps. The Research Oversight Committee at NIBSC monitors research opportunities through Horizon Scanning activities and engagement with the broader research environment through attending conferences and academic liaison which supports sharing of activities. Research gaps and new research avenues are assessed and prioritised in light of NIBSC overall Science Plan, and new programs are implemented as appropriate. NIBSC scientists actively pursue the publication of their research in open access peer-reviewed journals, whenever possible, to ensure others can access the findings of their research, to help raise awareness around the public health impact of this work.

14. We recognise that the majority of patients will have positive outcomes for any intervention. For a minority the intervention may have life-changing consequences. How are patient interests as a whole balanced in licensing and post-marketing?

As a regulator, our work is underpinned by robust fact-based judgments to ensure that benefits outweigh risks, and patient interests are at the heart of this. Decisions are not always straightforward and are based on data at a population level, which includes a range of individual experiences, either of benefit or of risk. Additionally, safety evidence accrues over time and the benefit:risk can change, necessitating continual review of the evidence by the Agency and the manufacturer throughout the product life-cycle.

Independent expert advice, including the advice of lay representatives, is a key part of our decision-making process. Increasingly we seek the direct input of patients to ensure that risks are well characterised and quantified, considered acceptable in view of known benefits, and clearly communicated.

The Agency will be enhancing our interactions with patients. This will include a step change in our degree of interaction and training for staff to enable them to engage in a more meaningful way when responding to patient concerns. Further than this, we are looking to see where we can embed the patient perspective more effectively into regulatory processes including when a safety issue emerges.

There is no doubt that the personal experiences of patients (both those who have had positive and negative experiences) needs to sit alongside the science and expert advice as early as possible to ensure that the full implications of any subsequent Agency decisions are well-informed, balanced and fully understood. Our aim is to ensure that the views and interests of patients, carers and the public are at the heart of our decision-making and culture.

15. What is the proportion of staff at different levels of the Agency who have a background in manufacturing device industry, and how has that changed over time?

We employ people with a wide range of skills, experience and background, and that includes some with experience of working in industry. Approximately 11% of staff in the medical devices division were previously employed in industry, this is up from 9% 5 years ago. The tables below provide the breakdown. Some staff have worked at hospitals that made medical devices; these hospitals are considered in-house manufacturers and they have been excluded from the figures below.

	Staff number at each grade (current 2019 workforce)	Employed previously in medical device industry
Administrative Officer (AO) Entry level	6	0
Executive Officer (EO)	15	0
Higher Executive Officer (HEO)	23	2
Senior Executive Officer (SEO)	33	3
Grade 7	20	5
Grade 6	10	0
Senior Civil Servant SCS1	6	1
Senior Civil Servant SCS2	1	1
Total	114	12 (11%)

	Staff number at each grade (2014 workforce)	Employed previously in medical device Industry
Administrative Officer (AO) Entry level	13	0
Executive Officer (EO)	12	0
Higher Executive Officer (HEO)	12	4
Senior Executive Officer (SEO)	27	1
Grade 7	11	1
Grade 6	5	0
Senior Civil Servant SCS1	1	0
Senior Civil Servant SCS2	1	1
Total	82	7 (9%)

The Agency maintains a register of financial or other relevant interests held by staff and members of their immediate family. Staff cannot hold direct financial interests in the healthcare industries. All staff are required to declare any interests, as and when they arise, and make an annual declaration. In addition, staff are obliged to consider and declare whether there are any other matters that could be regarded as affecting their impartiality.

Annex 1

Draft proposal for a UK valproate registry

MHRA, Feb 2019

Purpose of this document

The purpose of this document is to summarise the current draft proposal for a UK valproate registry, with updates as of February 2019 following the Valproate Registry Workshop held at the MHRA on 13th February reflected. Key updates made from the previous proposal of January 2019 are highlighted at the end of the paper.

It will be shared with key stakeholders for their comments and remains a working document and hence subject to change.

Introduction and regulatory background

This paper lays out a draft proposal for a UK valproate patient registry.

Sodium valproate is licenced in the UK for the treatment of generalized, partial or other epilepsy, and the treatment of manic episodes in bipolar disorder. It has been licenced in the UK since 1973. It is also known that it is used off-label (outside the licenced indication) for a wider range of psychiatric conditions, migraine prophylaxis, and neuropathic pain and fibromyalgia. Valproate is a known teratogen and, as more data have become available on the extent and characterisation of both the congenital malformation and neurodevelopment disorder risks for children whose mothers took valproate during pregnancy, measures have been taken which have aimed to ensure prescribers and women are aware of the risks and that valproate is only prescribed in women of childbearing potential when enrolled in a Pregnancy Prevention Programme. These changes have included regulatory changes to the licencing of valproate and changes to national and local prescribing guidelines.

The Pregnancy Prevention Programme can be summarised as follows:

Valproate medicines must not be used in women and girls of childbearing potential unless the conditions of the pregnancy prevention plan are met and only if other treatments are ineffective or not tolerated

- *Pregnancy should be excluded before initiation of valproate medicines with a negative plasma pregnancy test, confirmed by a healthcare professional.*
- *Women and girls of childbearing potential must use highly effective contraception if they are able to become pregnant.*
- *At initiation, and at a review at least every year, specialists should discuss the risks of valproate in pregnancy and complete and sign the Risk Acknowledgement Form with the patient (or their parent/caregiver/responsible person).*

The Pregnancy Prevention Programme is supported by additional measures including the introduction of smaller pack sizes (to ensure the patient information leaflet is given), a pictogram and a warning on valproate labelling, and information for patients and prescribers in the form of a patient card and specific booklets.

Following introduction of the most recent regulatory measures, including the introduction of the Pregnancy Prevention Programme, it has been proposed that a registry is established in

order to monitor the use of valproate in girls and women in the UK. The purpose of this paper is to provide further detail on the proposed valproate registry to facilitate wider consultation and to propose next steps.

Initial advice on the need for, and design of, a valproate registry has been sought from a subgroup of the MHRA Valproate Stakeholders Network with additional input from a number of academic and clinical experts and from the Commission on Human Medicines (CHM) Sodium Valproate Expert Advisory Group. The output of this discussion has been incorporated into the proposals in this paper.

Context and need for a valproate registry

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

It has been agreed that a registry for valproate will be highly valuable given the nature and magnitude of the risk, the historical high levels of prescribing, and the extent of the regulatory measures. Considerable support for a registry has been shown by healthcare professionals and patients through the Commission on Human Medicines Valproate Expert Advisory Group and the MHRA Valproate Stakeholders Network.

A number of existing activities making use of routinely captured health-related data as well as more active targeted research are already in place to monitor the impact of, and adherence to, changes in regulatory recommendations including the Pregnancy Prevention Programme. These include ongoing use by the MHRA of data from the Clinical Practice Research Datalink (CPRD), developing use of national databases in England (NHS Business Services Authority and NHS Digital), Scotland (Information Services Division), and Northern Ireland (Health and Social Care Northern Ireland) linking community drug dispensing and maternity services data where these are available, incorporation of data collection specifically on valproate in clinical audits run by healthcare professional organisations, and capture of data on patient experience via surveys conducted by charitable organisations and patient groups.

Further, a number of studies have been requested by the EMA Pharmacovigilance Risk Assessment Committee. These include an extension to the ongoing drug utilisation study using electronic healthcare records databases designed to assess the effectiveness of the valproate Pregnancy Prevention Programme and associated measures and to further characterise prescribing patterns in 5 EU countries (including the UK), an observational study to evaluate and identify the best practices for switching of valproate in clinical practice to provide guidance to clinicians on the switch and discontinuation of valproate, and two surveys (one among healthcare professionals and one among patients) to assess knowledge and behaviour around the valproate Pregnancy Prevention Programme and receipt/use of educational materials.

However, there are clear gaps in the data available and their timeliness of availability, and a need to ensure national prospective long-term monitoring, that necessitate further active data collection in UK. A registry, as opposed to a different study type, would facilitate detailed data capture on adherence to the different aspects of the Pregnancy Prevention Programme beyond what is available from existing routine data collections. It could also gather detailed data on the health and treatment of the mother and foetus during pregnancy and could capture data on pregnancy outcomes, the use of valproate in breastfeeding, and

can be used to further follow up on the child. Any registry could continue to be supplemented by the existing data collection and surveillance work streams discussed above, at least for a period of transition as it becomes established, to optimise the level of evidence available across the range of issues and perspectives.

Purpose of the valproate registry

The three main aims of a valproate registry should be to:

4. *Track the implementation of all aspects of the valproate Pregnancy Prevention Programme and facilitate early identification and investigation of any potential non-compliance and any resulting exposed pregnancies in order to indicate where additional action is required*

   This should be at a national, local, and individual patient level and enable monitoring over different sub-groups of patients and to a sufficient level of detail to inform additional action. It should monitor both prescriber and patient actions regarding the programme and their experiences. It should also help identify areas of good practice to facilitate sharing of good practice and any areas of concern.

5. *Help understand changes in the use of valproate in the UK and the impact of these changes on the health of women with epilepsy and bipolar disorder and their children*

   This will include monitoring where valproate lies in the therapeutic options available for women with epilepsy and bipolar disorder and any unintended consequences of changes in regulation and guidelines, for example in women who switch treatments. This will also provide evidence on the overall success, or otherwise, of risk minimisation measures and inform future regulatory and policy decision-making with regards to valproate and other teratogenic medicines.

6. *Facilitate further research into valproate-exposed pregnancies and childhood outcomes and enable monitoring and follow-up of any identified children born to women taking valproate during pregnancy*

   To do this the registry will need to allow data exchange and linkage to other data sources. It will also help ensure that all identified children potentially affected by valproate, either prospectively or retrospectively, are followed up for appropriate assessment.

Key stakeholders

There are a number of key stakeholders whose support and contributions will underpin the successful implementation of the registry and/or who will benefit from analysis of the data collected. These include:

- Patients and their families
- Healthcare providers and professional groups – including relevant clinicians and professional organisations e.g. the Royal College of Psychiatry, the Association of British Neurologists, the Royal College of Physicians, the Royal College of General Practitioners, the Royal College of Paediatrics and Child Health, the Royal College of Obstetricians and Gynaecologists, the Royal College of Midwives, the Epilepsy Specialist Nurses Association.

- Academic researchers - including the International League Against Epilepsy.
- Public health and regulatory authorities – including the MHRA, NICE, the Care Quality Commission, the General Medical Council, and the General Pharmaceutical Council.
- Government and the National Health Service – including DHSC and the devolved administrations, NHS England, NHS Digital, and NHS Improvement.

Cross-stakeholder collaboration will be required, however the level of involvement in the registry will vary across different stakeholder groups. It is proposed that valproate marketing authorisation holders have no direct role in development, funding, or running of the registry. This is important in order to maintain independence and ensure patient and public confidence in the data.

Principles for registry design

Valproate is used across a broad range of clinical specialisms and therefore patients being prescribed valproate for a diverse range of indications will need to be identified. Given this breadth of prescribing, it is clear that primary care should be one of the key target areas for patient recruitment and follow up. However, detailed data, for example on the exact form of epilepsy for which a patient is being treated, may only be reliably available from secondary care settings.

In order to address the proposed purposes for the registry, a product registry design is recommended. This will mean that all girls and women prescribed valproate would be eligible for inclusion from the time of their first prescription. This approach is required in order to monitor the wider implementation of the pregnancy prevention plan and the impact of changes in prescribing on patient health in particular. The registry should be open to all eligible females prescribed valproate in the UK, either through the NHS or from a private healthcare provider. Eligibility is based upon receipt of a prescription for valproate regardless of indication for treatment.

Regular follow up of all girls and women included in the registry should occur to capture longitudinal detailed data. Follow up should also continue for a period after a woman switches therapy away from valproate, if she does so while still eligible for inclusion in the registry based upon her age, to understand any impact of doing so. It is suggested that specific follow up happens on at least an annual basis for each patient although options for more frequent data collection for a core dataset, where the burden of this can be minimised, should be considered.

There is a clear opportunity for utilising other routine data collection and existing registries to facilitate a valproate registry by minimising duplication and hence burden, increasing robustness, and reducing missing data. These data sources include GP data, and registries including the UK Epilepsy in Pregnancy Registry.

Recruitment and data collection and extraction

Identification and retention of relevant patients could be facilitated by routinely extracted prescribing data. For example, in England, prescriptions dispensed in the community are well captured by the NHS Business Services Authority and can be linked to primary care practices who could then be targeted directly to recruit eligible women. Actively contacting

potentially eligible women themselves, although identifiable via the same data source, would be complicated by risks of accidental disclosure of sensitive patient information but patient identifiers could be provided to GP practices to encourage recruitment and track the coverage of the registry. Additional measures targeting GPs to maximise recruitment can be considered with NHS England. Alternatively, audit functions have already been included in all GP software systems which could be used by a GP practices to identify women prescribed valproate.

Broader communication efforts, likely coordinated by healthcare professional organisations in particular RCPCH, RCP, ABN, ESNA, and RCGP in collaboration with regulators and public health bodies, would be required to support recruitment and follow up within the registry. These could also target patients as a whole to enable eligible women to enrol themselves into the registry if not done so by their prescriber or another healthcare professional.

Routine extracts from GP software could also support data collection and patient follow up, potentially prepopulating case report forms for individual healthcare professional review or for direct reporting to the registry. This would require the availability of appropriate SNOMED codes, sufficient and robust coding of data by GPs, and development and implementation of a tailored extraction and data transfer protocol. Routine data extraction in secondary care is likely to be problematic and therefore active data collection may be required.

Similar opportunities for eligible patient identification and routine data extraction across the devolved nations will be explored.

Enabling patient reporting into the registry, and feedbacking data back to patients, can be a valuable way to support strong data collection. Consideration should be given to development of an online portal enabling patients to consent and submit data directly to the registry and to enable them to monitor the data captured on them.

Primary dataset and Patient Consent

A core primary data set for collection should be established which would include data on patient characteristics including medical history and the exact indication for treatment with valproate, prior use of valproate and alternative therapeutic options, details on future valproate prescriptions and switches of treatment, all other concurrent medicines, major clinical events including pregnancy and SUDEP for example, and sufficient data to monitor compliance with the pregnancy prevention programme. The extent of this data set should be kept to a minimum to support data completeness and registry coverage.

Any elements of this core data set that might be extracted from existing routinely collected data sources without specific individual patient consent should be identified and a mechanism put in place to do so routinely in order to maximise coverage of at least basic data elements and to help understand the reach of the wider registry. The need for any additional data collection should be carefully reviewed in order to ensure only essential data are captured and any additional burden is reduced. Where data collection requires patient consent then a mechanism for doing and recording this will need to be established.

Data linkage

Provisions should be made to enable data sharing with other registries e.g. the UK Epilepsy in Pregnancy Registry to enable additional detailed follow up of pregnancies and resulting children and to ensure any valproate exposed pregnancies reported to them are also included in the valproate registry. Wider linkage of the valproate registry to national data sources including NHS Digital Maternity Services Dataset could also enable some data from secondary care settings to be captured via routine extraction further reducing burdens on healthcare providers and increasing data completeness. The registry would need to be able to flag any children born following exposure to valproate to ensure their continued monitoring within the healthcare system. Further data collection from secondary care would require active contribution from prescribers or specialist nurses.

Linked to the ability of the registry to follow up exposed children is its potential role in facilitating further research. The extent of this should be further considered as the registry develops.

Leadership and governance

A steering group should be established to oversee design of the registry and its ongoing management. Experience shows that those registries led by invested academic and clinical groups have the greatest success, but a lead organisation or lead individuals would need to be identified. In this instance, further leadership from the healthcare system is also required.

The expertise required on the steering group includes relevant clinical knowledge, regulatory knowledge, registry science and implementation, data collection technology and database management, data protection and project management. Access to legal advice and quality assurance experience is also needed.

Organisations that should be involved therefore include representatives of the relevant clinical specialisms including neurology, psychiatry, and general practice, the Department of Health and Social Care, NHS England, NHS Digital, the MHRA, and the devolved governments. Patients should also be represented on the steering group. Consideration should be given for the need for other public or regulatory input which could also be on an ad hoc basis.

This steering group would also control access to the data by other researchers and should deliver annual reports from the registry to public health and government stakeholders as well as meeting any funder requirements

It is recommended that representatives from the pharmaceutical industry are not involved in the design or governance of the registry. It is proposed that implementation and maintenance of the registry is led by DHSC, the NHS, the devolved administrations, and the MHRA following the model of other registries including the breast and cosmetic implant registry.

Patient involvement

As already highlighted patient involvement in the development and operation of the valproate registry will be essential. Use of the newly launched NHS app, when it is sufficiently developed and established, and/or a specific patient web portal could support eligible patient identification and data collection and feedback. This could enable data to be gathered on the challenges faced by female patients and families in accessing information,

obtaining regular clinical review, the children affected by valproate in-utero and on the wider patient experience including their interactions with wider healthcare professionals including pharmacists. As already highlighted, patient involvement can also encourage higher quality data capture.

Patient group input into the registry design should be sought at an early stage in the development to maximise the benefit of further patient involvement and identify their specific requirements for a registry.

Challenges for successful implementation

Wide engagement across a range of stakeholders including patient groups is required in order to operate a successful registry. Its initiation is already supported by organisations across the public sector and healthcare professional organisations already engaged with the issues via the MHRA Valproate Stakeholder Network. However, further coordinated communication efforts will be required to maximise recruitment and drive high quality data collection.

Measures need to be taken to maximise data collection and reduce the impact of this on the representativeness and hence the value of the registry. As already highlighted identifying where data can be routinely extracted from existing data sources both with and without individual patient consent will be vital. However, changes may need to be made to the way certain data elements are captured in order to do this effectively e.g. the addition of new SNOMED codes for recording completion of different elements of the pregnancy prevention programme.

Collection of data from the private sector is likely to be more difficult but particularly important given the established extensive use of valproate and it potential for considerable off-label use which may be seen more frequently in the private setting. Involvement of the Private Healthcare Information Network may be beneficial.

If specific concerns are identified with individual patients or if more general issues, for example a new potential drug safety signal, are raised by the data collected within the registry it is important that the responsibility of the registry steering group is clearly defined. Ensuring a role of for relevant regulatory organisations is likely to be important in this respect.

Learning from other successful registries

It will be important to learn from existing registries in other clinical areas to understand how they operate and where they have successfully supported the accumulation of new evidence and increased our understanding of safety and benefitted patients i.e. The British Society for Rheumatology Biologics Register (BSRBR), the UK Breast and Cosmetic Implant Registry (BCIR), the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry, and the European Society for Blood and Marrow Transplantation (EBMT) patient registry.

In the first instance comparison with a similar registry being proposed in Ireland should be explored. This is being led by the Health Service Executive in Ireland. In the future, comparison with other data captured internationally would be valuable.

Funding and resource requirements

We propose that the registry should be funded from public resources. It could be established for England in the first instance but the inclusion of patients from Scotland, Wales, and Northern Ireland should be enabled by allowing wider collection by NHS Digital supported by the devolved administrations. The data controllers will need to work closely with the steering committee to enable linkage of the data to other data sources and secondary use of the data by researchers, subject to their obtaining additional funding.

Extrapolating from currently data on prescribing in England[3] suggests that in the region of 20,000 women aged 14-45 years were dispensed a prescription for valproate in the UK between October and December 2018 with an additional 4,000 girls aged <14 also receiving a prescription. This reflects a declining trend in use. Women will remain eligible for inclusion as long as they are being prescribed valproate, and for a specified duration after stopping valproate. There should be no cap on the number of patients included in the registry. Therefore, the registry will likely need to enable active data collection from this number of women at least at its start. Furthermore, the registry will need to continue for an extended period until at least a time that there was confidence that the regulatory measures have been effective and that there were no unintended pregnancies exposed to valproate. This duration is currently unclear, so the intention should be that it is open-ended.

Resource requirements from individual organisations to support their contribution to the registry will also need to be identified.

Next steps

Further efforts are now required to bring together all the key organisations to lead on development of the registry including establishing of a registry steering group to draw up a full study proposal and progress discussions on funding.

It has been suggested that a pilot study or feasibility assessment could be useful in designing an optimal registry. Specifically, a pilot could help address questions on the specific data to be captured on patient medical histories and pregnancies and their outcomes, how to optimise the value of patient involvement, and issues of patient retention.

Key updates made following the Valproate Registry Workshop meeting of 13th February 2019

Section	Changes made
Purpose of the valproate registry	Aim 1: The need for the registry to collect data on the actions and experienced of the prescriber and the patient has been highlighted. Aim 3: The role of the registry in ensuring any children retrospectively identified as having been exposed in utero are also followed up has been added.

[3] https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/sodium-valproate

Key stakeholders	The Epilepsy Specialist Nurses Association, the International League Against Epilepsy, and NHS Improvement have all been added as key stakeholders
Recruitment and data collection and extraction	Clarifications have been made as prescribing is identifiable at a GP practice level but not to an individual GP.
Data linkage	The potential role of the registry in facilitating further research is highlighted here with recognition it needs further consideration.
Primary dataset and Patient Consent	The need to capture data on the exact indication for treatment (including the form of epilepsy) as well as prior use of valproate and alternative therapeutic options has been added to the discussion on the core primary data set.
Challenges for successful implementation	Potential governance issues in the case that a new safety concern is identified by the registry are raised.
Funding and resource requirements	Amended to reflect support of Valproate Registry Workshop for seeking funding from central public finances.
Next steps	Updated to reflect proposed current next steps as of Feb 2019.

Katherine Donegan, Pharmacoepidemiology Research and Intelligence Unit Manager, VRMM, MHRA

25th February 2019

Annex 2

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON TOXICITY, CLINICAL TRIALS AND THERAPEUTIC EFFICACY

MEDICINES ACT 1968 - APPLICATION FOR A PRODUCT LICENCE.

No.	PL/0623/0001
Date received	7th Sept. 1971
Meeting	January 1972
Previously considered	-
Therapeutic class	Anti-convulsant

SUMMARY AND REPORT

1. LICENCE TO BE HELD BY: Pharmacy Products U.K. Ltd., London, W.1.

2. PERIOD OF VALIDITY: 5 years.

3. NAME UNDER WHICH THE PRODUCT IS TO BE MARKETED: Labazene Tablets.

4. DESCRIPTION AND COMPOSITION OF DOSAGE FORM:

Uncoated tablets containing Sodium dipropyl acetate 200mg.

5. MANUFACTURER:

5.1. of drug substance: Sapchim-Fournier-Cimag, Paris.

5.2. of dosage form: Arthur H. Cox, Brighton.

6. CHEMISTRY AND PHARMACY:

6.1. Active Ingredient - Chemical Identity

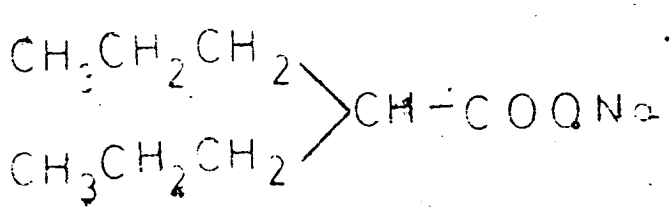
Names -

(i)	Approved Name	Valproic Acid (Sodium Salt)
(ii)	INN/USAN	None
(iii)	Laboratory Code	S2411N Sodium DPA
(iv)	Chemical Name	Sodium Dipropylacetate
(v)	Alternative Chemical Names	Sodium propyl-2-pentanoate Sodium propyl-2 valerionate
(vi)	Proprietary Name	Labazene
(vii)	Other Names	Depakine, Eurekene, Depakene.

Description

A hygroscopic, white, microcrystalline powder.

Structural Formula



6.2. Dosage Form complete formula

Active constituent	mg/tab
Sodium Dipropyl Acetate	200
Other constituents	
Starch BP	150
Kaolin BP	20
Magnesium Stearate BP	10
Colloidal Silicone Dioxide USNF	20

7. RECOMMENDED CLINICAL USE (Vol, 1, p. 112)

1) Generalised epilepsy (petit mal, grand mal, mixed epilepsy).
2) Focal epilepsy (psychomotor epilepsy).
3) Other epilepsy (myoclonic, akinetic).

8. RECOMMEND DOSAGE (Vol 1, p. 112)

Adults 1000-1400mg/day (divided doses b.d. or t.d.s.)

Children

20-30mg/kg (/day); minimal dose 400mg/day irrespective of age (divided doses b.d. or t.d.s.).

Valproic acid may be given with all other anti-epileptic drugs. With patients receiving other medication, valproic acid is "initiated progressively to reach the optimum dose in about 10 days. The previous medication is then reduced."

9. SIDE-EFFECTS (Vol 1, p.112)

Some patients have gastro-intestinal symptoms at beginning of treatment (nausea, "gastralgia", controlled by metoclopramide).

10. PRECAUTIONS AND CONTRAINDICATIONS (Vol 1, p.112)

1) Valproic acid potentiates phenobarbitone, the dosage of which should be reduced.

The dosage of other neuroleptic drugs should also be reduced.

2) Valproic acid is not indicated in "BJ epilepsy" (Bravais-Jacksonian).

3) Valproic acid must not be administered with "carbonated" or alcoholic drinks.

(NB. The draft technical booklet warns that valproic acid causes false positives in tests for urinary ketones).

11. PHARMACODYNAMICS (Vol 1)

A. Swinyard (pp. 119-167)

(i) Anti-convulsant Activity

a) Time to Peak Effects (pp. 121-124)

Using MES, valproic acid (500-600mg/kg) orally in rats and mice

gave peak effect in ½-1 hour c.f. 3 hours with phenobarbitone (6-35mg/kg) and phenytoin (15-40mg/kg). After i.v. administration, peak effect of valproic acid occurred at ¼-½ hour c.f. approximately 2 hours for phenobarbitone.

Judged from toxic effects, time to peak effect i.p. in rabbits and rats was ½ hour.

(NB. Concluded that valproic acid has "more rapid onset of action than clinically established anti-convulsants" but effects were also generally of much shorter duration.)

b) Comparative Anti-Convulsant Activity (pp. 126-134)

Assessed by MES, anti-Metrazol and minimal electroshock seizure threshold in mice and rats. Therapeutic ratios calculated from ataxia-producing dose and anti-convulsant ED_{50}. Valproic acid was generally less potent than phenobarbitone, phenacemide and phenytoin and more potent than troxidone; therapeutic ratio was less than with phenacemide and phenobarbitone but marginally better than troxidone and phenytoin.

Valproic acid was active against MES and Metrazol in cats and rabbits but therapeutic ratios were poor (0.3-1.6).

c) Other Anti-Convulsant Activity (pp. 135-136)

Prevented maximal audiogenic seizures (O'Grady mice) and CO_2 withdrawal seizures (Sprague-Dawley rats) with ED_{50} values of 142 and 146mg/kg and therapeutic ratios of 2.9 and 1.3 respectively.

ii) Other CNS Actions

a) Righting Reflex in Mice (pp. 135-137)
Less sedative than phenobarbitone but more sedative than troxidone or phenacemide.

b) Hexobarbitone Sleeping Time in Mice (pp. 135-139)

Equivalent fractions of the ataxia-producing dose prolonged hexobarbitone sleeping time more than phenobarbitone, phenacemide or troxidone, but less than phenytoin.

c) Tranquillising Activity (pp. 138-141)

No significant activity in ataxia-producing doses (amphetamine toxicity in aggregated mice; conditioned avoidance in rats).

d) Analgesic Activity (pp. 138-144)

Valproic acid, phenobarbitone and troxidone in ataxia-producing doses had no effect on rat tail flick whereas codeine was significantly analgesic.

e) Anti-pyretic Activity (pp. 144-147)

No effect on normal body temperature in mice and rats; inactive against yeast-induced hyperthermia in rats.

f) Spontaneous Motor Activity (p. 148)

No significant effect.

iii) Autonomic and Cardiovascular (pp. 148-151)

In anaesthetised cats, 25-100mg/kg valproic acid i.v. reduced blood pressure, not modified by autonomic blocking agents. No significant changes in heart rate, ECG, respiration or nictitating membrane.

iv) Other Pharmacological Properties

a) Anti-Histamine (pp. 151-153)

Inactive against histamine-induced asthma and egg white anaphylactic shock in guinea-pigs.

b) Renal Effects (pp. 153-156)

No significant diuretic or anti-diuretic effect.

c) Smooth Muscle (pp. 153, 157-158)

Spasmolytic action on rat ileum at 2×10^{-3} g/ml.

d) Coagulation and Prothrombin Times (p. 157)

Inactive at maximal anti-convulsant doses.

e) Acid-base balance (pp. 157-161)

MES ED_{50} dose inactive; ED97 gave hyperventilation and slight respiratory alkalosis.

f) Oxygen Consumption (p. 159)

Some reduction with ataxia-producing doses.

B) C. Carraz (pp. 169-209)

Results in routine laboratory tests broadly similar to those described in previous report.

ECoG recordings in rats showed pronounced antagonism of Metrazol-induced voltage changes (pp. 180-181)

Doses of generally 200mg/kg valproic acid i.p. were without anti-convulsant activity against strychnine, picrotoxin, thuyone or cocaine (pp. 185-189).

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Vitrually complete duplication of above report by Carraz.

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Wistar male rats dosed i.g. for 111 days with increasing doses of

phenobarbitone, phenytoin, ethosuccimide, troxidone or valproic acid; treatment then abruptly stopped.

Sudden withdrawal of valproic acid caused minimal signs (few leg extensions) c.f. total or partial convulsive seizures after withdrawal of standard drugs.

Concurrent dosing with valproic acid during last 5 days of treatment with standard drugs increased withdrawal signs.

Comcurrent dosing with valproic acid during last 5 days of treatment and continued during withdrawal of standard drugs reduced withdrawal signs.

Results explained in terms of altered brain GABA levels.

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Most pronounced effect was abolition of after discharges and associated grand mal seizures.

15. METABOLIC/BIOCHEMICAL (Vol 1)

i) Liver-damaged nephrectomised rats (pp. 162-166)

Pre-treatment with CCl_4 failed to prolong anti-convulsant effect whereas prior nephrectomy significantly prolonged activity.

Renal excretion and little metabolism or excretion by liver suggested.

ii) Absorption and Distribution (Separate Paper)

200mg/kg orally of drug labelled with C^{14} in carboxyl group.

a) Autoradiography

Activity present in blood and several organs after 6-12 minutes, maximal at 1 hour, declining at 2 hours and almost absent by 24 hours. Most activity in liver, lungs, kidney and testes.

b) Organ Distribution

Scintillation counting of organ extracts gave broadly similar results to autoradiography.

Liver and muscle contained highest percentages (6%) of administered radioactivity.

c) Elimination

Blood levels maximal at 30 minutes, almost absent by 24 hours.

Urinary excretion evident at 5 minutes; approximately 70% of administered dose excreted by 24 hours.

Approximately 2% of dose excreted as CO_2 in 24 hours; less than 3% in faeces.

Biliary radioactivity maximal at 1 hour, falling rapidly until 4 hours when approximately 7% of administered dose had been excreted. Enterohepatic circulation demonstrated by donor-recipient experiments. Radiochromatograms of bile showed spots corresponding to unchanged valproic acid and 6 unidentified metabolites.

d) Placental Passage

5-10μC/animal on day 15 of gestation in rats and day 10 in mice.

Autoradiography and scintillation counting showed negligible amounts of drug in foetus and only low concentrations in placenta.

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200 and 400mg/kg valproic acid significantly raised brain GABA without changing levels of aspartic or glutamic acids, glutamine or glycine.

Raised GABA levels not due to increased formation but may be related to in vitro inhibition of GABA-T.

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In rabbits on high cholesterol diet, 250mg/kg i.v. valproic acid for 40 and 60 days claimed unconvincingly to lower blood cholesterol levels but on return to normal diet blood levels definitely returned to normal more rapidly than in untreated animals. 125 and 250mg/kg i.v. valproic acid reduced fatty infiltration of liver macroscopically and microscopically.

Judged from BSP excretion, 250mg/kg valproic acid (like betaine) protects guinea-pigs against hepatotoxic effect of CCl_4.

The data is used to evidence lack of hepatotoxicity of therapeutic doses of valproic acid.

16. SINGLE DOSE TOXICITY STUDIES

Vol 1, pp. 123-126, 234-241.

Species	**Animals/ Group	Route	Duration (Days)	LD_{50} (mg/kg)
Mouse*	8	p.o.	1	1,700 (1,546-1,870)
	8	i.p.	1	1,060 (982-1,145)
	10	i.p.	-	832
	10	s.c.	-	860
	5	i.v.	-	>400
Rat*	8	p.o.	1	1,530 (1,224-1,913)
	8	i.p.	1	790 (738-845)
Rabbit	4	i.p.	1	1,200 (952-1,612)
Guinea Pig		p.o.	-	824
Cat	4	i.p.	1	565 (479-667)

Footnote

* Death by respiratory failure followed by circulatory collapse.
** Apparently females only used.

Judged by LD_{50} values and doses producing ataxia, valproic acid is of intermediate toxicity compared with phenobarbitone, phenytoin, troxidone and phenacemide.

17. REPEATED DOSE TOXICITY STUDIES (Vol 1)

Only minimal data is presented.

i) Mouse (pp. 241-243)

Swiss; females only.

Groups of 30 given 0,50,400 or 800mg/kg/day i.g. 5 days/week.

Top Dose

23 deaths by day 4. After 10 days 2 surviving animals autopsied: no macroscopic or microscopic lesions.

Middle Dose

9 deaths by 23 weeks. Autopsy of remaining animals: no macroscopic

or microscopic abnormalities.

Bottom Dose

For 46 weeks. No difference from controls in mortality, weight gain, macroscopic or microscopic findings.

ii) Rabbit (pp. 246-247)

4 males, 4 females dosed orally with 200mg/kg/day for 21 weeks. No control group.

Mortality: 2. Three females littered in 4th month. No abnormalities macroscopically or microscopically.

iii) Guinea Pig (pp. 243-246)

a) Oral Dosing

Unbalanced groups of 5-10 animals given 0,50,200 or 500mg/kg/day i.g. for 17 weeks.

Half of 200mg/kg animals dosed b.d.

Mortality nil in control and low dose. 5/10 200mg/kg and 5/7 500mg/kg animals died by end of study.

No differences between groups in body weight gain, haematology or at autopsy. No report on histopathology.

b) Intraperitoneol Dosing

2 groups of 10 animals dosed i.p. for 60 days with 0 or 100mg/kg.

Mortality nil. No differences between groups in weight gain, haematology, microscopic or macroscopic findings.

18. TERATOLOGY (Vol 1)

i) Mouse (pp. 287-305)

R.A.P. mice (n=31-36) given 0,30 or 90mg/kg of drug in diet for 8 days before mating and throughout gestation until littering.

Maternal

Pregnancy rate high in all groups. Foetuses/litter variable in all groups, lowest in controls (5-6/litter). Time to littering extremely variable (20-56 days in controls).

Foetal

No differences between groups in mortality or body weight at birth and at 30 days.

No malformations but "morphological aspect" only examined.

ii) Rat (pp. 306-347)

Wistar rats (n=31-35) given 0,30 or 90mg/kg i.g from 8 days before mating up to caesarean section (10 rats/group, day 21) or littering.

Maternal

Pregnancy rate, foetuses/litter, resorptions and average placental weights comparable between groups at caesarean section.

At birth, foetuses/litter lowest in controls. Time to littering extremely variable (controls 22-55 days).

Foetal

No malformations by gross morphological examination at caesarean.

No drug-related differences in foetal mortality or body weight up to 30 days after birth. No malformations by gross morphology; no differences in weights of major organs at autopsy.

iii) Rabbit (pp. 348-367)

15 NZW given 45mg/kg orally from 3 days before mating and throughout gestation to caesarean section (day 29). 10 control animals.

No differences between groups in pregnancy rate, foetal weights or number of implantations; viable foetuses low in treated animals whereas resorptions higher in controls.

Foetuses adequately examined by dissection and alizarin; two major malformations in treated group (cleft palate; coxo-femoral luxation), one in control (coelosomia, aberrant tail and hind limbs) considered spontaneous.

19. CLINICAL STUDIES

A. Volunteers (Vol, 1)

Caille (pp. 369-407)

Double-blind, cross-over study of 225-1000mg/day of valproic acid in 3 normal and 3 psychiatric "volunteers".

2/6 had diarrhoea; further 2/6 had tachycardia of 20 beats/min.

No significant change in EEG, wakefulness or urinary steroid excretion.

Poor study; poor translation.

B. Patients (Vol 2)

i) Mises (pp. 19-182)

Open study in 28 male and 45 female patients (38 children aged 9-15; 35 adults aged 16-80). All except two were confirmed epileptics, regularly receiving a variety of standard therapy.

400mg-1,400mg valproic acid for an average duration of 8 months (2-12 months) claimed to be effectively anti-epileptic: substituted completely for other anti-epileptic drugs in 21 patients and allowed dose reduction of standard drugs in most of remainder.

Claim that overall results with valproic acid indicate improvement, 57.5%; no change, 32.8%, deterioration, 9.7%. Drug well-tolerated but "tendency to neutropenia".

This catalogue of case histories was apparently the "official clinical trial" for marketing clearance in France although providing no objective proof of either efficacy or side-effects.

ii) Huertas (pp. 184-279)

Open study of valproic acid on agressive behavioural disturbances in 27 epileptic and 8 non-epileptic mental patients. Initial daily dose 200mg, increased to 1200-1400mg (maximum 1800mg) for 2-13 months. Most patients concurrently treated with other anti-convulsant and psychoactive drugs.

Concluded valproic acid alone is insufficient to control epilepsy but is beneficial with barbiturates. On behavioural symptoms, reduction in dosage of neuroleptic drugs was possible. Tolerance good.

Another catalogue of case histories: objective assessment impossible.

iii) Various Authors (pp. 281-294)

Abstracts or brief assertions from 21 studies claiming effective anti-epileptic action, good tolerance and emphasising associated improvement of behavioural syndromes.

No objective data reported for assessment.

iv) Tchicaloff (pp. 296-307)

Open study in 104 in-patients with clinical and EEG evidence of epilepsy given 400-1,200mg/day of valproic acid for up to 14 months.

All patients were under treatment with other drugs: valproic acid in most cases enabled doses of standard drugs to be reduced or replaced.

Results were 53 "very satisfactory"; 37 "satisfactory"; 8 "failures" and 6 "discontinued treatment" (g.i., 3; exacerbation of petit mal, 2; somnolence, 1).

Tolerance described as excellent; blood counts, liver enzymes and serum electrophoresis unaffected (no data given).

A less anecdotal but still subjective paper.

v) Matthes and Schmutterer(pp. 309-319)

Open study during $2\frac{1}{2}$ years of up to 3g/day valproic acid (mean 800-1,200mg) in 40 patients with various types of epilepsy (in 36 additional to existing treatment, in 4 as the only drug).

Best results (8/11) obtained in petit mal (3 c.p.s.) with absences. Benefit in other epilepsies less certain. No psychotropic effect.

Apart from some gastric effects and somnolence, good tolerance claimed; no allergic, haematological or renal toxicity, but no data given.

vi) Zelvelder (pp. 324-328)

Double-blind, randomised, cross-over study of valproic acid (400-1,800mg/day and placebo in 42 in-patients with various types of epilepsy and with epileptic symptoms at least 4 days/week for 3 weeks preceeding trial. Previous treatment with standard drugs continued unchanged throughout trial. Severity of disease scored numerically.

Valproic acid gave a statistically significant improvement (50% or more in symptom score) in 1 out of 3 patients.

3/42 patients dropped out of trial because of nausea headaches or mental dullness. Other p-tients had similar side-effects which improved with continued therapy.

The only objective study provided in the submission.

vii) Scollo-Lavizzari and Corbat (pp. 330-337)

Report of apparently open trial of 600-1,200mg/day valproic acid in various forms of epilepsy, claiming good efficacy and lack of toxicity.

No objective data provided.

20. MEDICAL COMMENT

Valproic acid is an anti-convulsant drug of novel chemical type which has been marketed in France since 1967; approximately 30-40,000 patients have received the drug and approximately 20,000 patients are currently under treatment.

In animals, its anti-convulsant potency is generally less than phenobarbitone, phenacemide or phenytoin and greater than troxidone. It seems to act by raising brain GABA levels consequent upon inhibition of GABA-T.

Only minimal data is provided of repeated dose toxicity studies in mouse, rabbit and guinea-pig. No further information has been requested from the manufacturer because the design and scope of the experiments are inadequate to provide evidence on the potential hazard of the drug in man.

Teratology studies were made in three species at one or two dose levels, the highest of which was only three times the recommended maximal human therapeutic dose of 30mg/kg. The timing of drug administration seems to have aimed at a combined fertility/teratogenic study but, in general, the data falls far short of the normal standards for either.

Apart from the trial by Zelvelder (19, B, vi) the clinical studies are largely anecdotal and fail to provide objective evidence of efficacy or safety.

21 RECOMMENDATION

The Committee may feel that a Product Licence should not be granted because of.

i) inadequate toxicological and teratological data in animals,

ii) inadequate evidence of efficacy and safety in clinical studies.

ABW.

Annex 3

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON TOXICITY, CLINICAL TRIALS AND THERAPEUTIC EFFICACY

MEDICINES ACT 1968 - APPLICATION FOR A PRODUCT LICENCE.

No.	PL/0623/0001
Date received	7th Sept. 1971
Meeting	January 1972
Previously considered	-
Therapeutic class	Anti-convulsant

SUMMARY AND REPORT

1. LICENCE TO BE HELD BY: Pharmacy Products U.K. Ltd., London, W.1.

2. PERIOD OF VALIDITY: 5 years.

3. NAME UNDER WHICH THE PRODUCT IS TO BE MARKETED: Labazene Tablets.

4. DESCRIPTION AND COMPOSITION OF DOSAGE FORM:

Uncoated tablets containing Sodium dipropyl acetate 200mg.

5. MANUFACTURER:

5.1. of drug substance: Sapchim-Fournier-Cimag, Paris.

5.2. of dosage form: Arthur H. Cox, Brighton.

6. CHEMISTRY AND PHARMACY:

6.1. Active Ingredient - Chemical Identity

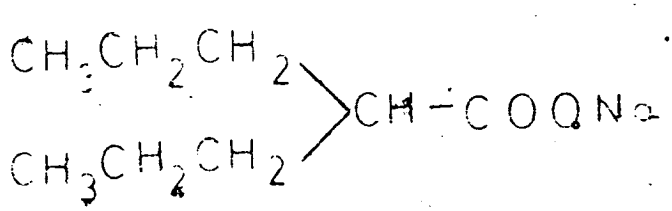
Names -

(i)	Approved Name	Valproic Acid (Sodium Salt)
(ii)	INN/USAN	None
(iii)	Laboratory Code	S2411N Sodium DPA
(iv)	Chemical Name	Sodium Dipropylacetate
(v)	Alternative Chemical Names	Sodium propyl-2-pentanoate Sodium propyl-2 valerionate
(vi)	Proprietary Name	Labazene
(vii)	Other Names	Depakine, Eurekene, Depakene.

Description

A hygroscopic, white, microcrystalline powder.

Structural Formula



6.2. Dosage Form complete formula

Active constituent	mg/tab
Sodium Dipropyl Acetate	200
Other constituents	
Starch BP	150
Kaolin BP	20
Magnesium Stearate BP	10
Colloidal Silicone Dioxide USNF	20

7. RECOMMENDED CLINICAL USE (Vol, 1, p. 112)

1) Generalised epilepsy (petit mal, grand mal, mixed epilepsy).
2) Focal epilepsy (psychomotor epilepsy).
3) Other epilepsy (myoclonic, akinetic).

8. RECOMMEND DOSAGE (Vol 1, p. 112)

Adults 1000-1400mg/day (divided doses b.d. or t.d.s.)

Children

20-30mg/kg (/day); minimal dose 400mg/day irrespective of age (divided doses b.d. or t.d.s.).

Valproic acid may be given with all other anti-epileptic drugs. With patients receiving other medication, valproic acid is "initiated progressively to reach the optimum dose in about 10 days. The previous medication is then reduced."

9. SIDE-EFFECTS (Vol 1, p.112)

Some patients have gastro-intestinal symptoms at beginning of treatment (nausea, "gastralgia", controlled by metoclopramide).

10. PRECAUTIONS AND CONTRAINDICATIONS (Vol 1, p.112)

1) Valproic acid potentiates phenobarbitone, the dosage of which should be reduced.

The dosage of other neuroleptic drugs should also be reduced.

2) Valproic acid is not indicated in "BJ epilepsy" (Bravais-Jacksonian).

3) Valproic acid must not be administered with "carbonated" or alcoholic drinks.

(NB. The draft technical booklet warns that valproic acid causes false positives in tests for urinary ketones).

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Judged from toxic effects, time to peak effect i.p. in rabbits and rats was ½ hour.

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16. SINGLE DOSE TOXICITY STUDIES

Vol 1, pp. 123-126, 234-241.

Species	**Animals/ Group	Route	Duration (Days)	LD_{50} (mg/kg)
Mouse*	8	p.o.	1	1,700 (1,546-1,870)
	8	i.p.	1	1,060 (982-1,145)
	10	i.p.	-	832
	10	s.c.	-	860
	5	i.v.	-	>400
Rat*	8	p.o.	1	1,530 (1,224-1,913)
	8	i.p.	1	790 (738-845)
Rabbit	4	i.p.	1	1,200 (952-1,612)
Guinea Pig		p.o.	-	824
Cat	4	i.p.	1	565 (479-667)

Footnote

* Death by respiratory failure followed by circulatory collapse.
** Apparently females only used.

Judged by LD_{50} values and doses producing ataxia, valproic acid is of intermediate toxicity compared with phenobarbitone, phenytoin, troxidone and phenacemide.

17. REPEATED DOSE TOXICITY STUDIES (Vol 1)

Only minimal data is presented.

i) Mouse (pp. 241-243)

Swiss; females only.

Groups of 30 given 0,50,400 or 800mg/kg/day i.g. 5 days/week.

Top Dose

23 deaths by day 4. After 10 days 2 surviving animals autopsied: no macroscopic or microscopic lesions.

Middle Dose

9 deaths by 23 weeks. Autopsy of remaining animals: no macroscopic

or microscopic abnormalities.

Bottom Dose

For 46 weeks. No difference from controls in mortality, weight gain, macroscopic or microscopic findings.

ii) Rabbit (pp. 246-247)

4 males, 4 females dosed orally with 200mg/kg/day for 21 weeks. No control group.

Mortality: 2. Three females littered in 4th month. No abnormalities macroscopically or microscopically.

iii) Guinea Pig (pp. 243-246)

a) Oral Dosing

Unbalanced groups of 5-10 animals given 0,50,200 or 500mg/kg/day i.g. for 17 weeks.

Half of 200mg/kg animals dosed b.d.

Mortality nil in control and low dose. 5/10 200mg/kg and 5/7 500mg/kg animals died by end of study.

No differences between groups in body weight gain, haematology or at autopsy. No report on histopathology.

b) Intraperitoneol Dosing

2 groups of 10 animals dosed i.p. for 60 days with 0 or 100mg/kg.

Mortality nil. No differences between groups in weight gain, haematology, microscopic or macroscopic findings.

18. TERATOLOGY (Vol 1)

i) Mouse (pp. 287-305)

R.A.P. mice (n=31-36) given 0,30 or 90mg/kg of drug in diet for 8 days before mating and throughout gestation until littering.

Maternal

Pregnancy rate high in all groups. Foetuses/litter variable in all groups, lowest in controls (5-6/litter). Time to littering extremely variable (20-56 days in controls).

Foetal

No differences between groups in mortality or body weight at birth and at 30 days.

No malformations but "morphological aspect" only examined.

ii) Rat (pp. 306-347)

Wistar rats (n=31-35) given 0,30 or 90mg/kg i.g from 8 days before mating up to caesarean section (10 rats/group, day 21) or littering.

Maternal

Pregnancy rate, foetuses/litter, resorptions and average placental weights comparable between groups at caesarean section.

At birth, foetuses/litter lowest in controls. Time to littering extremely variable (controls 22-55 days).

Foetal

No malformations by gross morphological examination at caesarean.

No drug-related differences in foetal mortality or body weight up to 30 days after birth. No malformations by gross morphology; no differences in weights of major organs at autopsy.

iii) Rabbit (pp. 348-367)

15 NZW given 45mg/kg orally from 3 days before mating and throughout gestation to caesarean section (day 29). 10 control animals.

No differences between groups in pregnancy rate, foetal weights or number of implantations; viable foetuses low in treated animals whereas resorptions higher in controls.

Foetuses adequately examined by dissection and alizarin; two major malformations in treated group (cleft palate; coxo-femoral luxation), one in control (coelosomia, aberrant tail and hind limbs) considered spontaneous.

19. CLINICAL STUDIES

A. Volunteers (Vol, 1)

Caille (pp. 369-407)

Double-blind, cross-over study of 225-1000mg/day of valproic acid in 3 normal and 3 psychiatric "volunteers".

2/6 had diarrhoea; further 2/6 had tachycardia of 20 beats/min.

No significant change in EEG, wakefulness or urinary steroid excretion.

Poor study; poor translation.

B. Patients (Vol 2)

i) Mises (pp. 19-182)

Open study in 28 male and 45 female patients (38 children aged 9-15; 35 adults aged 16-80). All except two were confirmed epileptics, regularly receiving a variety of standard therapy.

400mg-1,400mg valproic acid for an average duration of 8 months (2-12 months) claimed to be effectively anti-epileptic: substituted completely for other anti-epileptic drugs in 21 patients and allowed dose reduction of standard drugs in most of remainder.

Claim that overall results with valproic acid indicate improvement, 57.5%; no change, 32.8%, deterioration, 9.7%. Drug well-tolerated but "tendency to neutropenia".

This catalogue of case histories was apparently the "official clinical trial" for marketing clearance in France although providing no objective proof of either efficacy or side-effects.

ii) Huertas (pp. 184-279)

Open study of valproic acid on agressive behavioural disturbances in 27 epileptic and 8 non-epileptic mental patients. Initial daily dose 200mg, increased to 1200-1400mg (maximum 1800mg) for 2-13 months. Most patients concurrently treated with other anti-convulsant and psychoactive drugs.

Concluded valproic acid alone is insufficient to control epilepsy but is beneficial with barbiturates. On behavioural symptoms, reduction in dosage of neuroleptic drugs was possible. Tolerance good.

Another catalogue of case histories: objective assessment impossible.

iii) Various Authors (pp. 281-294)

Abstracts or brief assertions from 21 studies claiming effective anti-epileptic action, good tolerance and emphasising associated improvement of behavioural syndromes.

No objective data reported for assessment.

iv) Tchicaloff (pp. 296-307)

Open study in 104 in-patients with clinical and EEG evidence of epilepsy given 400-1,200mg/day of valproic acid for up to 14 months.

All patients were under treatment with other drugs: valproic acid in most cases enabled doses of standard drugs to be reduced or replaced.

Results were 53 "very satisfactory"; 37 "satisfactory"; 8 "failures" and 6 "discontinued treatment" (g.i., 3; exacerbation of petit mal, 2; somnolence, 1).

Tolerance described as excellent; blood counts, liver enzymes and serum electrophoresis unaffected (no data given).

A less anecdotal but still subjective paper.

v) Matthes and Schmutterer(pp. 309-319)

Open study during $2\frac{1}{2}$ years of up to 3g/day valproic acid (mean 800-1,200mg) in 40 patients with various types of epilepsy (in 36 additional to existing treatment, in 4 as the only drug).

Best results (8/11) obtained in petit mal (3 c.p.s.) with absences. Benefit in other epilepsies less certain. No psychotropic effect.

Apart from some gastric effects and somnolence, good tolerance claimed; no allergic, haematological or renal toxicity, but no data given.

vi) Zelvelder (pp. 324-328)

Double-blind, randomised, cross-over study of valproic acid (400-1,800mg/day and placebo in 42 in-patients with various types of epilepsy and with epileptic symptoms at least 4 days/week for 3 weeks preceeding trial. Previous treatment with standard drugs continued unchanged throughout trial. Severity of disease scored numerically.

Valproic acid gave a statistically significant improvement (50% or more in symptom score) in 1 out of 3 patients.

3/42 patients dropped out of trial because of nausea headaches or mental dullness. Other p-tients had similar side-effects which improved with continued therapy.

The only objective study provided in the submission.

vii) Scollo-Lavizzari and Corbat (pp. 330-337)

Report of apparently open trial of 600-1,200mg/day valproic acid in various forms of epilepsy, claiming good efficacy and lack of toxicity.

No objective data provided.

20. MEDICAL COMMENT

Valproic acid is an anti-convulsant drug of novel chemical type which has been marketed in France since 1967; approximately 30-40,000 patients have received the drug and approximately 20,000 patients are currently under treatment.

In animals, its anti-convulsant potency is generally less than phenobarbitone, phenacemide or phenytoin and greater than troxidone. It seems to act by raising brain GABA levels consequent upon inhibition of GABA-T.

Only minimal data is provided of repeated dose toxicity studies in mouse, rabbit and guinea-pig. No further information has been requested from the manufacturer because the design and scope of the experiments are inadequate to provide evidence on the potential hazard of the drug in man.

Teratology studies were made in three species at one or two dose levels, the highest of which was only three times the recommended maximal human therapeutic dose of 30mg/kg. The timing of drug administration seems to have aimed at a combined fertility/teratogenic study but, in general, the data falls far short of the normal standards for either.

Apart from the trial by Zelvelder (19, B, vi) the clinical studies are largely anecdotal and fail to provide objective evidence of efficacy or safety.

21 RECOMMENDATION

The Committee may feel that a Product Licence should not be granted because of.

i) inadequate toxicological and teratological data in animals,

ii) inadequate evidence of efficacy and safety in clinical studies.

ABW.

Annex 4 - Examples of studies conducted by the MHRA

Allen C, Donegan K. The impact of regulatory action on the co-prescribing of renin-angiotensin system blockers in UK primary care. Pharmacoepidemiol Drug Saf 2017; 26(7): 858-862.

Datta-Nemdharry P, Thomson A, Beynon J, et al. Patterns of anti-diabetic medication use in patients with type 2 diabetes mellitus in England and Wales. Pharmacoepidemiol Drug Saf 2017: 26(2): 127-135.

Donegan K, Beau-Lejdstrom R, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine 2013; 31(43): 4961-7.

Donegan K, Owen R, Bird H, et al. Exploring the potential routine use of electronic healthcare record data to strengthen early signal assessment in UK medicines regulation: proof-of-concept study. Drug Saf 2018. doi: https://doi.org/10.1007/s40264-018-0675-x.

Michelle Kelly, Katherine Macdougall, Oluwafisayo Olabisi, Neil McGuire. In vivo response to polypropylene following implantation in animal models: a review of biocompatibility. Int Urogynecol J. 2017; 28(2): 171–180.

The MHRA commissioned toxicology research on the silicone within un-implanted PIP implants. The MHRA also conducted a survey of implanting centres asking for information about the rate of rupture and removal but this did not involve examination of actual explants. Information on these studies is found here.

EC taskforce including the MHRA set up to draft a remit for The Scientific Committee on Emerging and Newly Identified Risks (SCENIHR) to provide a scientific opinion on 'The Safety of surgical meshes used in urogynecological surgery'. Report is found here.

The MHRA commissioned a literature study of mesh as described in *Summaries of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse*.

Sabah SA[1], Moon JC[2], Jenkins-Jones S[3], Morgan CL[3], Currie CJ[4], Wilkinson JM[5], Porter M[6], Captur G[7], Henckel J[8], Chaturvedi N[9], Kay P[10], Skinner JA[11], Hart AJ[11], Manisty C[7]. The risk of cardiac failure following metal-on-metal hip arthroplasty. Bone Joint J. 2018 Jan;100-B(1):20-27. doi: 10.1302/0301-620X.100B1.BJJ-2017-1065.R1.

Medicines & Healthcare products Regulatory Agency

MHRA

Valproate Stakeholders' Network – Note of the meeting
Date: Monday 19 November 2018
Time: 10.45am to 2.30pm
Location: MHRA Offices, 10 South Colonnade, Canary Wharf, London E14 4PU.
Attendees – see Annex 1

Introduction

1. MHRA welcomed attendees to the meeting and explained the purpose of the meeting was to take stock of progress with the implementation of the valproate Pregnancy Prevention Programme and to consider what further actions were required. MHRA updated on progress with the actions agreed at the last VSN meeting in July.

The new PPP measures: implementation, monitoring and measurement of impact

2. MHRA provided an update on progress with the implementation of the Pregnancy Prevention Programme and the latest information from sources of prescribing data on the impact of the measures taken. The meeting noted the generally positive trends in reduced prescribing of valproate in women of childbearing age and in particular the negligible levels of new prescriptions to adolescent females. The meeting also noted the plans for a valproate registry to include all women and girls treated with valproate.

Patient views of progress – six months on

3. MHRA invited patient organisations and charities to provide their view on the progress of the implementation.

FACSaware

4. The representative of FACSaware gave some positive feedback from the Facebook group of parents about the regulatory actions and communications. The Group was disappointed by reluctance of the media to be more engaged and noted that the Channel 5 "GPs behind closed doors" programme had mentioned 'Epilim' but did not promote the PPP, even though the patient filmed was a young mother being treated with valproate.

5. The representative raised a concern that patients receiving dosset box medication delivered to their door were not getting a Patient Information Leaflet (PIL) in the box. the representative emphasised the importance of use of the consulting rooms in pharmacies in promoting the message about the PPP and voiced concern that there is not an equivalent requirement for online pharmacies.

INFACT

6. Representatives from INFACT were not able to be present in person but had provided slides to be shown which described the results of their survey between June and September 2018 to which 72 patients has responded. The following results were highlighted:

    58% received no PIL in the box
    92% received no patient card
    88% had not been asked to sign the Annual Risk Acknowledgement Form (ARAF)

7. From June to November women reported receiving ‘white boxes’ without warning stickers, without PILs and without patient alert cards. MHRA outlined the actions taken in response to the survey findings.

Medicines and Birth Defects Group

8. Feedback from representatives of the Medicines and Birth Defects Group was that the message from the “top level down” in the NHS had not been getting through. Representatives reported that the message seems to be getting through better for patients with epilepsy but there was a gap in provision of information for patients with learning disabilities. The Medicines and Birth Defects Group had evidence that in certain pharmacies the materials are being kept behind the counter and not given out. The representatives commented that there were inequalities in availability of materials and information on the PPP in geographical areas, and overall patchy implementation.

OACS/OACS Ireland

9. The representative for OACS gave positive feedback from the experience of a hospital visit in Wales and the member said they were given all relevant information at the appointment and given a pregnancy test. Feedback from other members suggested a ‘postcode lottery’ situation across the UK. The representative from OACS Ireland said that in Ireland they have had a focus on genetics services for valproate-affected children as well as identifying and referring women on valproate for specialist review. Every woman on valproate in Ireland had received a letter from the Irish health service advising them to go to the GP and this had been possible because of the Irish valproate registry initiative. There was a free phone advice line to call for those whose children have been affected.
10. OACS Ireland commented that they had feedback that valproate was used for pain management and this off-label use patient community should be represented on VSN.

Patient representative (bipolar)

11. The patient representative (bipolar) said she had heard that GPs are receiving “push back” from psychiatrists when requesting referrals for women on valproate and that referrals to the psychiatrists were being led through community mental health teams. The member said she was considering a Freedom of Information request to find areas of bad practice. The representative commented that she felt the RCPsych was still not engaged with the implementation of the PPP in patients with bipolar disorder.

12. The representative mentioned that the Maudsley prescribing guidelines for psychotropic medicines were being updated and that the revisions were to be discussed in December at an international conference. The representative raised concerns that representatives from mental health charities have not been attending the VSN meetings.

Patient representative (epilepsy)

13. The patient representative (epilepsy) provided feedback that generally the PPP was being implemented well for patients treated in hospital but that community pharmacy experience was very variable.

<u>Charities</u>

Epilepsy Action (EA)

14. The representative of Epilepsy Action informed the network that they had run a campaign on their website and promoted the PPP through social media. EA also reported that the media were reluctant to engage. The ‘GP behind closed doors’ programme was noted and had generated interest. EA had evidence that all women had been recalled for review in Yorkshire but members reported geographical variation in PPP implementation. EA had published articles in its magazines, including one aimed at community pharmacists. EA will repeat the

patient survey. EA had not noted an increase in calls to their helpline since the PPP had been communicated. The representative said concern had been raised about women who don't want to be on contraception and children with learning difficulties. They had feedback that women who want a pregnancy, feel "pushed off" valproate. The need for the Annual Risk Acknowledgement Form (ARAF) to be made available in alternative languages was raised.

Epilepsy Society (ES)

15. ES said that they had noted an increase in phone calls to the helpline since May but this was not quantified. The helpline had received calls from parents who did not consider their daughter to be at risk of pregnancy. ES said that they would like to see materials made available for those patients with learning difficulties. The representative had attended a conference where there was concern about increases in SUDEP because women were not on the most appropriate medication.

Young Epilepsy (YE)

16. The representative of Young Epilepsy (YE) said there was a lack of guidance for the 10% of young women without capacity and no support who could not give their consent to the PPP and were finding it traumatic to comply with the conditions of the PPP. YE said they were involved in ongoing work with the GMC to address this.

Migraine Trust (MT)

17. The representative of the Migraine Trust (MT) said they thought that there was a low number of women on valproate for migraine prophylaxis based on a lack of response to MT's communications on this issue. Despite publicising the PPP they had not had any enquiries.

Epilepsy Research UK (ERUK)

18. The meeting was provided with a written update that ERUK was funding Dr Rebecca Bromley's research on neurodevelopmental effects – the Neurodevelopment after Prenatal Exposure to Seizures (NAPES) study.

<u>Updates from the health system and healthcare professional stakeholders</u>

19. MHRA invited representatives from the healthcare system organisations, professional regulators and healthcare profession bodies to provide an update on the implementation of the PPP.

British National Formulary (BNF)

20. The BNF representative said that it was to publish a case study which covered the clinical steps when prescribing valproate. This would soon be accessible on the BNF website and via an e-newsletter. The content of the case study was compiled from information already contained in the BNF.

NHS Digital (NHSD)

21. The representative from NHS Digital updated the network that all 4 prescribing system suppliers had now implemented 'red box' warning messages in their systems. Audit functionality was in place for GP practice systems to allow GPs to identify relevant female patients on sodium valproate. NHSD said they would ask the suppliers if it was possible to measure uptake of the audit functionality. The representative was aware that dispensing systems suppliers were also adding the warning. NHSD commented that secondary care needed to come on board with electronic prescribing, so hospital databases could be used to identify all female patients on valproate. The possibility of developing new SNOWmed codes to record when discussions had taken place with a patient on valproate had been met with some resistance because GPs were not consistently using the already existing codes. NHSD offered to explore whether electronic records could be used to identify patients with previous valproate exposure at any time in their history.

NHS England

22. The NHSE representative said that on 22 October the Chief Pharmaceutical Officers and MHRA had sent a Central Alerting System message to pharmacies to reiterate risks and the actions that pharmacists should take. In response to a question from the meeting, NHSE said that there was currently no way to monitor the number of referrals to secondary care.

NICE

23. The NICE representative reported that a prescribing advice guidance for valproate was being developed and that this will be for all indications. This would include MHRA information and be presented as a visual summary. The timelines for this would be notified to the VSN when available. The NICE representative said that the consultation for the Epilepsy guideline due for publication in Jan 2021 would start in January 2019. MHRA asked for previews of the guideline that it could share with VSN members. NICE said that there was a scoping workshop for the NICE Epilepsy and Epilepsy in Children guidelines in November and MHRA said that they would send a representative.

UK Teratology Information Service (UKTIS)

24. The representative from UKTIS confirmed it had updated the valproate monograph and information on its website. UKTIS had trained enquiry service staff to respond to valproate queries. There had been very few enquiries and overall contact on valproate was decreasing.
25. The UKTIS representative said that they were aware of 3 inadvertent exposures to valproate during pregnancy since the new regulations came into force. MHRA asked UKTIS asked if they could seek any further information on why these women had become pregnant on valproate.
26. UKTIS was commended by the members for quality of their patient leaflets and good use of social media on valproate (tweets).

Care Quality Commission (CQC)

27. The representative from the CQC said that they had been asking all providers questions on how they are receiving, responding to and acting on safety alerts and that there was a focus on valproate in GP practices. The representative said that failing to act was a breach of fundamental standards and would have an effect on “SAFE” ratings. One GP practice had been suspended for not responding appropriately. The CQC mentioned that the valproate alert was in the thematic review on “Never Events”. Each trust was required to have a central list of patients on valproate. Chief Pharmacists were being asked by CQC how they assured themselves they are using medicines safely and effectively in their trusts in “well lead” inspections. CQC stated they would expect the same level of service from online pharmacies as physical pharmacies.

General Medical Council (GMC)

28. The GMC representatives confirmed there was ongoing consultation for revised guidelines on consent to treatment. GMC would like to do a case study on the use of the valproate ARAF, perhaps focused on the discussion and understandability of the ARAF. In relation to evidence of non-compliance, the GMC said that it could only respond to complaints about individual doctors and would use its standard procedure to assess the fitness of that individual to practice.

Community Pharmacy Patient Safety Group (CPPSG)

29. The CPPSG has issued communications on the valproate PPP. There had been blogs in the ‘Chemist and Druggist’ publication and there was an e-learning network. They were working hard to encourage members to realise the valproate message was not a one-time conversation and that it needed to be sustained and reiterated at every interaction between pharmacist and patient. They said that they would discuss the valproate PPP with

representatives from pharmacies with an online presence in a meeting at the end of November.

30. The representative from the CPPSG said that they would take back views on regional variation of implementation and follow up with community pharmacists and superintendents.
31. The representative presented results of the Company Chemists Association (CCA) audit. The first audit was conducted in July and involved 6,649 pharmacies. The results showed 96% of pharmacy teams were aware of the risks, and 84% aware of the regulations. Of all prescriptions for valproate 1 in 4 included the indication of PPP from the prescriber. The audit will be repeated for the time period Nov 2018 to March 2019.
32. The CPPSG suggested that a copy of the ARAF could be given to the dispensing pharmacist so they know the patient is “on a PPP.” It was otherwise difficult to know the status of the patient before dispensing.

General Pharmaceutical Council (GPhC)

33. The GPhC said that they had published a statement on the valproate PPP and sent alerts to all pharmacists in October highlighting the MHRA advice and the responsibilities of pharmacists. GPhC had included an article on valproate in a newsletter to all pharmacists and pharmacy owners and was pleased that NetMums had retweeted this. Inspectors were checking pharmacy compliance with the new regulations and from 2019 Inspection reports would be published.
34. In response to the feedback on gaps in implementation of the new regulations, GPhC said that they would respond to complaints received about pharmacies and that there was information on their website about raising a complaint. They said that they thought the availability of smaller packs of valproate would help with the issue of women receiving a ‘white box’ without a PIL.

The Royal Pharmaceutical Society (RPS)

35. The RPS said it was providing support materials for ongoing education of members and that dispensing valproate safely was to be picked up as a topic in upcoming conferences. RPS said that they thought it was currently not sufficiently clear to pharmacists that the patient alert card needed to be given to the patient every time valproate was dispensed.

Community Pharmacy Scotland (CPS)

36. CPS said that they had issued a circular and newsletter on the valproate PPP and had discussed valproate at face to face meetings with RPS and National Pharmaceutical Association support.

Community Pharmacy Wales (CPW)

37. CPW said that it had included articles on valproate in their weekly newsletters. CPW presented figures from an audit in April showing that, of 744 women aged 13-45 years on valproate, 402 had been given the patient booklet.

Scottish Government

38. The Scottish Government representative said that they were working closely with MHRA and would look at how NICE updates on valproate could be adopted into SIGN guidance

Royal College of General Practitioners (RCGP)

39. The RCGP representative said that they had contributed to the Cumberledge review. The representative updated on progress with the pan-college guidance which was being drafted by the Association of British Neurologists, Royal College of Physicians and the RCGP that was aiming to provide clarity of advice for healthcare professionals on the use of the ARAF for those patients for whom the PPP does not apply and for managing contraception in patients aged 10–18 years.

Association of British Neurologists (ABN)

40. The ABN raised issues regarding those patients who could not consent to intercourse or contraception and had limited capacity, and how the annual review should be adapted for them. The proposal for a registry of women on valproate which could be used to investigate compliance with the PPP and follow up women who had been switched from valproate to other antiepileptics was supported.

International League Against Epilepsy (ILAE)

41. The ILAE representative said that they had been supporting local audits. ILAE raised concerns about the rate of sudden unexplained death in epilepsy (SUDEP) and cited a figure of 21 deaths per week related to SUDEP in the UK. There was no data on whether these patients were women of child bearing potential or whether these deaths were patients taking valproate or switching from valproate to another antiepileptic. The ILAE highlighted the SUDEP Action 21 campaign which was ongoing.

Royal College of Psychiatrists (RCPsych)

42. The RCPsych said that there had been promotion of the PPP messages via their congress and on their website. An increase in referrals from primary care had not been noted to date. In Greater Manchester there is a move to get the ARAF into electronic records.

Epilepsy Specialist Nurse Association (ESNA)

43. The ESNA representatives commented that their members were in the best position to implement the PPP and provide advice for women on valproate. This was because patients saw nurses more often than consultant neurologists or psychiatrists. In any communication, the ESNA advised making a clear distinction between nurses who were independent prescribers from those who were not. Members of the ESNA had seen an increase in the number of referrals to neurologists with a special interest in epilepsy.

44. In Norfolk and Norwich an audit had been conducted using the System 1 GP software system to identify women on valproate and a flowchart had been developed to help triage patients. Norfolk and Norwich had been working to develop materials for patients with learning disabilities. Norwich CCG had employed a nurse specifically to implement the 'Prevent' (Valproate PPP) programme and to co-ordinate all relevant personnel across the different health agencies involved.

The Royal College of Midwives (RCM)

45. The RCM representative raised ethical concerns with the ARAF particularly in signing up patients aged 10-15 to contraception discussions.

<u>Roundtable discussion and conclusions</u>

46. MHRA noted from discussion during the updates from the different organisations that there were a number of themes emerging. The prescribing data showed a positive downward trend in prescribing of valproate to women and girls, however the feedback from patient organisations was that the implementation of the PPP was patchy and therefore there was more to be done.
47. The MHRA noted the feedback that the Annual Acknowledgment of Risk form should be amended so it was possible to record where appropriate that a woman or girl was not at risk of pregnancy.
48. In addition, there was a need for some card or documentation that the patient could carry which could make clear her 'PPP status' and let a pharmacist know that it was safe to dispense valproate without intrusive questioning about the woman's use of contraception or risk of pregnancy.

49. Nevertheless, there was a clear view that information on the PPP (with supporting materials if appropriate) should be given at each interaction between the patient and the pharmacist.
50. MHRA thanked all the attendees for their contributions and said that they would circulate action points and a date for the next meeting.

VRMM
20 December 2018

Annex 1
Attendees

MHRA:

- June Raine, Director of Vigilance and Risk Management of Medicines
- Sarah Morgan, Pharmacovigilance Risk Management Group Manager
- Katherine Donegan, Pharmacoepidemiology Research and Intelligence Unit Manager
- Sarah Mee, Senior Medical Assessor
- Leigh Henderson, Pharmacovigilance Risk Management Group Unit Manager
- Louise Rishton, Medical Writer
- Mike Dykes, Engagement Manager
- Susan Doherty, Engagement Specialist

Valproate Stakeholders' Network:

Organisation(s)	**Name**	**Role**
Association of British Neurologists/Royal College of Physicians	Sanjay Sisodiya	Chair of the Association of British Neurologists Advisory Committee for epilepsy
Bipolar – patient representative	Josie Tapper	Patient Representative
British National Formulary c-team	Angela McFarlane	Content Editor
Care Quality Commission	Sarah Billington	Head of Medicines Optimisation
Community Pharmacy Patient Safety Group (CPPSG)	Janice Perkins	Chair
CPPSG	Kate Livesey	Patient Safety Lead
Community Pharmacy Scotland	Adam Osprey	Policy and Development Pharmacist
Community Pharmacy Wales	Judy Thomas	Director of Contractor Services
Epilepsy – blogger representative	Faye Waddams	Patient Representative
Epilepsy Action	Louise Cousins	PR and Campaigns Manager
Epilepsy Society	Nicola Swanborough	Content Editor – Epilepsy Review
Epilepsy Specialist Nurse Association (ESNA)	Phil Tittensor	Chair
ESNA	Erica Chisanga	Consultant Nurse – Epilepsies
ESNA	Dee Elleray	Bank Epilepsy Nurse (former Epilepsy Lead)
FACSaware	Emma Friedmann	Campaigner/Patient Representative
FACSaware	Andy Friedmann	Patient Representative
General Medical Council	Chris Brooks	Policy Officer
General Medical Council	Christine Buicke	Policy Manager
General Pharmaceutical Council	Laura Oakley	Engagement Manager
International League Against Epilepsy (ILAE) UK Chapter	Manny Bagary	Consultant Neuropsychiatrist
Medicines and Birth Defects	Deborah Mann	Campaigner/Patient Representative
Medicines and Birth Defects	Karen Buck	Campaigner/Patient Representative
Migraine Trust	Susan Haydon	Information & Enquiry Manager

NHS Digital	Manpreet Pujara	Directorate Professional Lead and Clinical Director for Electronic Prescription Service
NHS England	Bruce Warner	Deputy Chief Pharmaceutical Officer
NHS Improvement	Karen Hooper	Patient Safety Clinical Lead – Maternity & Neonates
NICE	Louise Bate	Associate Director – Medicines Education
Organisation for Anti-Convulsant Syndrome (OACS)	Susan Cole	Secretary
OACS	Jo Cozens	Chair
OACS Ireland North & South/FACS Forum Ireland	Karen Keely	Campaigner/Patient Representative
Royal College of General Practitioners	Judy Shakespeare	GP Representative
Royal College of Midwives	Kim Morley	Epilepsy Specialist Midwife Practitioner
Royal College of Psychiatrists	Ipshita Mukherjee	Consultant Perinatal Psychiatrist
Royal Pharmaceutical Society	Sandra Gidley	Chair of the English Pharmacy Board
Scottish Government	John Hannah	Pharmacy & Medicines Division
UK Teratology Information Service	Luke Richardson	Senior Medical Information Scientist
Young Epilepsy	Rosemarie Pardington	Director of Integrated Care

Apologies received from: British Paediatric Neurology Association, Department of Health & Social Care, Epilepsy Research UK, INFACT/FACSA, Juliet Tylor (Epilepsy Patient Representative), Mind, Public Health England, School and Public Health Nurses Association (SAPHNA).

Valproate Stakeholders' Network

Minutes of the meeting held on 13 February 2019 in The Round Room, MHRA 10th Floor, 10 South Colonnade, Canary Wharf, London, E14 4PU

Attendees: See Annex 1

Introduction

1. The MHRA welcomed attendees to the meeting which was the 11th meeting of the Valproate Stakeholder Network and explained that the purpose of the meeting was to take stock of progress with the implementation of the valproate Pregnancy Prevention Programme and to consider what further actions were required. The MHRA thanked attendees for the helpful information provided in response to the questionnaire circulated in advance of the meeting, aimed at building a picture of the efforts in hand by all stakeholders to fully implement the valproate PPP, any barriers or hurdles, and current activities to optimise compliance by health care professionals.

Pregnancy Prevention Programme: implementation, monitoring and measurement of impact

2. The MHRA presented a reminder of the latest data on prescribing of valproate (which had been presented at the November VSN meeting) and updated on progress with the actions agreed at the last VSN meeting held in November 2018. MHRA provided feedback on the discussions of the Valproate Expert Working Group of the Commission on Human Medicines on 29 November and presented the latest draft of the revised Annual Risk Acknowledgement Form (ARAF) which had been updated to include a section for completion when the PPP does not apply as the patient is considered not to be at risk of pregnancy.

3. The patient representative from FACSaware raised concerns that the ARAF included a section which referred to use of valproate during pregnancy. MHRA clarified that this was to reflect that if a woman did become pregnant on valproate there may be a decision made that it was not possible to switch treatment during pregnancy.

4. The patient organisation INFACT asked how the form was going to be enforced. It was confirmed that it would part of the PPP and should be reflected in the guidance being produced by the professional bodies. INFACT said there should be more explicit reference to patients who lack capacity to make informed decisions.

Action points:

Action: MHRA to consider how the ARAF could better address considerations around those who lack capacity to make an informed decision.

Patients' views of progress – ten months on from implementation of the PPP

5. MHRA invited patient organisations and charities in turn to provide their view on the progress of the implementation of the valproate PPP.

5.1 INFACT presented data from their latest survey which had begun on 11 December 2018 and had asked questions about whether women were receiving the PPP and were being offered alternatives to valproate. Seventy-two women had taken part in the survey. 42% had not discussed the PPP with their GP. Of those who said they had discussed the PPP with their GP or specialists, 38% said that they had not fully understood. 63% had not been asked to sign the Annual Risk Acknowledgement Form. INFACT said that the survey indicated that there were still significant gaps in compliance with the PPP.

In the discussion, the Epileptic Specialist Nurse Association (ESNA) said that women frequently asked about whether they had to change medication and what the risks were with valproate compared with other antiepileptic medications. ESNA also said that the requirement for serum pregnancy tests was problematic as not all clinics had access.

5.2 Medicines and Birth Defects said that GP services seemed to be overwhelmed and there was still a lack of awareness of the PPP. The MHRA agreed that awareness and training of primary care staff was key. In the discussion NHS Digital said that changing prescribing behaviour was a long process and from the experience of NICE it took financial incentives (QOF) to change GP prescribing in relation to NSAIDs. MHRA said that there should be an offline discussion on learnings from the NICE experience and how it could be applied to valproate.

5.3 A patient representative with Fetal Valproate Syndrome (Branwen Mann) said she considered that the new updated Annual Risk Acknowledgement Form looked good but raised the point that valproate was being prescribed to individuals with fetal valproate syndrome and that this exacerbated their health problems.

5.4 A patient representative from OACS informed the VSN that she remained on valproate out of choice and that she had been referred for specialist review by her GP. She said that she had gone into Superdrug 2-3 months ago and the PPP materials were under a lot of junk mail. Medicines were delivered in a white box with no sticker, no card and no patient leaflet in the box (this had been from an independent small chain pharmacy).

5.5 The patient representative from FACSaware considered that the INFACT survey was very informative. In Leicester there was a wait of one year to see a neurologist. Shared care should be formalised. Information was not reaching the front line – there should be someone in each GP surgery whose job it was to read important communications such as Drug Safety Update and ensure the information is passed on to relevant prescribers. GMC should start looking at fitness to practice. FACSaware asked whether the Private Care Providers Network should be invited to the VSN to ensure that those prescribing valproate in private practice were aware. FACSaware raised concerns about the implementation of the PPP where patients were being treated for mental health conditions. The RCPsych representative responded that the recent guideline published by RCPsych addressed off label use of valproate in psychiatric indications.

Charities and Voluntary Organisations' positions on progress with the PPP

The MHRA then sought views from the Charitable and Voluntary organisation representatives present.

6. The Epilepsy Society informed the VSN they had had feedback from people concerned about the PPP and who did not want to come off valproate treatment. The Epilepsy Society said that a patient survey would be conducted in August and asked if MHRA could support them. The MHRA said they would be happy to do so as they had in the design of previous surveys.

6.1 Young Epilepsy said that they have seen a surge in the number of patients since November whose valproate prescriptions had been dispensed in white boxes and they had raised this with a major pharmacy chain. They also mentioned that there had been local supply issues with Epilim. The MHRA indicated that they were aware of this and were in liaison with the DHSC.

6.2 Epilepsy Research UK said that they were looking at funding research on the impact of seizures in pregnancy and were holding a closed international workshop in March. They said that they would share with the network anything relevant to valproate.

6.3

Action points:

Action: MHRA agreed to raise supply issues with DHSC colleagues to ensure appropriate communications to pharmacy.

Action: MHRA to work with Epilepsy Society on developing and promoting the patient survey

Health system bodies and healthcare professional stakeholders – guidelines and audits

7. MHRA invited health system bodies and healthcare professional stakeholders to update on actions taken to embed the PPP.

7.1 The NHSE representative informed the meeting about updates to the GP contract. Twenty-eight of the current indicators were being retired and 15 new ones are being introduced. Importantly, a Quality Improvement indicator was being introduced on prescribing safety (worth 74 points) which included NSAIDs, lithium, valproate and end of life care. It would pay practices to have a sustainable system to ensure safe prescribing of valproate and NHSE would flag the existing tools to be used. It aimed to encourage GPs to think about how they engaged with patients around their medication, making sure that they could make informed choices. In discussion of the new GP contract, it was noted that the Quality Outcomes Framework no longer existed in Scotland and therefore alternative mechanisms to incentivise compliance by GPs would be needed there.

7.2 The Association of British Neurologists (ABN) said that managing the referral activity resulting from the strengthened valproate risk minimisation measures was challenging and prioritisation was needed. There was continued pressure on services but the importance of expediting the valproate referrals was accepted by neurologists. Where there was sufficient demand, special clinics were set up. Later in discussion, the ABN said that there were problems with the use of the ARAF in hospitals because of the need to print it out and made a plea for NHSD to make it an online form. NHSI said that an online form would have to be linked via the NHS number which would allow audits and reporting of metrics. A number of concerns were raised in discussion about the PPP including a view from one neurologist that it was a blunt instrument and the name could be off-putting to some women.

7.3 The Epilepsy Specialist Nurses Association (ESNA) said that they were aware that waiting times for referrals were an issue and that there was work ongoing to look at different ways of structuring local services to improve this. ESNA said that it was important that the implementation was done correctly and that took resources. Norfolk had identified and triaged patients and 1/3 of patients had been switched from valproate.

7.4 The Royal College of General Practitioners (RCGP) said that they were planning to publish the pan-college guidance at the same time as the revised ARAF, in the coming couple of weeks. This would meet the need for practical guidance for GPs.

Post-meeting note: *The Pan-college guidance was published on 28 March* https://www.rcgp.org.uk/about-us/news/2019/march/thirteen-uk-healthcare-bodies-launch-pragmatic-guidance-on-valproate-use.aspx

7.5 The Community Pharmacy Patient Safety Group raised the question as to whether every pharmacist should have a mandatory training course on safe dispensing of valproate.

7.6 In response to a view expressed by one neurologist that the risk of harms from valproate in pregnancy was very low at doses of or under 1,000mg per day, there was a discussion about whether the risks of valproate in pregnancy were dose-related. The MHRA confirmed that a safe dose of valproate in pregnancy had not been identified in any studies. Reference was also made to the risks of other antiepileptics in pregnancy and the MHRA said that the safety of all antiepileptics was reviewed regularly through Periodic Safety Update reports which were assessed at EU level. Concerns were raised that downplaying of the risk associated with valproate by some healthcare professionals was a barrier to implementing the PPP.

Action points:

Action: MHRA to formally review the evidence of pregnancy risk of all antiepileptics so that women could be make appropriately informed decisions. The MHRA to provide an update on scope and timelines of the review at the next VSN.

Regulators and clinical guidance providing organisations' activities

8. The MHRA then invited the professional regulators and organisations providing clinical guidance to update the Network.

8.1 The Care Quality Commission (CQC) said that they were working to understand better the risks around prescribing and what indicators really matter in relation

to valproate prescribing. Currently the CQC is using valproate as the 'test' for systems in relevant healthcare organisations such as GP practices.

8.2 The representative from NICE indicated by telephone link to the meeting that they were working on an overarching guideline due to be published in March 2019 and that the revised epilepsy guideline would be published in 2021. (Changes had been made in April 2018 to all NICE guidelines which refer to valproate to reflect the strengthened risk minimisation measures).

8.3 The representative from NHS Improvement said that the Medicines Safety Officers' network monthly Webex meetings had featured valproate in 9 out of the last 12 meetings. The National Reporting and Learning System database was analysed on a weekly basis and NHSI could provide an update on that data at a future meeting. No reports in that database had been received recently in relation to valproate. The National Patient Safety Strategy had been published for consultation and was proposing a patient safety specialist in every CCG.

8.4 The General Medical Council said that they would be developing a repository of valproate resources and that they were analysing the responses to the consultation on their revised consent guidelines with a view to publishing in the Autumn. The GMC addressed concerns raised previously in discussion by outlining their role in investigating concerns about doctors.

8.5 The General Pharmaceutical Council outlined their activities to raise awareness of the PPP including posting on social media and said that GPhC inspections were continuing to check compliance with the PPP during pharmacy inspections.

Action points:

Action: MHRA asked NHSE to send a summary of what the Quality Improvement indicator entails and how it will work to be shared with the VSN.

Action: MHRA to discuss with the Scottish Government the need for equivalent action to the Quality Indicator for valproate in Scotland.

Action: NICE to send the overarching valproate guideline to MHRA to circulate to the VSN. [Post meeting note – guideline was sent to VSN on 28 March : https://www.nice.org.uk/guidance/cg137/resources/valproate-in-children-young-people-and-adults-summary-of-nice-guidance-and-safety-advice-pdf-6723784045]

Action: GMC to circulate information on regulatory tools available.

Options for next steps to expedite compliance with the valproate PPP

9. The MHRA presented the following options for next steps to strengthen compliance with the risk minimisation for valproate in pregnancy for discussion by the VSN:

- Continue current action (awareness raising, QOF implementation) and monitor implementation for another 6 months
- Registry establishment – aims to ensure every woman on valproate is tracked (likely to take approximately 1 year)
- Restriction to specialist prescribing only with supply through designated pharmacies
- Further regulatory action – eg contraindication of valproate in girls and women of childbearing potential

10. The meeting discussed the need to do more to ensure that all women are contacted and have completed the ARAF. There was a discussion about the possibility of contacting women directly and it was agreed that this should be explored further in the context of the registry. The question of legal action against individual healthcare professionals was raised by a patient group adviser. Some members were aware of legal cases, however the MHRA advised that discussion of legal issues was outside of the remit of the VSN. The meeting discussed the regulatory tools that the GMC had available and it was agreed that the GMC should circulate information on these.

11. The meeting considered that it may be necessary to move towards specialist use only for valproate and to engage more specialist nurses and establish designated and accessible pharmacies with specially trained staff. It was agreed that the practicalities and resource implications of this move would have to be carefully thought through so as not to disadvantage women. The meeting noted the treatment pathway developed in Norfolk which encompassed women taking valproate for both epilepsy and mental health conditions and agreed that this could be considered as a model.

Action points:

Action: ESNA to circulate further information on the Norfolk treatment pathway.

Action: GMC to provide information on their current tools to underpin prescribers' compliance with the valproate statutory position.

Conclusion

12. The MHRA thanked the participants for their helpful and considered contributions both in the meeting and beforehand, and said they would circulate

the slides presented at the meeting alongside a draft note including the agreed action points.

VRMM

April 2019

Annex 1

Attendees

MHRA:

June Raine, Director of Vigilance and Risk Management of Medicines (Chair)
Sarah Branch, Deputy Director of Vigilance and Risk Management of Medicines
Sarah Morgan, Pharmacovigilance Risk Management Group Manager
Stephanie Dellicour, Associate Pharmacoepidemiologist
Sarah Mee, Senior Medical Assessor
Leigh Henderson, Pharmacovigilance Risk Management Group Unit Manager
Louise Rishton, Medical Writer
Mike Dykes, Engagement Manager
Susan Doherty, Engagement Specialist

Valproate Stakeholders' Network:

Organisation(s)	**Name**	**Role**
Association of British Neurologists/Royal College of Physicians	Sanjay Sisodiya	Chair of the Association of British Neurologists Advisory Committee for epilepsy
Bipolar – patient representative	Josie Tapper	Patient Representative
British National Formulary c-team	Angela McFarlane	Content Editor
Care Quality Commission	Sarah Billington	Head of Medicines Optimisation
Community Pharmacy Patient Safety Group	Janice Perkins Kate Livesey	Chair Patient Safety Lead
Community Pharmacy Wales	Judy Thomas	Director of Contractor Services

Epilepsy Action	Louise Cousins Daniel Jennings	PR and Campaigns Manager Senior Policy and Campaigns Officer
Epilepsy Research UK	Caoimhe Twohig-Bennett	Research Manager
Epilepsy Society	Nicola Swanborough	Content Editor - Epilepsy Review
Epilepsy Specialist Nurse Association	Phil Tittensor Erica Chisanga	Chair Consultant Nurse - Epilepsies
FACSaware	Emma Friedmann	Campaigner/Patient Representative
Fetal Valproate Syndrome – patient representative	Branwen Mann	Patient Representative
General Medical Council	Chris Brooks Claire Garcia	Policy Officer
General Pharmaceutical Council	Laura Oakley	Engagement Manager
INFACT/FACSA	Janet Williams Emma Murphy Mikey Argy	Campaigner Campaigner Adviser
International League Against Epilepsy (ILAE) UK Chapter	John Paul Leach	Consultant Neurologist
Medicines and Birth Defects	Deborah Mann	Campaigner/Patient Representative
Mind	Rachel Boyd	Information Manager
National Pharmacy Association	Arti Shah	Advice and Support Pharmacist
NHS Digital	Paul Brown	Clinical specialist in Prescribing, Medicine and Pharmacy
NHS England	Rachel Foskett-Tharby	Senior Policy Lead – General Practice Strategy and Contracts
NHS Improvement	Graeme Kirkpatrick	Head of Patient Safety (Advice & Guidance)

NICE	Louise Bate	Associate Director – Medicines Education
Norfolk Community Health & Care NHS Trust	Dee Elleray	Bank Epilepsy Nurse
Organisation for Anti-Convulsant Syndrome (OACS)	Jo Cozens Carol Lapidge	Chair
Rethink Mental Illness	Will Johnstone	Senior Policy Officer
Royal College of General Practitioners	Judy Shakespeare	GP Representative
Royal College of Midwives	Kim Morley	Epilepsy Specialist Midwife Practitioner
Royal College of Psychiatrists	David Baldwin	Professor of Psychiatry & Head of Mental Health Group, University of Southampton
Royal Pharmaceutical Society	Sandra Gidley	Chair of the English Pharmacy Board
Scottish Government	John Hannah	Medicines Team
UK Epilepsy in Pregnancy Register/Epilepsy Action	Jim Morrow	UKEPR committee member
Young Epilepsy	Rosemarie Pardington	Director of Integrated Care

Apologies received from: Antiepileptic Drugs in Pregnancy, Community Pharmacy Scotland, Department of Health and Social Care, Faye Waddams (Epilepsy Patient Representative and Blogger), Karen Buck (Patient Representative – Medicines & Birth Defects), Mary Toms (Patient Representative – FACSaware), Migraine Trust, OACS Ireland North & South/FACS Forum Ireland, Public Health England, School and Public Health Nurses Association, Susan Cole (Epilepsy Patient Representative), UK Teratology Information Service.

NOT FOR PUBLICATION

MC 76/112 A

MEDICINES COMMISSION

A NOTE ON EPILIM - SODIUM VALPROATE

1. This paper, which is a companion paper to MC 76/112 on Hazardous drugs - the wider issues, outlines some of the problems posed by Epilim.

HISTORY

2. Epilim (sodium valproate), a novel and potent anti-convulsant, was cleared by the Committee on Safety of Medicines in 1972, subject to certain restrictions on its marketing. These restrictions are known as monitored-release which is defined as: "The release by a national drug regulatory authority of a new medicinal preparation for marketing when it is considered necessary to impose certain restrictions. It involves an obligatory feedback within a stated time of certain information to clarify questions of safety in relation to efficacy in wide-scale usage" (E L Harris WHO 1973).

3. Epilim was developed outside the UK and has been on the market in France since 1969, in Belgium and Holland since 1971, in Switzerland since 1972, and in Germany since 1973. The clinical trial data that was supplied to us in the Product Licence application suggested that the agent is effective when orthodox anti-epileptic treatment has failed. However the clinical trials had been conducted on a patient sample which differed from the majority of patients in the United Kingdom in its genetic composition, dietary intake, and other drugs administered concomitantly. Moreover, animal studies showed that it produced teratogenic effects and might therefore have a damaging effect on the human foetus. The manufacturer was not in a position to organise clinical trials in the United Kingdom and as a compromise the Committee on Safety of Medicines advised that a Product Licence to market could be issued provided that supply was restricted to specified epileptic colonies and that all patients treated with the drug be monitored for safety and efficacy.

4. The Company subsequently provided additional data from studies carried out in the United Kingdom which showed that this is a useful drug in the treatment of epilepsy and that patients resistant to other therapeutic agents may be satisfactorily and safely controlled. In 1974 the Product Licence holders applied for a variation of their Licence so that the restriction on the supply to specialised centres be removed. This meant that the medicine could become generally available for supply on prescription only.

5. The Committee on Safety of Medicines recommended that the licence should be varied in this way on condition that

   i. the indications for use are 'for use in generalised, focal or other epilepsy. In women of child-bearing age it should be used only in severe cases or in those resistant to other treatments'

ii. the product literature stated "Women of child-bearing age. This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the possible hazards suggested by these findings."

Following careful consideration of the issue involved the licensing authority accepted the advise of the Committee.

6. Teratogenic warnings. In the past it has been the practice of the Committee on Safety of Medicines to clear medicines for supply on prescription when a teratogenic hazard had been demonstrated in animal studies, provided the product literature contained suitable warnings. Examples of this are all the fluorinated steroids used in dermatological preparations. They are all potent teratogens and the Committee, in agreement with the ABPI and various manufacturers, devised a suitable warning which all manufacturers of such products include in their promotional literature. Another example is Co-trimoxazole (Trimethoprim and Sulphamethoxazole) marketed in this country as Septrin and Bactrim. This combination is a potent teratogen and the product literature clearly states that, in animal studies, foetal abnormalities have been produced and that this finding should be taken into account when the drug is used in women of child-bearing potential. However, it should also be pointed out that there have been a number of publications in the British press on the use of this mixture in urinary infections during pregnancy and to date we know of no foetal abnormalities that have resulted.

7. Epilepsy, anti-convulsant agents and foetal abnormalities In 1972, Speidel and Meadow published in the Lancet a report of a retrospective survey in Leeds into the outcome of 427 pregnancies to 186 women with epilepsy in which it was shown that there was twice the expected frequency of congenital heart disease, cleft lip (with or without cleft-palate) and micro-cephaly in the offspring.

8. An editorial in the Lancet at the same time discussed the possible role of anti-convulsant therapy and concluded that "anti-convulsant drugs are as helpful and necessary during pregnancy as they are at other times in the life of the person with epilepsy. For the individual mother with epilepsy the chance of an abnormal baby is small."

9. In January 1974 Professor Lowe, from the Department of Social and Occupational Medicine, Welsh National School of Medicine, published the result of a survey of infants born to mothers in Cardiff over a 7-year period. This revealed a malformation rate of 2.7 per cent. Where the mother had a history of epilepsy and had been on anti-convulsants during the first trimester the rate was 6.7 per cent. He concluded: "Bearing in mind the importance of anti-convulsant therapy in epilepsy and the possibility that the transient anoxia associated with an epileptic fit may itself be teratogenic, one must conclude that, on the evidence available, there is no great cause for alarm."

10. In May 1973 Sir Eric Scowen and Sir Richard Doll in the Committee's annual letter to doctors, on the subject of anti-convulsants stated: "Meanwhile it is now clear from other studies that the use of anti-convulsants during

pregnancy (including phenobarbitone and Promodone as well as Phenytoin, singly or in combination) is liable to produce other abnormalities as well as harelip and cleft-palate. The risk appears to be low and not sufficient to justify stopping the use of anti-convulsants when they are necessary for the control of epilepsy."

11. On 18 February 1974 Sir Eric Scowen, [redacted] and the Secretary of the Committee met Dr [redacted] of the BMA to discuss methods on how best to draw doctors' attention to the dangers associated with teratogenicity of anti-convulsants. They all felt it was important to avoid causing panic amongst patients with epilepsy and inducing doctors to withdraw anti-convulsant therapy because it was clear that the hazards associated with their continued use were less than those associated with their withdrawal.

12. Legal position - licensing. In law the decision on an application is made by the Licensing Authority (Ministers, or generally speaking, officials acting on their behalf) and not by the Committee on Safety of Medicines. Although the Licensing Authority almost always acts on the advice of the Committee on Safety of Medicines, the Committee have said that they would understand if, in view of the great public interest in the question of damage to the unborn child, the Licensing Authority decided to take a different view. If the Licensing Authority had decided to refuse this application, the applicant would have been entitled under the Medicines Act to make written representations to the Licensing Authority or to a hearing before an independent person (appointed by the Licensing Authority), which can be in public if the applicant so wishes. The person appointed would presumably have been an eminent medical authority; his function would have been to prepare a report for consideration by Ministers, but there would have been no obligation on them to act on his recommendations.

13. In view of the implications of licensing a drug which might have teratogenic effects, this problem was given careful consideration. It was noted that a number of other products which had been found to be potential teratogens had been allowed to be marketed, for use on prescription only, provided that adequate warnings were given. The evidence which suggested that other anti-convulsants might be teratogenic was also noted, as was the need to take into account the risk that transient anoxia associated with an epileptic fit might itself be teratogenic. The difficulties of restricting medicines to use by specialists (discussed in paragraphs 5-10 of Paper MC 76/112) were also borne in mind.

14. The view was expressed however that this drug should not be generally released and that it was important that a method of releasing medicines should be developed in a way that would enable the Department to be assured that women of child bearing age would not receive it. This meant that the medicines might have to be restricted to hospitals, and it was suggested that if the drug was of particular value a general practitioner could make a special arrangement with a consultant. The difficulties of restricting drugs to hospitals only were however recognised and it was noted that the teratogenic effects of Epilim, although different, appeared to be of the same order of magnitude as those produced by other commonly used anti-convulsants.

6

It was also pointed out that the balancing of the risk and the therapeutic advantage is a difficult one - to deprive a woman of anti-convulsant therapy because she is or is likely to become pregnant can be equally hazardous to her child - the foetus may be injured as the result of a fit. Moreover, it will always be a matter of difficulty to establish whether any abnormality in a child is due to the medicine or to the mother's condition. If a licence were to be granted in the terms suggested by the Committee on Safety of Medicines it would be likely that in some cases the medicine would be taken by pregnant women. If such a pregnant woman gave birth to a malformed child, the Department might be censured for this. On the other hand, if present restrictions were to be maintained (ie if the use of the medicine were still limited to hospitals and other centres specialising in the treatment of epilepsy) it might be that a valuable treatment would be withheld from people who might benefit from it, particularly those who do not respond to other anti-convulsant medicines. It was hardly practicable to contemplate any legal restriction on the use of the medicines by women likely to become pregnant.

15. In the light of this consideration Ministers after discussion with the Chairman and the Medical Assessor of the Committee on Safety of Medicines agreed to licence Epilim as advised by the Committee.

PRESENT POSITION

16. There have been considerable difficulties in controlling the promotion of this product, although some of these problems would not in fact have been so serious had we then had available the powers to regulate advertisements currently provided by the standard provisions for Product Licences. It is, in particular, difficult to restrict the promotion by pharmaceutical representatives of such products though this does not appear to have been a particular problem with Epilim. In the case of Epilim, we were particularly concerned about one letter which was sent to general practitioners by the Company. This made no mention of the teratogenicity of Epilim, merely relying on the data sheet which it enclosed, but did state that "Epilim represents an advance on traditional therapies, in offering effective control of seizures, as well as the virtual absence of unacceptable side effects".

17. Had there been a category of drugs whose prescribing was restricted to specialists in the treatment of the particular disease, it is clear that Epilim would have been included in this category, at least initially until its place in the treatment of epilepsy had been assessed. In these early stages it could not have been regarded as the drug of choice in view of the hazards in women of child-bearing age, but it was important that it should be available for patients in whom existing therapy had disadvantages and who had been assessed by a consultant as suitable for the new form of treatment in the light of all the risks. It has also illustrated the importance of using the flexible powers conferred by the standard provisions to control the advertising of such "second line" products in order to make sure that appropriate warnings are in fact given in all literature.

18. Epilim has in fact turned out to be a useful drug, and the Drug and Therapeutics Bulletin (1975, 13, 97) concluded that, while it could not yet be recommended as the drug of first choice, it was worth giving as an additional drug to those who had not had adequate help from other drugs. However Professor [redacted] is understood to consider it to be the drug of choice for children with epilepsy. Epilim is also mentioned in the BNF 1976-78.

NOT FOR PUBLICATION

CSM/AR/74/36

COMMITTEE ON SAFETY OF MEDICINES
SUB COMMITTEE ON ADVERSE REACTIONS

Review of recommendations - September 1974

The following paragraphs indicate the up to date position of the various recommendations submitted to the Main Committee since January 1973.

1. OXYMETHOLONE

The licensing authority have been advised of the recommendation that the whole group of products containing C.17 Alkyl substituted testosterone derivatives should be noted for early consideration in association with the forthcoming review of all product licences of right.

2. JAUNDICE AND ERYTHROMYCIN ESTOLATE

A leaflet was despatched to all doctors on 18 July 1973.

3. JAUNDICE FOLLOWING EXPOSURE TO HALOTHANE

There has been some criticism of the Committee on Safety of Medicines' action in publishing the letter on jaundice and halothane and this is the subject of a separate item on the agenda.

4. DRUG FORMULATIONS - NEED FOR MORE INFORMATION

So far no appropriate cases have come to notice where it would be necessary for the licensing authority to ask for excipients to be declared.

5. ANTI-CONVULSANT TERATOGENICITY

The Main Committee are still actively considering this problem and whether action should be taken to warn doctors of the dangers associated with anti-convulsants. The licensing authority have asked licence holders of anti-convulsant preparations which are actively promoted, and which contain phenytoin and phenobarbitone to insert a warning in their data sheets.

6. SAFETY OF MEDICINES ADVISERS

There has been very little progress on this although the Department's Chief Medical Officer agreed to make a further attempt to set up a means of communication with hospitals.

7. IDENTIFICATION OF NEW DRUGS

The general principles for specially marking recently introduced products in MIMMS and in data sheets have been accepted, although one or two points of detail remain to be settled.

Follow up questions from the Yellow Card oral hearing session

Devices contribution

Reporting statistics, by reporter categories (e.g., patients, pharmacists, nurses, GPs etc) and any similarities with FAERS

Yellow Card reporter categories
Yellow Card device reports do not offer a mandatory picklist for the position/profession of the reporter, instead they are asked to provide their "position" in a free text field.

For example, in 2018 Yellow Card reports 1400 were blank for 'position' and there were 1000 different 'types' of positions submitted.

Searching for 'nurse', 'sister' and 'matron' showed a total of 381, 89 and 31 respectively. Similarly, 'doctor', 'consultant' and 'registrar' showed 124, 379 and 17 respectively.

When a Yellow Card report is received, our staff manually select the report source from a picklist (static categories as shown in the table below) when processing the report via our Adverse Incident Tracking System (AITS database).

With the planned modernisation of the Devices applications we will in future have a static/controlled list of professions for users to select. We will have more detail on the profession of the people in the healthcare system who are reporting to us. This would further help us to target awareness of Yellow Card to certain professions if necessary.

Data
Below is a breakdown of all reports for the past 10 years (to end of 2018) for all medical devices as requested. It includes voluntary reporting by users (Yellow Card) and mandatory reporting by manufacturers under the Vigilance system (see MHRA written evidence page 43).

These numbers are accurate at the time we extract them from our database.
It should be noted that this information does not necessarily indicate a fault with any particular device.

Reporting Source	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Manufacturers	3800	4791	5353	6813	7490	8657	10391	11355	12806	13952
Healthcare Professionals	3588	3550	3454	4441	3150	3368	3809	3120	3155	3652
Competent Authority	618	660	583	610	848	651	352	420	390	325
Devolved Administration	8	234	856	886	925	936	876	944	934	964
Member of the Public	104	192	205	316	182	164	400	273	745	1039
MHRA	71	108	34	22	29	22	62	36	49	67
Others	903	727	400	458	723	752	1060	1350	1481	710
Total	9092	10262	10885	13546	13347	14550	16950	17498	19560	20709

Summary of the data

In 2018, a total of 20,709 medical device events was received by the MHRA. Of these:

1. manufacturers made up 67% (mandatory reports to MHRA outside of Yellow Card)
2. reports submitted via the Yellow Card Scheme by healthcare professionals (including those in private practice) and members of the public making up 18% and 5% respectively of all medical device reports.

As stated in MHRA written evidence to IMMDSR, MHRA devices have operated a reporting system for adverse incidents associated with medical devices since the 1980s which has been open to all to report. A computerised reporting system was introduced in 2001.

The Yellow Card scheme then became the route for healthcare professionals and patients and the public to report adverse incidents with medical devices to MHRA in November 2014. The manufacturer may already be aware of these adverse incidents and they must tell us about certain adverse incident reports or safety issues with medical devices which come to their attention (see MHRA response to Q20; Vigilance system).

For the past 5 years, MHRA Devices has seen:

- 9% year on year average increase
- 4% average year on year increase in reporting by healthcare professional (including private)
- 63% average year on year increase in reporting by members of the public

Individual highs and lows of reporting sources could be attributed to the factors given in the SUI and POP mesh data below.

We continue to raise awareness of Yellow Card reporting by users through many workstreams including use of social media, and contact with patient groups, professional bodies and Royal Colleges.

FAERS

MHRA have led the debate and foundation work to develop this type of medical device vigilance transparency within Europe for several years. Indeed, MHRA have put significant investment, into building the European/International IMDRF (International Medical Device Regulators Forum) terminology for use within the European manufacturer incident report (MIR) form that will facilitate an EU scheme. MHRA also led the development of the new EU MIR form that enters use in January 2020, and MHRA are exploring options for UK and EU medical devices transparency facilities based upon this form.

Urogynaecology mesh data – Healthcare professional and Public reports

In MHRAs written evidence submitted in October 2018, we provided many graphs in Annex D with the number of reports since 2010 for SUI, POP and urogynaecological mesh of unknown indication (up to end of September 2018). Some graphs combined reports from healthcare professionals and members of the public.

These numbers have been separated at your request and is like the breakdown for all medical devices above. For consistency against the data we provided in the written evidence, we have completed a breakdown of that data for the period we provided.

Coding has improved over the years, and resource has been dedicated to data cleansing to ensure we improved the quality of data we hold. Any data going back further would be open to interpretation.

Data

The footnotes on page 181 in Annex D of MHRA written evidence must be read in conjunction with the data below. Including, individuals may report an incident at any time after the event so numbers below may not necessarily mean the event occurred in the year it

was reported. These numbers are accurate at the time we extract them from our database. It should be noted that this information does not necessarily indicate a fault with any particular device.

Surgical Mesh incidents for Stress Urinary Incontinence (SUI)

Reporting source	2010	2011	2012	2013	2014	2015	2016	2017	2018
Manufacturers	25		7	7	12	4	7	3	4
Healthcare Professionals	3	2	21	27	86	85	81	183	175
Devolved Administration			1		7	22	12	37	10
Member of the Public	9	33	26	22	22	89	27	115	223
Others				3	45	57	44	3	1
Total	**37**	**35**	**55**	**59**	**172**	**257**	**171**	**341**	**413**

Surgical Mesh incidents for Pelvic Organ Prolapse (POP)

Reporting source	2010	2011	2012	2013	2014	2015	2016	2017	2018
Manufacturers	1	3	5	4	21	8	5	1	8
Healthcare Professionals	1	1	31	20	48	61	25	57	65
Devolved Administration				1	3	4	3	6	4
Member of the Public	2	6	2	10	3	24	15	50	98
MHRA									1
Others					28	21	6	3	
Total	**4**	**10**	**38**	**35**	**103**	**118**	**54**	**117**	**176**

Surgical Mesh incidents for Unknown Indication*

Reporting source	2010	2011	2012	2013	2014	2015	2016	2017	2018
Manufacturers							2		
Healthcare Professionals			2		1	6	18	53	105
Competent Authority			1						
Devolved Administration						1	6	12	2
Member of the Public		3	1	4		6	10	231	142
Others						3	3	2	
Total		**3**	**4**	**4**	**1**	**16**	**39**	**298**	**249**

Summary of the data:

In 2018 (up to end September 2018), a total of 838 reports were received by the MHRA for SUI, POP and unknown indication of urogynaecological mesh. Of these:

1. manufacturers made up about 1% (mandatory reports to MHRA outside of Yellow Card)
2. reports submitted via the Yellow Card Scheme by healthcare professionals and members of the public making up about 41% and 55% respectively of all reports.

In comparison with the trend in reporting sources for all medical devices, a significant percentage of reports are by healthcare professionals and members of the public for urogynacological mesh.

MHRA think the notable increase in 2015 is due to factors such as:

- increased awareness by patients, carers and their families through the important work of the patient groups to encourage reporting to MHRA.
- recommendations for healthcare professionals to report to MHRA made in the 2015 NHS E Mesh Oversight Report and Scottish Independent Review
- increased Yellow Card reporting awareness from activities by MHRA such as meeting with Royal Colleges and clinical bodies and media channels
- professional bodies promoting reporting (links to our website for example)

*In the summer of 2018, we made a small change to Yellow Card, so the public are asked what the device is used for (if they know). MHRA feel this will reduce the number of 'unknowns' reported to MHRA and help with our analysis of this data.

Examples of rapid signals and actions

Devices have provided examples below of rapid identification of a signal requiring several timely actions to protect public safety. As outlined in our evidence signals can came come from one or more incidents and/or a range of sources, not just isolated to Yellow Card reports (see page 24 of MHRA written evidence).

1. MHRA Devices received an adverse event via Yellow Card reporting a potential risk to patients who may change their insulin delivery pump without discussing it with a healthcare professional first. Gathering and analysing all relevant information and the risk to patients was assessed within 5 days. A Medical Device Alert for actions to be taken by healthcare professionals and a press release (to reach out to the public) was issued within 20 working days of receipt of report . The reason for the safety message was to prevent risk of hyperglycaemia for example by ensuring patients knew the importance of checking with their healthcare professional/diabetes specialist before agreeing to trial or use a new insulin delivery pump which may not be suitable for use.

2. In March 2015 MHRA received a Yellow Card report of a patient death where a mechanical heart valve was implanted upside down in error, contrary to the warnings given by the manufacturer in their instruction for use. This is very rare (5 reports worldwide in about 15 years) and a 'NHS never event'. An investigation started immediately, including contacting manufacturers of this type of valve for design information, gathering, analysing that information and making conclusions and recommendations. We also contacted EU and non-EU regulators for details of similar reports and a consensus in July was reached that a design change may reduce likelihood of such an event.

   After extensive discussion by November 2015, MHRA successfully got manufacturers to redesign their devices. Some have already changed design, and some are in the process of appropriate and robust design validation, verification and regulatory approval.

Sling the mesh written evidence and 2014 MHRA report

IMMDSR Question: Can the MHRA explain the discrepancy of data shown in the STM Annex and the MHRA published report?
The Sling the Mesh table displayed in Annex 13 of their written evidence is marked 'all mesh' and their table includes hernia mesh reports submitted to MHRA in 2001-2011 where death

was reported, and vaginal mesh reports submitted in 2013-2015 where death was also reported.

MHRA's 'A summary of the evidence on the benefits and risk of vaginal mesh implants' gives data from 2005-2013 for vaginal mesh only. It does not contain hernia mesh (of which there are many types) and therefore explains the difference in the numbers presented by Sling the Mesh and that in the MHRA summary report.

Data MHRA provide upon request (e.g. Freedom of Information requests) will give a description of the device so that hernia mesh and vaginal mesh are clearly identified.

It is important to note our report states:
'From the information we have, all four deaths are consistent with complications related to the surgical procedure itself. This does not implicate the mesh implants in the deaths.'

Any reports of death may not be associated with the device implanted but due to unrelated patient factors. Details of the reports of death may have changed since the report was submitted.

In reference to the *'Was the manufacturer contacted'* column in Annex 13 of the Sling the Mesh evidence, all incidents in which the name of the manufacturer has been provided by the reporter are sent to the manufacturer for them to investigate and anonymised as appropriate if a member of public does not give consent to release their personal information. We thought it useful to clarify this.

IMMDSR Question: Is this a coding /poor quality data problem?

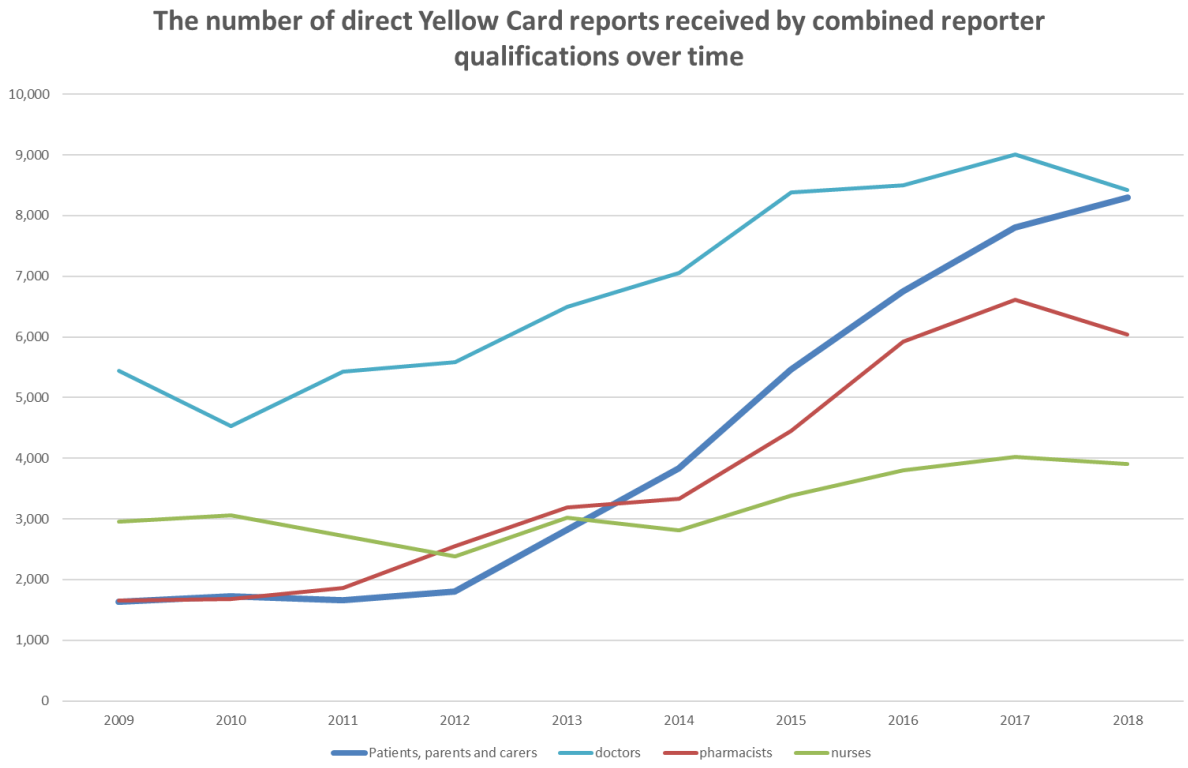
No, the reasons above demonstrate the data given by MHRA is correct for vaginal mesh.

Follow up questions from the Yellow Card oral hearing session

Medicines contribution

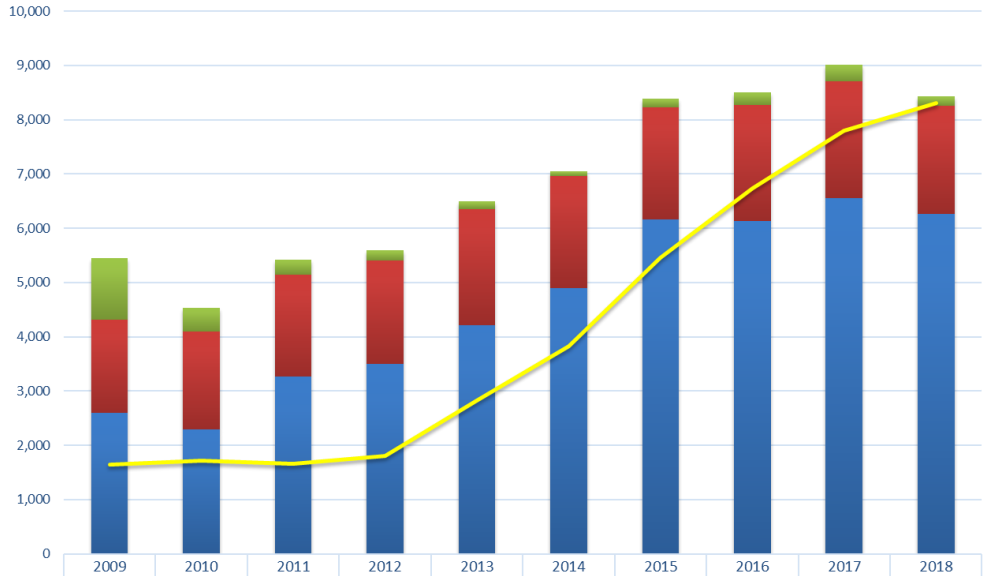
Adverse drug reaction reporting data by reporter category for both medicines going back 10 years (eg patients, pharmacists, nurses, GPs etc) and any similarities with FAERS

Yellow Card reporting for suspected adverse drug reactions (ADRs) has increased by 93% (14,358 Yellow Card reports) over a ten-year period.



Patient Yellow Card reporting is at the highest to date. More Yellow Card reports are received from patients than GPs who have previously been the cornerstone reporters of the Scheme since it was established over 50 years ago. The graph below shows how Yellow Card reporting from members of the public compares with the two largest groups of doctors that report to the Scheme over time. As shown by the yellow line in the graph, members of the public have reported more Yellow Cards than GPs since 2016 and by 2018, members of the public are reporting more than GPs and hospital doctors combined.

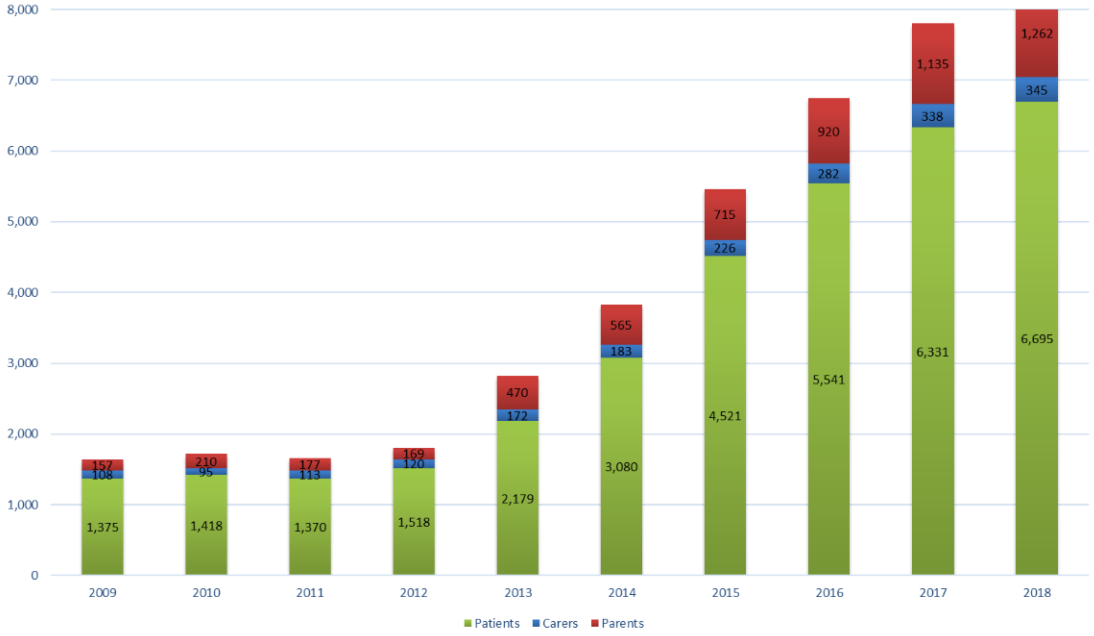
Direct Yellow Card reports of suspected adverse drug reactions received by the MHRA from doctors over time and patient reporting (includes parents and carers)



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Physician	1,131	430	277	192	143	93	152	235	307	165
Hospital doctor	1,723	1,806	1,875	1,899	2,145	2,069	2,074	2,128	2,151	1,990
GPs	2,593	2,291	3,274	3,500	4,210	4,890	6,157	6,137	6,549	6,269
Patients, parents and carers	1,640	1,723	1,660	1,807	2,821	3,828	5,462	6,743	7,804	8,302

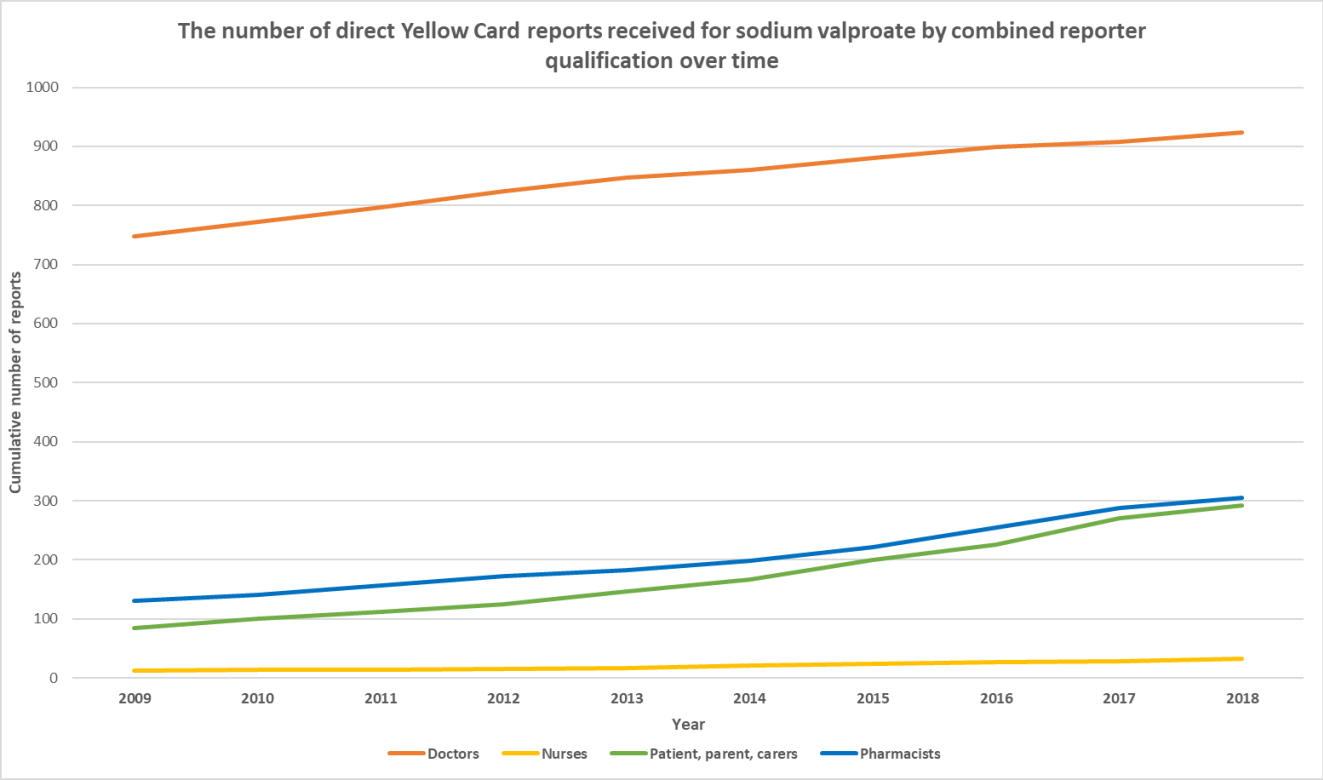
In 2018, reporting from members of the public increased by 7% compared to 2017. The graph below shows this increasing trend over the last decade. This is due to MHRA and its five regional Yellow Card centres continuing outreach work with patients directly, mainly through their organisations and charities, via campaigns, social media, videos, animations, messages about the Yellow Card Scheme within medicine patient information leaflets, and information about the importance of reporting being added to trusted sources of information online. In turn, more patient safety signals are being detected from patient reports than ever before.

Suspected side effect (adverse drug reaction) reports received via the Yellow Card Scheme from memebers of the public over time



Adverse Drug Reaction reports received through the Yellow Card Scheme from patients, public and healthcare professionals associated with sodium valproate

Since the Yellow Card scheme was established, a total of 4,800 UK spontaneous Yellow Card reports associated with sodium valproate have been received. Reports received directly from members of the public account for 6% of the total number of reports received for sodium valproate. Of these reports, 1815 reports, have been received in the last 10 years. Since 2009, 37% (666 reports) were received directly from members of the public and healthcare professionals. The graph below shows the number of Yellow Card reports received by reporter qualification over the 10-year period.

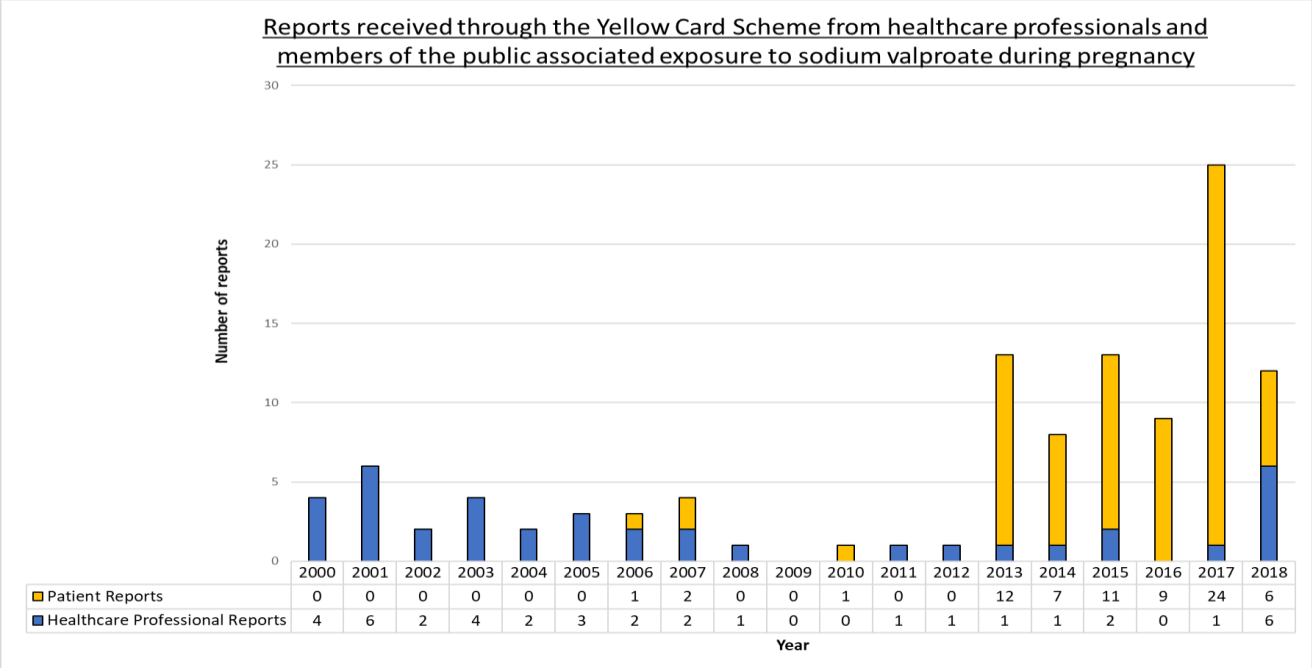


The graph shows that the number Yellow Card reports for sodium valproate received directly from patient, parents and carers has increased the most (244%, 207 reports) over the last 10 years. This is followed by reports from pharmacists with an increase in reports of 133% (174 reports). Reports from doctors have increased by 23% over the last 10 years. In this time period reports from nurses regarding sodium valproate has remained static.

Adverse Drug Reaction reports received through the Yellow Card Scheme from patients, public and healthcare professionals associated with sodium valproate in pregnancy

Since 1976, MHRA have received 325 Yellow Card reports associated with a suspected adverse reaction to sodium valproate use during pregnancy directly from members of the public (patients, parents and carers) and healthcare professionals. Please note that the data below may refer to an adverse reaction(s) experienced either by the mother and/or the child.

Of the 325 direct Yellow Card reports received for sodium valproate 34% (111) have been received since 2000. The graph below details the number of direct Yellow Card reports received by the Yellow Card Scheme associated with an exposure to sodium valproate during pregnancy each year since 2000. In addition, the graph shows whether the reports were received from patients, parents and carers (patient reports) or from healthcare professionals for each year. Please note that the number of the reports in the graph does not equate to more than the number of direct reports as one report may have more than one reporter.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Patient Reports	0	0	0	0	0	0	1	2	0	0	1	0	0	12	7	11	9	24	6
Healthcare Professional Reports	4	6	2	4	2	3	2	2	1	0	0	1	1	1	1	2	0	1	6

The graph shows that since 2000, patients have been the most frequent reporter group of suspected adverse reactions to Valproate use during pregnancy. The majority of reports from patients have been received from 2013 onwards. In 2013, following significant new data the MHRA initiated an EU wide safety review (referral). This also corresponds with increased communications and work with stakeholders to raise awareness of sodium valproate use during pregnancy and women of child-bearing potential. The peak in patient reporting in 2017 may be attributed to an increase in awareness from a Patient Safety Alert from NHS Improvement.

There were also two peaks in reporting from healthcare professionals in 2001 and 2003 which corresponded with updates to the product information which were communicated to healthcare professionals.

For all report types, direct and indirect reports received via companies (marketing authorisation holders), there has been a total of 488 suspected Yellow Card reports associated with valproate use during pregnancy over the last 10 years. In this time period, a total of 83 reports have been received directly from patients and healthcare professionals and 405 reports have been received from companies. The table below shows a further breakdown of the direct Yellow Card reports associated with sodium valproate exposure during pregnancy for each reporter group since 2009.

Yellow Card reports associated with sodium valproate exposure during pregnancy received via the Yellow Card Scheme from each reporter category

Reporter Qualification	Year									
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Patients, parents, Carers	0	1	0	0	12	7	11	9	24	6
Pharmacists	0	0	0	0	0	1	0	0	0	2
Other healthcare professionals	0	0	0	0	0	0	0	0	1	0
Midwives	0	0	0	0	0	0	1	0	0	0
GP	0	0	1	0	0	0	0	0	0	0
Hospital Doctor/ Physician	0	0	0	1	1	0	1	0	0	4
Marketing Authorisation Holders	15	26	8	57	63	21	19	8	117	71

Of the total number of reports received for sodium valproate exposure during pregnancy, themajority of reports (83%, 405 reports) have been received from companies (marketing authorisation holders). Of the 405 reports received from companies, 53% (215 reports) originated from literature reviews by the company. Patients, parents and carers represented 14% (70 reports) of the total number of reports.

How does the UK's Yellow Card Scheme compare to FAERS?

The USA's 'FDA Adverse Event Reporting System' (FAERS) receives 4% reports directly from healthcare professionals and members of the public through the system called 'MedWatch', which is equivalent to the Yellow Card Scheme.

In 2018, a total of 69% of ADR reports received by the MHRA's Yellow Card Scheme were submitted directly from members of the public and healthcare professionals. The MHRA believes there is great value from the richness of ADR data received directly from patients

and healthcare professionals reporting to the Yellow Card Scheme, which adds to the value of the Yellow Card Scheme to detect signals.

Both Yellow Card and FAERS ADR reporting systems follow the international safety reporting guidance issued by the International Conference on Harmonisation. The MHRA and FDA are also members of the World Health Organisation Programme for International Drug Monitoring which has operated since 1968.

Awareness of Yellow Card Scheme

We constantly strive to improve public awareness of the Yellow Card Scheme. The most recent annual ADR awareness week social campaign run by the MHRA in November 2018, involving 36 medicines regulators internationally, had a special focus on raising awareness about the importance of reporting suspected side effects in infants and children, and during pregnancy, including when breastfeeding. The campaign week saw an increase of 24% in direct reports from 643 to 800 suspected ADR reports compared to a similar week the year before and the hashtag #medsafetyweek reached over 8 million people within a week. This was followed by a 7% (139) increase in direct suspected ADR reporting in December 2018 compared to December 2017.

Examples of rapid responses to safety signals from Yellow Cards

Since its inception over 50 years ago, Yellow Card reporting has helped to identify numerous important safety issues which were not previously recognised as being related to a particular medicine until the MHRA received information on Yellow Cards.

Some examples of action to protect public health which illustrate the wide range of safety signals form the Yellow Card Scheme are given below.

Aspirin and fatal Reye's Syndrome in children

A 13-year-old girl died from Reye's Syndrome after taking Beecham's powders (including aspirin). The Yellow Card report was rapidly analysed at the time and a paper was taken to the next Committee on Safety of Medicines (CSM). The CSM advised changing advice so that children should not be given aspirin below the age of 16 years. This was widely publicised five days later to make sure that health professionals, parents and children were aware of the new advice.

Warfarin and cranberry juice

A Yellow Card report of a gastrointestinal and pericardial haemorrhage in a 70-year old man on warfarin who had been drinking cranberry juice led to an investigation of a possible interaction. Together with 7 other Yellow Cards, this enabled the CSM to communicate publicly about the risk and a letter was published in the British Medical Journal.

Nexplanon (etonorgestrel) contraceptive implants and device migration

Following a number of cases of the Nexplanon contraceptive implant migrating away from the insertion site via the vasculature and reaching the lung, a rapidly issued Drug Safety Update gave advice to healthcare professionals about insertion and to women to check placement of the device frequently for the first few months.

Daclizumab (Zinbryta) and reports of encephalitis

Yellow Card reports from neurologists describing delayed onset encephalitis associated with the multiple sclerosis drug daclizumab enabled a letter to be sent to warn clinicians to be alert and ready to diagnose and promptly treat this adverse reaction even months after the drug had been withdrawn.

Off-label use of hydrocortisone muco-adhesive buccal tablets and risk of acute adrenal crisis Issue

A paediatric endocrinologist raised concerns in Yellow Card reports about the use of hydrocortisone muco-adhesive buccal tablets in children for the treatment of adrenal insufficiency, potentially leading to acute adrenal crisis due to poor absorption. This led to prompt advice from the CHM Paediatric Expert Group and updates to the product information.

Recall of irbesartan containing products

A Yellow Card report received from a pharmaceutical company raised a signal of an impurity, a possible N-nitrosodiethylamine (NDEA) contamination, in irbesartan-containing products. The MHRA rapidly issued a recall as a precautionary measure. People were advised to not stop their medication and speak to a doctor or pharmacist if they had any concerns.

Independent Medicines and Medical Devices Safety Review

MHRA paper on medical device registries

February 2019

Summary of key points

1. MHRA supports the development of a comprehensive system of medical device registries (with particular focus on implantable devices) in support of patient safety. This would be in line with new European Regulations, which encourage the establishment of registries and which introduce the use of Unique Device Identifiers and their capture within healthcare records.

2. Registries should be embedded in the health care delivery system with data collection being integrated with work flow of clinical teams using (for example) scanning technologies. This approach has been successfully demonstrated via the ***Scan4Safety*** work programmes.

3. Registries have the demonstrated ability to be a key part of healthcare quality assurance systems by providing information about both device safety/performance and variability of clinical practice that is:

- Comparative
- transparent; and
- tailored

to the needs of patients, medical device regulators, other healthcare regulators and healthcare professionals/institutions.

4. While it is not within MHRA's current remit to run medical device registries, we have been a long-term advocate of them and have worked internationally to promote their use and coordination. Our experience leads us to conclude, that in order to be effective, it is vital that registries, should have:

- clearly defined aims and objectives which are accepted by key stakeholders
- sustainable long-term funding
- governance structures to ensure data confidentiality, transparency and appropriate reporting / feedback to key stakeholders

Value of registries

Medical device registries are powerful tools for gathering information about the safety and performance of devices and clinical practice associated with their use. Such information can be of significant value to:

- **patients** - to inform them about the safety of the devices that they are exposed to and the clinical practice of the healthcare professionals and institutions that treat them
- **MHRA/healthcare regulators** - to inform regulatory decision-making about device safety and performance and healthcare practice throughout the device lifecycle
- **manufacturers** - to improve monitoring of the safety and performance of their devices throughout their lifecycle; covering initial introduction; post-market clinical follow-up; and longer-term post market surveillance

- **healthcare professionals and professional institutions** - to provide feedback a) to clinicians about their clinical performance in comparison with their peers b) to professional bodies in support of clinical audit; c) for decision making about choice of devices if implanted devices safety/performance is found to be sub-optimal in certain situations.

An example of how MHRA uses registry data to inform safety evaluation and regulatory decision making is given in box 1.

Box 1

MHRA use of registry data

Information from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man (NJR) is frequently used by the MHRA as a post market surveillance tool to detect poorly performing orthopaedic devices. MHRA has direct access to NJR data through the supplier feedback system, enabling the MHRA to obtain detailed denominator and revision data on all hip, knee, ankle, elbow and shoulder joint replacements implanted in the UK. MHRA is also a member of the NJR implant performance group and since 2009 have been notified of outlier devices, which the MHRA have subsequently investigated.

Analysis of data from the NJR was pivotal to MHRA being the first regulator worldwide to publish safety information for clinicians about the risk of soft tissue reactions to metal wear debris in patients implanted with metal-on-metal (MoM) hip replacements (Medical Device Alert MDA/2010/033). The MDA also provided advice on the clinical management of such patients. The most recent iteration of the MHRA advice for clinicians managing MoM patients was published in MDA/2017/018 and the analysis of NJR data again played a significant role in the generation of the recommendations made in this important safety communication.

European regulatory requirements

The new European Medical Device Regulation (EU) 2017/745 introduces the use of Unique Device Identifiers and their capture within healthcare records in support of patient safety (Article 27(9)). The regulation also requires Member States to take all appropriate measures to encourage the establishment of registries and databanks for specific types of devices, setting common principles to collect comparable information (Article 108) and it says that registries should contribute to the independent evaluation of the long-term safety and performance of devices and the traceability of implantable devices.

International Guidance on medical device registries

The International Medical Device Regulator's Forum (IMDRF) - a voluntary group of medical device regulators from around the world - has developed a set of regulatory principles for medical device registries – see http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf . This guidance document defines a **medical device registry** as:

An organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by

exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system).

In addition, IMDRF identifies eight qualifiers which define the impact, value and sustainability of a medical device registry ie:

1. DEVICE: The registry should contain sufficient information to uniquely identify the device. Ideally, the unique device identifier would be included, but when the UDI is not available, the registry would include a combination of identifiers (catalog, number, manufacturer, description) that, in combination, will assist in uniquely identifying the device.

2. QUALITY IMPROVEMENT SYSTEM: The registry should be part of a health care delivery quality improvement system or evolving into one as device technologies are diffused into practice and need continuing evaluation (including outlier identification).

3. BENEFICIAL CHANGE: The registry should have established mechanisms to bring about beneficial change in health care delivery through stakeholder participation, ownership and integration into the relevant health care systems.

4. EFFICIENCY: The registry should be embedded in the health care delivery system so that data collection occurs as part of care delivery (i.e., not overly burdensome, not highly complicated, not overly costly, etc.) and integrated with work flow of clinical teams.

5. ACTIONABLE DATA: The registry should provide actionable information in a relevant and timely manner to decision makers.

6. TRANPARENCY: The governance structure, data access, and analytical processes of the registry should be transparent.

7. LINKABILITY: Information in the registry should be able to be linked with other data sources for enhancement including adequate follow up achievement.

8. TOTAL DEVICE LIFE-CYCLE: The registry should be able to serve as infrastructure for seamless integration of evidence throughout the device life cycle.

An exemplar of such a registry is the National Joint Registry (NJR) of England, Wales, Northern Ireland and the Isle of Man (http://www.njrcentre.org.uk/njrcentre/default.aspx) . See Appendix 1 for more information on the NJR and how it fits with the eight qualifiers outlined above.

Key requirements for registry success

MHRA's experience with registries shows that for a device registry to be successful, the following criteria need to be fulfilled:

*(i) The registry **aims and objectives should be clearly defined** and accepted by key stakeholders.*

Questions that the registry needs to answer (and hence the data that needs to be collected) can only be identified based on this. While there will be a lot of common data elements for all device registries there will also be specific data requirements (particularly relating to clinical practice and indications for use) for each type of device

The mission statement and goals of the National Joint Registry (NJR) illustrate this point – see box 2 below.

Box 2

The NJR mission and goals are as follows:

NJR mission statement:

'The purpose of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man is to collect high quality and relevant data about joint replacement surgery in order to provide an early warning of issues relating to patient safety. In a continuous drive to improve the quality of outcomes and ensure the quality and cost effectiveness of joint replacement surgery, the NJR will monitor and report on outcomes, and support and enable related research.'

NJR goals:

•Monitor in real time the outcomes achieved by brand of prosthesis, hospital and surgeon, and highlight where these fall below an expected performance in order to allow prompt investigation and to support follow-up action.

•Inform patients, clinicians, providers and commissioners of healthcare, regulators and implant suppliers of the outcomes achieved in joint replacement surgery.

•Evidence variations in outcome achieved across surgical practice in order to inform best practice.

•Enhance patient awareness of joint replacement outcomes to better inform patient choice and patients' quality of experience through engagement with patients and patient organisations.

•Support evidence-based purchasing of joint replacement implants for healthcare providers to support quality and cost effectiveness.

•Support suppliers in the routine post-market surveillance of implants and provide information to clinicians, patients, hospital management and the regulatory authorities.

From MHRA's perspective, for a medical device registry to be of use in informing regulatory decision making about device safety, the aims/objectives of the registry should include:

- to monitor the performance of the devices to improve patient safety and take action where necessary
- to identify possible trends and complications relating to specific devices (outlier detection)
- to identify patients implanted with specific devices in the event a subsequent device recall or the need for enhanced patient follow-up (track-and-trace).

(ii) The registry should have a ***sustainable long-term funding mechanism***

Implant registries can only yield useful information on device performance and patient safety if they can be maintained in the long term on a firm financial footing. Funding should include adequate provision for:

a) data collection;

b) promotion of the value of the registry to users (to optimise participation/compliance);

c) data analysis and

d) transparent feedback/reporting to key stakeholders.

It is also worth noting that the lead time for acquisition of sufficient meaningful data to make a positive contribution to patient safety will often be lengthy (particularly for implants) based upon the average period for which the device is implanted and the fact that problems may not become apparent for 5+ years after the device is introduced to clinical use. There are no quick fixes in this area, but if organised as proposed the investment delivers earlier outlier identification and options for intervention.

The funding model adopted by the NJR illustrates one mechanism by which sustainable registry funding can be achieved - see box 3.

Box 3

Funding arrangement of for the NJR:

The NJR is funded through a subscription model raised on hip, knee, ankle, elbow and shoulder procedures.

Under these arrangements, each provider organisation is issued with an annual invoice directly from the Healthcare Quality Improvement Partnership (HQIP) for an NJR subscription charge based upon the provider's prior year's procedure volume.

HQIP manages the NJR income in a restricted fund that is overseen by the NJR Steering Committee and spent in accordance with the strategic plan.

*(iii) The registry should have **appropriate governance structure and mechanisms** in place:*

Oversight by a steering committee or similar (involving key stakeholders) to ensure appropriate data confidentiality arrangements and transparency (including reporting / feedback to key stakeholders). It would, in particular, oversee the effective running of registry to support the performance monitoring of the implants and the clinicians/clinical procedures.

See (for example) a summary of the role and responsibilities of the NJR Steering Committee – see box 4.

Box 4

Role and responsibilities NJR Steering Committee

The NJRSC sets the strategic direction of the NJR, and it is responsible for the overall NJR budget and approval of work, supported by appropriate business case(s), aligned to the NJR's Strategic Plan. The NJRSC ensures:

- That the NJR budget is effectively managed/monitored
- That outcomes achieved by brand of prostheses, hospital and surgeon are monitored and where these falls below expected performance are highlighted to enable prompt investigation and follow-up by relevant implant suppliers, regulators, commissioners and providers of orthopaedic care
- That appropriate stakeholders, for example patients, clinicians, providers and commissioners of healthcare, regulators and implant suppliers, are involved in and consulted on the work of the National Joint Registry as appropriate and are informed of the outcomes achieved in joint replacement surgery
- That patient awareness of joint replacement outcomes is enhanced to better inform patient choice and patient's quality of experience through engagement with patients, patient organisations and providers of care
- That appropriate governance and monitoring arrangements are in place to facilitate the use of NJR data to support and enable related research.

Convergence of medical device registries with DHSC Scan4Safety programme (or similar standards based electronic data capture across the UK)

The ***Scan4Safety*** methodology uses standards-based electronic data capture of the primary inputs to care. A range of technologies can be utilised as data carriers to enable real time data capture using barcodes, RFID or biometrics (fingerprint/facial recognition). The goal of ***Scan4Safety*** is to match these inputs to clinical outcome data (such as morbidity, readmission rates, patient satisfaction etc) in order to allow best (and worst) practice to be identified and unwarranted clinical variation to be addressed.

Accurate data captured electronically is clearly of significant value to medical device registries and ***Scan4Safety*** data can be structured to feed registries. ***Scan4Safety*** and the MHRA are currently working with the NJR to develop a solution to provide orthopaedic implant data to the NJR without the need for using paper forms etc. for initial data recording. Such an approach should be equally applicable to other UK medical device registries.

Any infrastructure development, like ***Scan4Safety*** in England, requires significant investment costs, but this programme has already demonstrated net operational cost savings in Trusts where it has been implemented. In the longer term it may therefore be possible to develop a system whereby key information is held in patient electronic records (rather than in standalone registries) allowing direct assessment of patient outcomes / implant performance for all types of implantable device and obviating the need for device specific registries. This may represent a lower cost option to traditional registries. This approach is envisaged by Sir Bruce Keogh in his Review of the Regulation of Cosmetic Interventions – 2013 - see recommendation 20 from:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192028/Review_of_the_Regulation_of_Cosmetic_Interventions.pdf

Appendix 1 – Information about the NJR and how it fits with the eight IMDRF registry qualifiers

The National Joint Registry (NJR) of England, Wales, Northern Ireland and the Isle of Man (NJR) was established by the English Department of Health and Welsh Government in April 2003 to collect information on and to monitor the performance of joint replacement implants. The registry includes data on all hip, knee, ankle, elbow, and shoulder joint replacements across the National Health System (NHS) and the independent healthcare sector, and is the largest joint replacement registry in the world – currently the registry includes over 2 million records. The data from the NJR are used to monitor clinical outcomes data (rates of mortality) following surgery and also implant survivorship (measured as the time between procedures), at the level of hospital, surgeon and implant, tracking and linking information on primary and revision procedures.

The NJR is managed by the Health Quality Improvement Partnership (HQIP) on behalf of the Department of Health and the Governments of Wales and Northern Ireland. Day-to-day operations of the Registry is subcontracted to Northgate Public Services, a software and outsourcing business that manages collection and reporting of the data. Since April 2014 the NJR has been funded through subscriptions charged to hospitals (on a cost per procedure basis) and to industry (for data and reporting services). The NJR reports in excess of 95% coverage nationally and is currently undertaking Data Quality Audit to validate underlying data quality. The registry publishes an in-depth annual report in September of each year and provided regular updates about device performance to manufacturers and regulators and about surgeon performance to clinicians and hospitals.

NJR fit with IMDRF qualifiers

→ **DEVICE:** NJR has detailed information on each device component
→ **QUALITY IMPROVEMENT SYSTEM:** NJR regularly monitors surgeon and device performance and has "surgeon outlier" and "implant scrutiny" groups.
→ **BENEFICIAL CHANGE:** NJR informs professionals, regulators and manufacturers about device use, choices and performance. Number of documented outlier devices was no longer used as a result.
→ **EFFICIENCY:** NJR data collection is not currently embedded in the delivery of care in some delivery sites, is extensive but easy to complete. Submission is mandatory for NHS. Data capture is electronic including bar code scanning but the majority of the data are collected on paper first.
→ **ACTIONABLE DATA**: NJR reports back to each participating hospitals to compare against others. Device and surgeon outcome analysis is done twice yearly and is reviewed by a designated panel. Device outliers are reported to manufacturers and competent authorities.
→ **TRANSPARENCY**: NJR has a formal governance system overseen by a steering committee. The NJR publishes annual detailed report. Provides manufacturers, clinicians and the UK regulator has "real-time" electronic access to relevant information to conduct their own analyses.
→ **LINKABILITY**: Linkages are carried out between NJR and hospital episode statistics. UK regulators can cross-correlate NJR data on implants with manufacturer vigilance reports.
→ **TOTAL LIFE-CYCLE:** NJR can be used to collect data on joint replacement performance for both pre-market and post-market phases. It is also used to collect/analyse data for post-market clinical follow-up.

In the MHRA evidence you refer to 450 medication and 350 medical devices safety officers on the ground. These are not outward, patient facing operatives. They are intended to help improve the quality and frequency of the Trust providers' adverse event/incident reporting. Have they reversed the decline in clinician adverse event reporting? Typically, what rank of organisational seniority are they?

The MDSO and MSO networks were established following Patient Safety Alerts issued in March 2014 [Annex 1 and 2] asking providers to identify an MSO and MDSO in their organisation and board level directors to oversee reporting and learning.

All NHS trusts now have MSOs and MDSOs, and an increasing proportion of CCGs and private providers of NHS-funded care have also created MSO and MDSO roles. Many new and under-recognised patient safety issues relate to medicines and medical devices, partly because of the level of innovation and new products, making these networks a key route for communicating new or under-recognised risks (p27 in attached *Patient safety review and response report April to September 17, NHS Improvement*) [Annex 3]

MDSOs

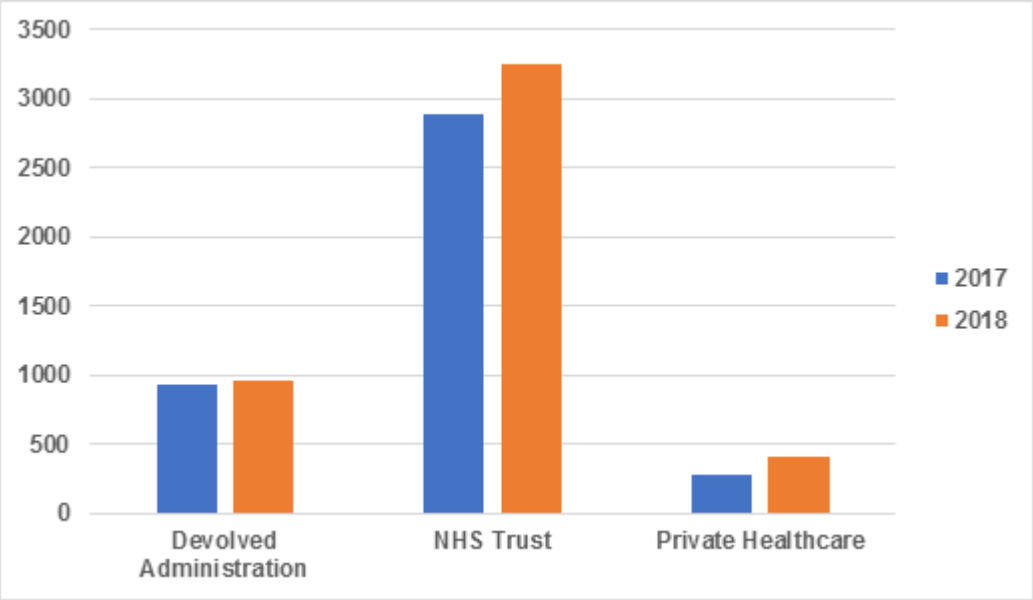
A recent survey of Medical Devices Safety Officers (MDSOs) undertaken by MHRA and NHSI indicated that MDSOs are drawn from diverse sectors, with an increase in MDSOs describing themselves as 'other professional background', but a large group continue to be drawn from clinical engineering. Attached is the poster that was presented at the annual MDSO and MSO conference in January 2019 [Annex 4].

The purpose of clinical engineering is to manage medical devices within NHS Trusts/Healthcare providers to ensure that the benefits of medical devices are maximised and risks minimised. This involves pre-purchase evaluations, acceptance tests, maintenance and development of specialist items. Clinical Engineers also train and educate medical device users, assist with risk management following incidents and where medical devices are subject to safety notices.

The thinking behind the development of MDSO roles was to increase the 'reach' of MHRA and NHSI within NHS Trusts and healthcare providers to promote the patient safety agenda and to increase the quality and quantity of adverse incident reports we receive. MDSOs also have an important role to play in disseminating safety information such as Medical Device Alerts. We hold monthly webexes with the MDSO network and provide an annual joint conference, with NHSI, for MDSOs and MSOs to support them in their role.

Our data indicates that adverse incidents from NHS and private healthcare providers are increasing, rather than declining, although it is not possible to say that this is because of the actions of the MDSOs, it could be due to a number of factors. The way we collect the data means that we cannot completely ascertain if the reports originated from clinicians. There are 3 main areas where reports from clinicians would appear: NHS Trusts, Private Healthcare and via reports shared with us by the Devolved Administrations. Here is a snap shot from the last 2 years.

Report Source	2017	2018
Devolved Administration	934	963
NHS Trust	2880	3242
Private Healthcare	275	411



In terms of the organisational seniority of MDSOs. We don't have any very recent data. We did undertake a survey in January 2015 which asked about the grade of individuals doing the MDSO role in NHS Trusts. 102 people responded to this survey although not all respondents answered the question on grade. The highest grade cited was NHS Agenda for Change (AfC) Band 8d with the most frequently occurring Band being cited as AfC Band 7 or below.

The presentation on The Role of Medical Device Safety Officers (MDSO) in the UK by Paul Lee at Morriston Hospital (2017) may be of interest https://www.youtube.com/watch?v=e1rWdbkxUZw.

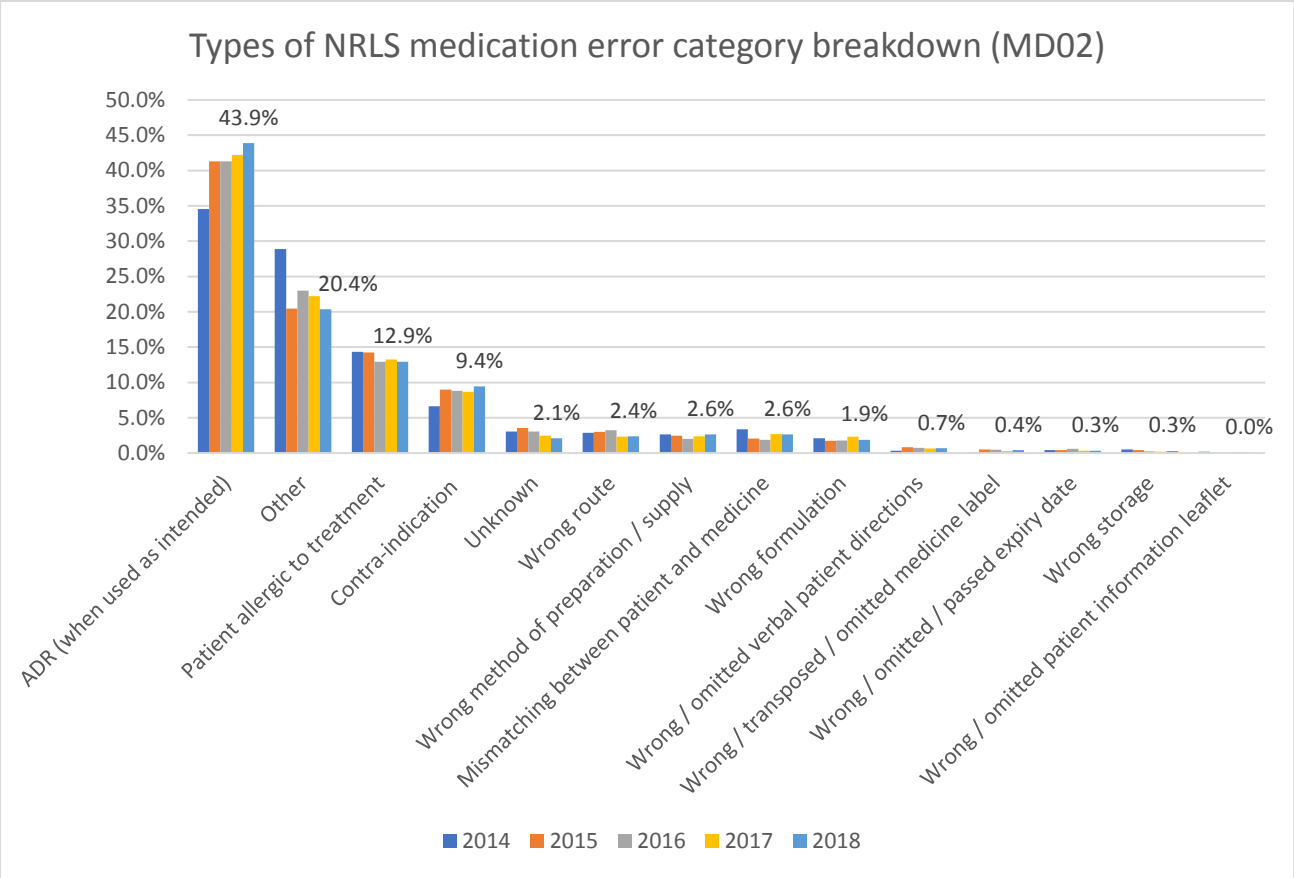
MSOs

The National Medication Safety Network was established in 2014, and as part of this there are around 500 registered Medication Safety Officers (MSOs) who work by promoting reporting and improving the quality of reports in their local areas. The vast majority of MSOs are hospital pharmacists; however the MHRA does not hold any current data on the seniority of their roles.

The MSOs encourage reporting of incidents via local risk management systems which feed into NHS Improvement's National Reporting and Learning System (NRLS). The MHRA has a data sharing agreement with NHSI to share details of medication incident reports where harm

has occurred. These data are reviewed by the MHRA and reports can be uploaded in the pharmacovigilance database as Yellow Card reports, where applicable. All medication related incident reports from the NRLS are reviewed, and approximately a third of these are valid ADR reports. Reports of interest such as, but not limited, to those which may lead to detecting signals are uploaded as Yellow Cards in the MHRA database. Medication incident data received from the NRLS has increased by 80% since 2014 and was at its highest in 2018. This upward trend may be due to the increasing role of MSOs but other factors may also play a part.

The quality of reports received via the NRLS has also increased over the time we have received such reports. The proportion of valid ADR reports (where harm has occurred as a result of administration of a medication, and the report contains all the necessary details required for a valid report) has increased from 28% to 32% therefore suggesting the reports received contain more usable information. Additionally, the quality of categorising medication error reports has increased over time, and the number of reports categorised as "unknown" or "other" has decreased as shown below.



As well as encouraging safety incident reporting in their local area, MSOs have contributed to signal detection activities such as highlighting safety concerns about products based on their knowledge and experience in clinical practice. Examples of these include: concerns about patient technique in use of Braltus (tiotropium bromide) and poor instructions and misunderstanding on how to use the Zonda inhaler causing a choking risk; and dabigatran being dispensed into dosette boxes which led to degradation of the capsules. Both of these issues were brought to the attention of MHRA by MSOs before they would have been flagged up in routine signal detection activities, therefore enabling the MHRA to take regulatory action

more promptly. Other signals where the majority of reports were received from NRLS include a recent signal on enoxaparin, and the contraindicated use of certain oral anticoagulants.

Annex 1: Patient Safety Alert. 20 March 2014. Improving medication error incident reporting and learning. https://www.england.nhs.uk/wp-content/uploads/2014/03/psa-med-error.pdf

Annex 2: Patient Safety Alert. 20 March 2014. Improving medical device incident reporting and learning. https://www.england.nhs.uk/wp-content/uploads/2014/03/psa-med-device-inci.pdf

Annex 3: Patient safety review and response report April to September 2017: *A summary of how we reviewed and responded to the patient safety issues you reported.* NHS Improvement. 21 March 2018. https://improvement.nhs.uk/documents/2526/Patient_Safety_Review_and_Response_Report_Apr-Sept_2017.pdf

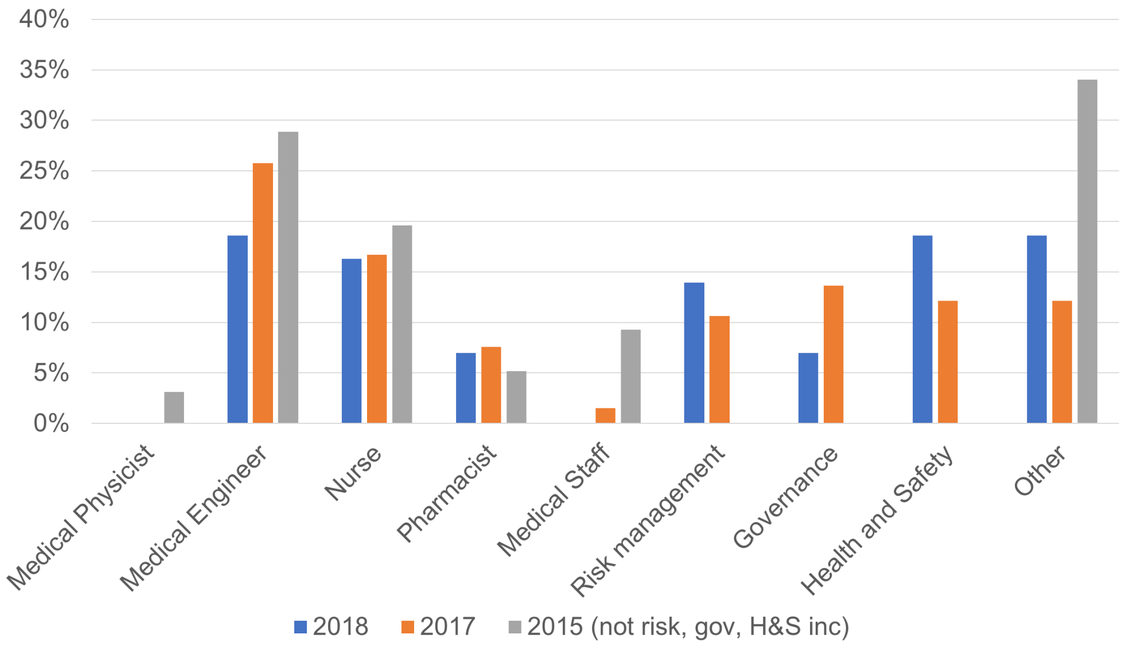
Annex 4:

Medicines & Healthcare products Regulatory Agency

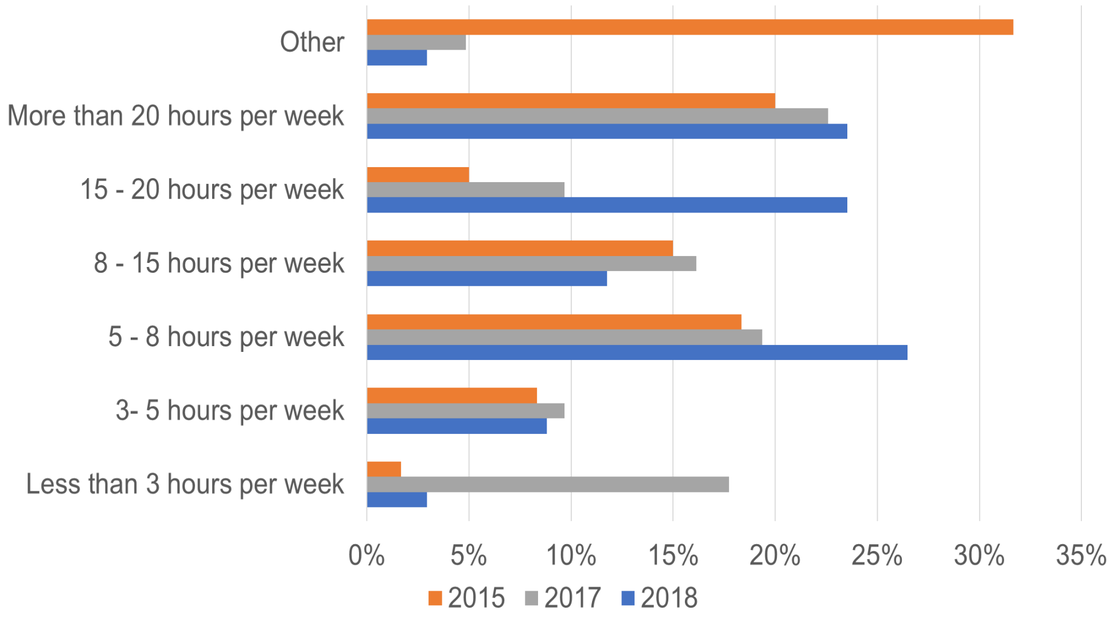
A comparison between MDSO Surveys taken in 2017 and 2018 – operational themes

Catriona Blake (MHRA) and Sarah Jennings (NHSI)

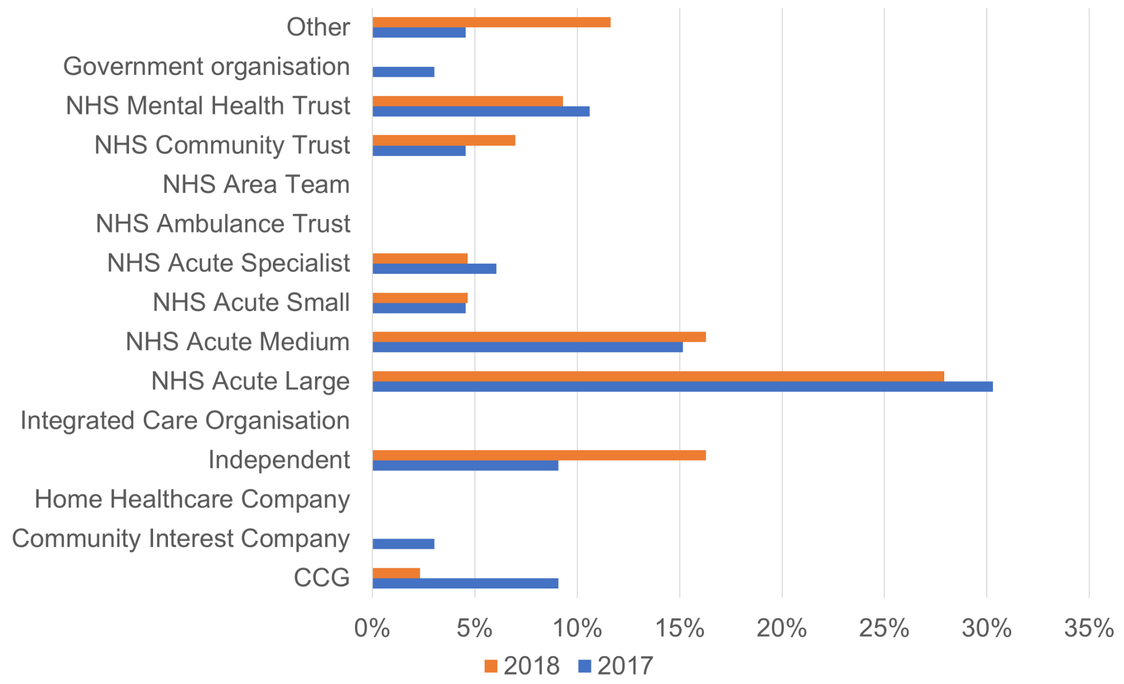
What is your predominant professional background as it relates to healthcare and your MDSO role?



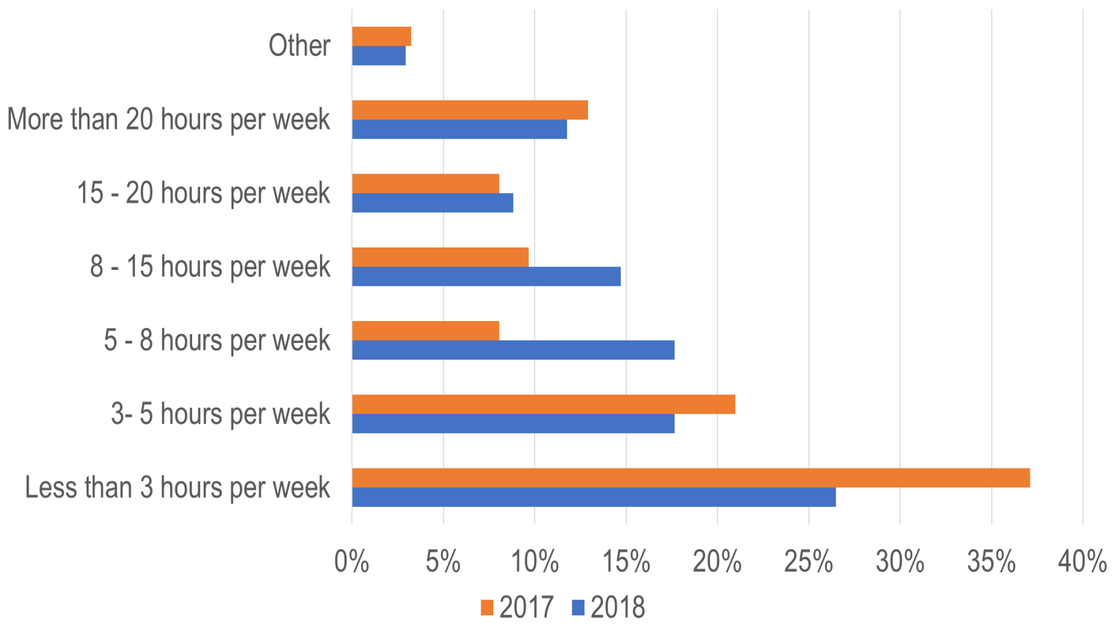
What is the ideal amount of time you would like to dedicate to your MDSO role?



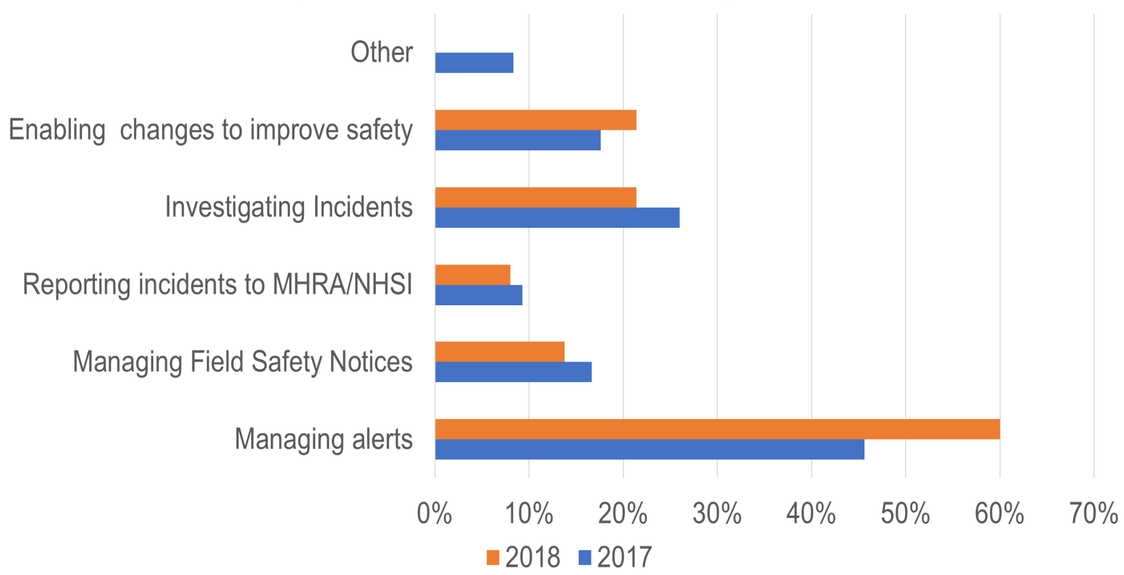
Please indicate the organisation that you work in.



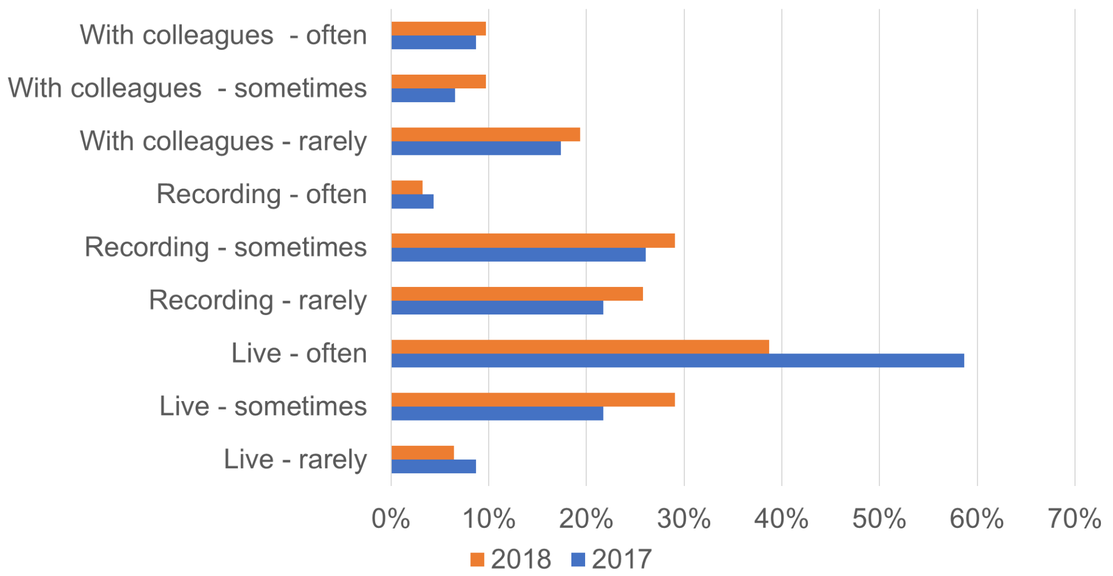
Please estimate how many hours on average you are able to devote to your MDSO role per week.



What are your main priorities in fulfilling the MDSO role?



How do you access the MDSO monthly webex?



What, if anything, has changed about the MDSO role and responsibilities in the last 3 years? 2018 only

TEAM WORK

- In this Trust, there is a named MDSO but the Medical Devices Governance Team perform the role
- Our Trust has developed a proactive and collaborative approach to managing this role.
- In our trust it has really become too diluted. I am MDSO on behalf of a group of people
- Now employed as Trust wide Medical Equipment Manager
- For this organisation there wasn't an MDSO. Each head of department took responsibility for their area. My role now ensures that the key messages are discussed in a monthly forum and I take responsibility for dissemination of alerts

WORKLOAD INCREASE

- The role has developed within the Trust and I now have more to do than I did initially. This is partially because people now know who I am so send me work to do
- It is a more focused and defined role.
- The importance of the role for safety
- The workload has grown
- Volume and complexity of management of incidents reported to the MHRA has increased.
- I am only 2 years into the role and many changes have happened, until I took up the role only minimum time was spent
- It has got busier with increased responsibilities.
- The reduction in CAS alerts and the increase in FSN's. This has meant an increase in the amount of admin work for the MDSO.
- People are now more aware of my role and asking me to investigate and be involved more often

NHS Improvement

Medicines & Healthcare products Regulatory Agency

A comparison between MDSO Surveys taken in 2017 and 2018 – safety themes

Catriona Blake (MHRA) and Sarah Jennings (NHSI)

Thinking about your organisation, what barriers do you perceive need resolving before medical device safety issues can be adequately addressed? 2018 only

COMMUNICATION
•Cascading information through clinical teams is not always robust enough
•Getting feedback on alerts is very difficult at times.
•Greater collaboration with clinical colleagues.
•Improved communication following incident investigation/closure.

HUMAN FACTORS
•Manufacturers need to assess the potential user errors on the shop floor and take these seriously before getting a licence to sell the device. We already look for FDA approval as this gives us more assurance that the CE/UK process.
•Mandatory user education
•Medical device user focussed training.
•Staff training and training records

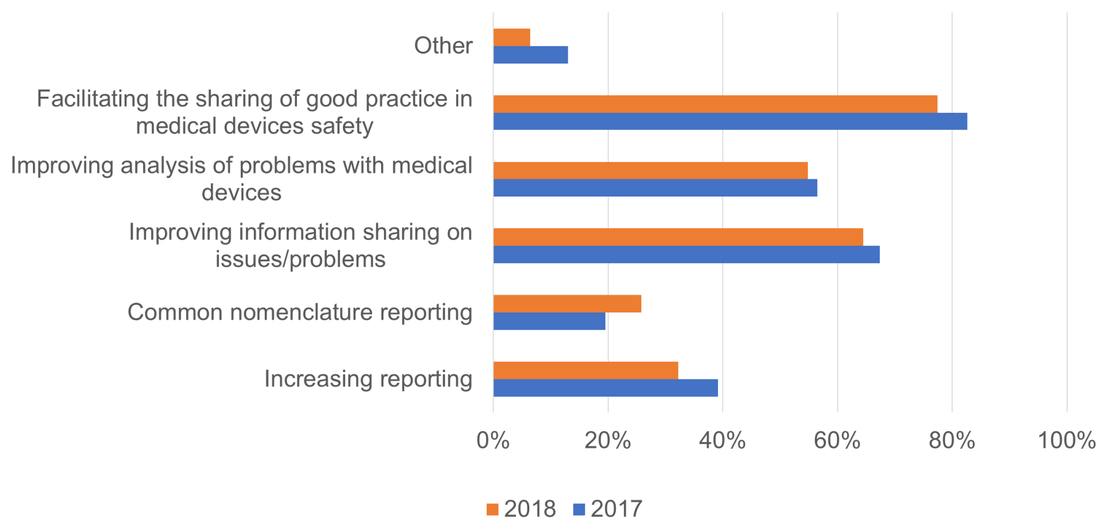
ROLE
•The role needs to be taken seriously and be reviewed by the CQC
•By focusing more on needs of the role, not to have as an add-on to an already busy role
•P/T MDSO needs to be appointed who can dedicate their time to the role
•Insufficient time for role
•More importance given and teams developed by Trusts rather than individuals trying to undertake the role.
•More time required. The role needs to be re-defined and revisited locally
•Raising awareness that medical device safety is as important as medicine safety.
•taking equipment issues more seriously
•more resources required to allow all staff to act in a timely manner and have enough time to evaluate and work with the MDSO in all aspects of medical devices management
•The role should involve a number of people.
•Staff time on the wards to answer queries

REPORTING and INVESTIGATION
•All staff understanding the process we have, completing Datix appropriately, and having a multidisciplinary approach to reviewing
•Make Datix more user-friendly.
•Getting the staff to understand the importance of reporting to MHRA. Being small and independent the issues are not seen as big however, we could be one of a much larger group experiencing a similar issue with the same device.

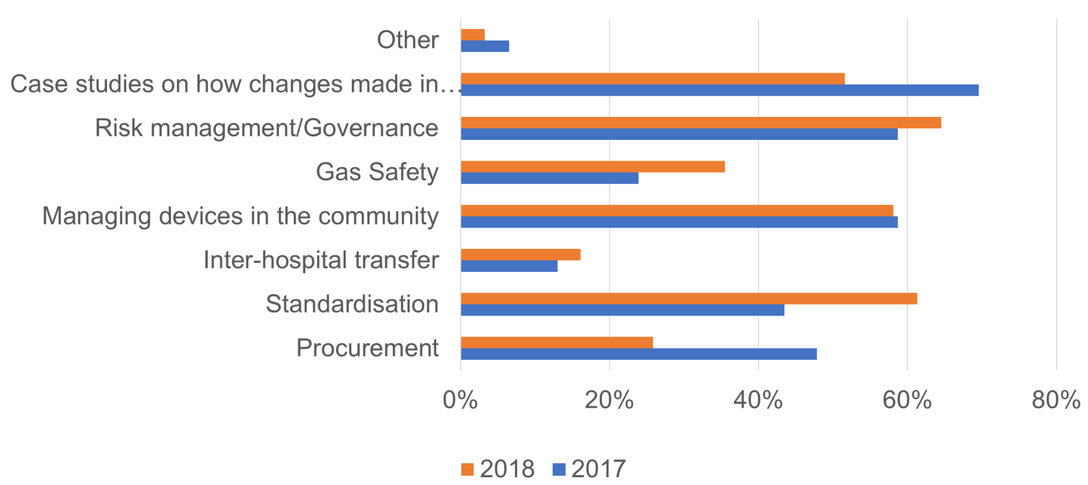
PROCUREMENT
•Purchasing decision making processes in place prior to the purchase of equipment.

REPORTING
•Reason for yellow card reporting and complete staff involvement
•Datix reporting system is a time consuming effort therefore I don't feel we see all incidents being reported.
•The main problem is getting alerts closed down. If its an FSN then there is rarely a deadline and these can run on for months, sometimes over a year. This is usually because we are waiting for a supplier to carry out the actions required to close the alert.
•With CAS alerts MDSO has to constantly remind and chase up responsible persons to ensure they carry out the alert actions…...

In your opinion what are the most pressing medical device safety issues that we need to tackle nationally?



What topics would you like covered in the Webex?



Have you any other ideas on further work or engagement on medical devices safety? 2018 only

MORE LINKS and BREADTH
•To hear from manufacturers and how they are patient safety focused.
•Links with CQC
•Be aware that not all NHS Trusts are acute, engage more with ambulance, community, and mental health trusts

•Yellow Card Reporting

FEEDBACK and SHARING
•More case studies and toolkits.

Example
•We have a problem accessing equipment for routine service... We are moving to a risk based system whereby we prioritise certain devices and make every effort to ensure they have a service within reasonable time periods. Lower risk items are not serviced if they are not available or are not found on the service visit. We know other trusts have this sort of system in place and would welcome feedback as to how well it works.

NHS Improvement

MHRA provided the Review with the minutes of the 5th and 6th meetings of the Hormonal Pregnancy Tests Working Group.

They can be found on the following link:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

5th Meeting: 18th October 2016 (p43)

6th Meeting: 27th March 2017 (p63)

16. Papers

16.1 Evaluation of systematic review and meta-analysis of studies on oral hormone pregnancy tests, including Primodos – proposal for an ad hoc expert group

16.1.1 The following Commissioners declared non-personal, non-specific interests, however this did not debar them from taking part in proceedings:

- Professor Jonathan Friedland - GlaxoSmithKline; Merck, Sharpe and Dohme; and Pfizer
- Dr Richard Gilson - GlaxoSmithKline; Merck, Sharpe and Dohme; and Pfizer
- Professor Malcolm Macleod - Pfizer; and Sanofi
- Professor Sarah Meredith - Bayer; GlaxoSmithKline; Merck, Sharpe and Dohme; and Sanofi
- Professor Stuart Ralston – Pfizer and Sanofi

16.1.2 Professor Angela Thomas declared an 'other relevant interest' in Pfizer as a consequence of Pfizer providing a grant to a separate body who have then funded educational activities by Professor Thomas. Pfizer has no control as to how the grant is administered and Professor Thomas has no direct or indirect relationship with Pfizer as a result of the grant.

16.1.3 The CHM was informed of the publication of a systematic review and meta-analysis by Heneghan et al.[3] which concluded that use of oral HPTs in pregnancy is associated with increased risks of congenital malformations (overall odds ratio 1.40 [1.18, 1.66]), with significant increases in the risk of congenital heart disease, nervous system malformations and musculoskeletal malformations. The Commission noted that the Committee for Medicinal Products for Human Use (CHMP) would be discussing the MHRA's request for an opinion by the CHMP on the Heneghan et al. publication (under Article 5(3) of Regulation (EC) No. 726/2004) at its December 2018 meeting.

16.1.4 Commissioners endorsed the formation of an ad hoc group of experts to evaluate the Heneghan et al. 2018 publication and its terms of reference: to advise the CHM on the systematic review and meta-analysis of Heneghan et al, 2018 and in particular, the suitability and robustness of the methodology, including the selection and application of the data quality score, and any clinical implications. In view of the nature of the publication, Commissioners recommended two statistical experts as additional members and also considered that, if possible, experts from the original HPT EWG should be available to respond to any questions that arise from the deliberations of the new ad-hoc group..

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[3] Carl Heneghan, Jeffrey K. Aronson, Elizabeth Spencer, Bennett Holman, Kamal R. Mahtani, Rafael Perera, Igho Onakpoya. Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis [version 1; referees: awaiting peer review]. F1000Research 2018, 7:1725 Last updated: 31 OCT 2018. https://f1000research.com/articles/7-1725/v1

Participants of the EWG to review Heneghan et al.

Chair	**Affiliation**
Professor Philip Hannaford	Professor of epidemiology Interim Senior Vice-Principal University of Aberdeen
Members	
Professor Julian Higgins BA(Hons) PhD	Professor of Evidence Synthesis and Director of Research for Population Health Sciences Bristol Medical School
Professor Jonathan Sterne BA, MSc, PhD	Professor of Medical Statistics and Epidemiology, University of Bristol
Prof. Ruth Newbury-Ecob Honorary Professor	Dept of Clinical Genetics St Michael's Hospital, Bristol BS2 8EG
Dr Sarah Floud	Senior epidemiologist Cancer Epidemiology Unit University of Oxford
Invited expert	
Professor Liam Smeeth MBChB FRCGP FFPH FRCP MSc PhD FMedSci	Professor of Clinical Epidemiology Faculty of Epidemiology and Population Health London School of Hygiene and Tropical Medicine
Observers	
Mrs Marie Lyon	Chair of the Association for Children Damaged by HPTs
Mr Nick Dobrik	Thalidomide campaigner
Mrs Linda Pepper	Lay Representative
Dr Sonia Macleod	Independent Medicines and Medical Devices Safety Review Representative
Visiting expert	
Professor Carl Heneghan BM, BCH, MA, MRCGP, DPhil	Professor of Evidence-Based Medicine University of Oxford
Professor Jeffrey Aronson MA DPhil FRCP HonFBPhS HonFFPM	Consultant Physician and Clinical Pharmacologist University of Oxford

CHM's Expert Working Group on Hormone Pregnancy Tests - Clarification points arising during the oral hearing on 28th January 2019

Details of the independent verification/quality assessment of the epidemiology studies using the seven criteria (what the process was and minutes relating to how to analyse the data in a clear way using a traffic light system – minutes of 5th meeting (pages 6-7) and sixth meeting (pages 5-6 and 10-11).

The EWG considered that formal meta-analysis of the epidemiological studies was not appropriate because the studies were too heterogeneous in design and since the weighting system for meta-analysis is usually based on study size, this would not be appropriate because many of the studies suffered from other extensive limitations. Similarly, a numerical weighting scale was not explored due to the subjectivity that would be introduced when deciding on weights to be used. The Group also commented that applying current scientific rigour as inclusion/exclusion criteria for further assessment in a formal meta-analysis would exclude the majority of the studies that were identified.

Instead, the EWG believed it was more appropriate to develop a formal quality scoring system based on those aspects considered to be most important in studying an association between HPTs and congenital anomalies, for example comparability of cases and controls/exposed and unexposed, confounding factors such as reproductive history, definition of exposure and exposure ascertainment. The Group suggested that these aspects could be most helpfully scored using a traffic light scale of green/amber/red to indicate for each whether it was considered to meet a pre-specified definition of good, moderate or poor quality, respectively. The data should be presented using Forest plots, where odds ratios were not presented in the original papers, these should be calculated using any proportions data available and cohort and case-control studies should be presented separately.

A senior epidemiology assessor at the MHRA worked with Professor Pat Doyle, one of the epidemiologists on the EWG and Professor of Epidemiology at the London School of Hygiene and Tropical Medicine to develop the quality criteria which were then agreed by the Group.

Each study was then carefully reviewed by the assessor and a colour assigned for each of the quality criteria. The draft assessment was peer reviewed by two levels of MHRA management before circulation to the EWG.

All members of the EWG (full members, invited experts and observers) had three weeks to review the MHRA assessment prior to its discussion at the 6th EWG meeting.

The minutes of the 5th and 6th meetings which summarise the Group's discussion and conclusions on the studies are provided (and published on the CHM website[1]). The relevant text may be found on pages 6-7 for the 5th meeting and pages 5-6 and 10-11 for the sixth meeting. A summary of the quality scoring process and the colour scores assigned to each criteria are also provided in section 5.3.4.2, Table 16 and figures 2-4 of the EWG's final report and in more detail in Annex 27.

[1] https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests

Update on the new CHM ad-hoc group and how it is being set up (process/minutes of CHM)

A new ad hoc EWG of the CHM is being set up to independently review the Heneghan meta-analysis. To avoid any possible concerns over bias and to ensure independence, the new group will not include any experts who participated in the original CHM Expert Working Group.

CHM endorsed the formation of an EWG, its terms of reference and proposed membership at its meeting in December 2018 (minutes attached).

The MHRA has also asked the European Commission for Medicinal Products for Human Use (CHMP) to consider the paper in a parallel review. The latter process will be entirely independent of the UK. This review process has been agreed with Health and Social Care Ministers and is the same procedure that was followed for review of Professor Vargesson's zebrafish work.

Professor Liam Smeeth MBChB FRCGP FFPH FRCP MSc PhD FMedSci, a professor of clinical epidemiology and practicing GP, has agreed to Chair the Group and a number of relevant experts have accepted an invitation to attend. A list of those who have accepted an invitation to participate is attached. Mrs Lyon will observe the meeting and we committed to honour her availability when agreeing a date for the meeting.

The meeting will take place on 18th March.

Check any changes between the report that went to CHM and the final report and also confirm that no forest plots were excluded in later draft

Peer review of the EWG report by CHM

The CHM acts as peer reviewer to all its EWGs.

A draft report of the EWG was sent to the CHM in September 2018 for consideration at the 5th October meeting. The same draft was also sent to Mrs Lyon, who was invited to give a statement to CHM.

At its meeting the CHM listened carefully to Mrs Lyon's statement and went on to discuss the EWG review and report. The Commission reflected on the points made by Mrs Lyon, which suggested that the scientific process and language used in certain areas needed clarification to avoid misinterpretation or misunderstanding. The CHM advised that it would be important to address these before finalising the report to ensure it was as clear and digestible as possible.

On 9th October an updated report was sent to the CHM for its comments.

On 20th October the EWG agreed the changes proposed by CHM and the report was endorsed by the CHM at its meeting on 3rd November.

Updates to the draft report

Clarifications

Based on the statement of Mrs Lyon to CHM the report was amended in a number of places to: clarify the purpose of the review, explain in more detail how some conclusions were reached, and provide more information on the evidence provided by the members of the Association for Children Damaged by HPTs.

CHM was sympathetic to Mrs Lyon's point that the statement in the draft final report referring to an "inability to reach a definitive conclusion" contradicted the overall conclusion that the evidence "did not support a causal association" and advised that the former statement be deleted.

Forest plots

The draft EWG report included one forest plot for 'all anomalies'. The CHM considered it would be helpful to also include the forest plots for those anomalies considered by the EWG to have limited evidence for a weak association (congenital heart disease, limb reduction defects and oesophageal atresia). These four forest plots are therefore included in the final report.

Forest plots for all other anomalies considered by the EWG (VACTERYL, skeletal defects, genital defects, urinary system defects, orofacial clefts and abdominal wall defects) are published in Annex 27 of the EWG report on the CHM website (https://mhra.filecamp.com/public/files/2ou7-p1dlcbo2#/public/file/2qu8-ia1d831e).

Conclusions

The conclusion in the draft report considered by CHM in October 2017 stated:

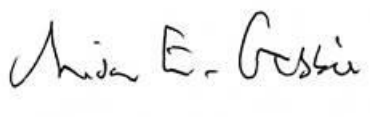
Having reviewed all the available relevant evidence with the benefit of up-to-date knowledge within the relevant specialisms, the limitations of the methodology of the time and the relative scarcity of data means it is not possible to reach a definitive conclusion. Nevertheless, based on an extensive and thorough review the EWG's overall finding is that the available scientific evidence does not support a causal association between the use of HPTs such as Primodos, during early pregnancy and adverse outcomes.

After reviewing the draft report the CHM asked the Expert Working Group to consider about removing the statement on a 'definitive conclusion' because it was unnecessary and could be confusing in light of the overall conclusion of the Group, that the available data did not support a causal association.

The EWG agreed with the CHM and the overall conclusion as re-drafted in the final report stated that:

The EWG's overall finding is that the available scientific evidence, taking all aspects into consideration, does not support a causal association between the use of HPTs, such as Primodos, during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital anomalies.

The text in red was identical in the draft and final reports.



Dr Ailsa Gebbie

Chair of the CHM's Expert Working Group on Hormone Pregnancy Tests

February 2019

NHS Resolution

NHS Resolution shared the following leaflets at the Oral Hearing:

- Saying Sorry https://resolution.nhs.uk/resources/saying-sorry/

- The benefits of supported decision making (consent) https://resolution.nhs.uk/resources/the-benefits-of-supported-decision-making-consent/

Private Healthcare Information Network (PHIN)

Following their attendance at the Oral Hearing session (10th January 2019), PHIN have provided the following documents and further information as requested by the Review.

Written evidence to The Independent Medicines and Medical Devices Safety (IMMDS) Review

Dr Andrew Vallance-Owen, Chair of the Private Healthcare Information Network

Matt James, Chief Executive of the Private Healthcare Information Network

We would like to thank the review team for the opportunity to give evidence. Speaking on behalf of PHIN, we welcome the chance to play a small role in helping to protect patients in the future. We believe that the better use of data, and the production and publication of robust information, has an important role to play in providing valuable evidence to support clinical governance, regulation, and assist in improving the care delivered to patients.

PHIN is the independent, government-mandated source of information on privately funded healthcare in the UK. Under our mandate from the Competition and Markets Authority (CMA) we are responsible for collecting quality and safety data on privately funded healthcare, and publishing information on performance to support patient choice.

In line with our mandate, our data collection started in earnest in 2016. Unfortunately, this means that the specific areas of investigation by the review pre-date our data collection. However, where we are unable to provide statistics to support the review, we can assist the Review's understanding of the data collection and reporting landscape for private healthcare and how this interacts with the NHS.

In our below statement we will cover the following topics which you have kindly asked us to consider.

- Data collection and information sharing in the private and public sectors
- Registries and Audits
- GDPR and information security

We will make a series of recommendations aimed at making best use of the data and current data collection systems to ensure a comprehensive and sustainable approach to supporting clinical governance.

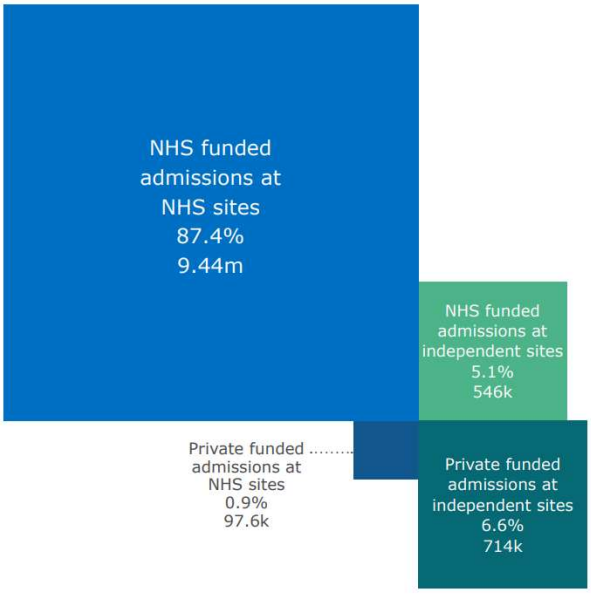
The Review team have also asked us to consider several specific questions. The answers to those questions are appended at the end of this written evidence.

Data collection and information sharing in private and public sectors

The boundaries between Private healthcare and the NHS are far more fluid than is commonly understood. The majority of consultants working in private practice also work in the NHS and most private elective care in England is provided to patients who would otherwise be entitled to use the NHS. Of the 135[1] NHS Trusts and Foundation Trusts in England, 121 undertake private work, whether through dedicated through Private Patient Units or less formally, and the majority of independent

[1] https://www.nhsconfed.org/resources/key-statistics-on-the-nhs

hospitals undertake NHS-funded work through choice and sub-contracting arrangements. People – both patients and professionals - move fluidly between the public and private healthcare systems.



Breakdown of elective care in the UK 2017 [2]

That said, there have been significant historical differences of approach between the NHS and private healthcare, and policy and national systems tend to deliberately ignore private healthcare. As a result, there has been little system-wide (public and private) collection and use of data to analyse quality or safety. At a local level, in clinical governance processes, information sharing, and analysis is fraught with cultural, legal and commercial difficulties.

PHIN, working under the mandate provided by the CMA's Private Healthcare Market Investigation Order (2014)[3], is making good progress toward ensuring that private healthcare produces data that is interoperable with NHS data. For the first time, providers of private healthcare services are required to collect and report data using NHS definitions and standards.

Using this data, PHIN has begun to publish performance measures, by procedure, at hospital and consultant level, in accordance with the CMA's Order. This information is primarily intended to promote effective choice by patients acting as consumers and will create a new level of information transparency for activity and outcomes across private healthcare. The greater the transparency that exists, the more information will be available to more effectively understand the impact of clinical interventions on patients, both in terms of positive outcomes and risks.

However, while PHIN's work to date represents important progress, private healthcare data is still not always available to national quality and safety reporting systems used by the NHS. PHIN and NHS Digital are seeking to address this through the Acute Data Alignment Programme ("ADAPt"). This is a

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[2] PHIN 2017/2018 Annual Report - https://www.phin.org.uk/news/211/phin-launches-2017-18-annual-report

[3] https://www.gov.uk/government/publications/private-healthcare-market-investigation-order-2014

joint initiative to promote further alignment of the collection and analysis of data, and make the aligned private data visible to national reporting systems to support effective clinical governance, regulation and service improvement. The programme remains in the design phase but offers the prospect of a more complete and sustainable solution than would otherwise be possible.

ADAPt will take the process of alignment as far as is possible within the bounds of current legislation and regulation, but it is possible that some changes may ultimately be helpful or required. If approached with care, we believe the removal of some of the differences that persist in the application of legislation to private healthcare would be welcomed and could also reduce the burden of data collection.

I believe that PHIN's information could play a significant role in assisting clinical governance and investigatory processes where concerns exist, for example by providing information on the workload and clinical profile of a consultants practice since PHIN can see what care has been undertaken and in what locations, whether privately funded or NHS funded, and whether in independent or NHS hospitals.

However, in my view, it is unlikely that the data currently collected across the system on its own would have provided the necessary evidence to identify poor outcomes in the clinical areas of interest to the Review. We believe that there are two key areas where additional data may be required with regards to medical devices.

Registries and Audits

Existing clinical registries and audits play an increasingly important role in measuring activity and quality, and we fully support their role in ensuring safety and standards, especially where prostheses or other implantable devices are used. Over the next year PHIN will begin incorporating registries and audits into our data set. However, we caution against the creation of a new and bespoke data collection in response to the issues being addressed by this Review, or any other problem-specific approach. Rather, we believe it is time for a comprehensive and structured national approach, albeit one which should remain responsive to the particular requirements of each clinical approach, led by the relevant medical specialties and managed by experts in the field such as HQIP.

In recent years, a number of registries have been created for devices implanted in patients during surgery. Each registry has been specific to a clinical specialty, range of procedures or range of devices, with bespoke approaches to objectives, information specifications, governance arrangements, whether reporting is mandatory or voluntary, scope, funding, and so on. Examples include the National Joint Registry and the Breast & Cosmetic Implant Registry. We gather that a similar approach has been discussed in the early stages of this Review.

Each registry is narrow in scope and some, notably the Breast and Cosmetic Implants Register, are reactions to specific issues that have arisen. Consequently, we suspect that there are many implantable devices and other technologies that are not within scope of any current or planned registry, but which potentially present similar risks to the safety of future patients as those that are covered by virtue of having caused issues in the past.

Some elements of the approach taken by registries are also, in my view, reactions to a lack of clinical confidence in the routine data collections at the heart of NHS secondary care, notably the 'SUS' data collection that becomes 'HES' data outputs. We hear frequent concerns from clinicians about the accuracy of HES data, and that is increasingly acknowledged by data experts. However, it is not a

surprise, since HES was not originally intended to support clinical analysis, and has not been developed to support that end, even though much analysis does, in practice, rely upon it, including our own. We would welcome greater efforts to improve the clinical reliability and utility of HES to reduce the imperative to create workarounds – in the form of parallel primary data collections - through registries.

I believe that all devices implanted should be recorded in a reasonably consistent fashion, across all types and clinical specialties. That is not to say that every detail required to be collected, or the specific outcomes recorded, will be the same in every case; far from it. Each procedure is different, and the leadership of the relevant medical specialties and other groups will continue to be required. However, we believe that some meaningful standardisation of underlying data standards, where that data is housed, how it can be accessed, the lawful basis supporting collection and so on would be beneficial. Notably, there is no good reason for a patient's demographic details and general medical history to be collected and stored in many different ways to different standards in different systems.

The benefits of clinical specialty ownership and professional engagement are clear and should be maintained, but data should be held centrally by the appropriate information authority (e.g. NHS Digital) to common standards. Some efforts toward standardisation are already underway, illustrating an existing understanding of the problems of non-standardisation and the benefits of standardisation of approach; these include HQIP's commitment to promoting the use of routine data in registries as specified by NHS England. It seems to us that HQIP has unrivalled expertise in managing registries and audits and must be fully involved in developing the next generation.

There is a clear need to standardise an approach to creating clinical audits and registries in terms of information architecture, governance and use of data. This is to ensure that each national data collection conforms to necessary standards and clear objectives, and that any such initiative is optimal in terms both of its intended function and to maximise benefits such as clinical learning and promotion of patient safety whilst minimising cost and burden of collection across healthcare.

Any initiatives should be comprehensive and inclusive, including both NHS and privately funded healthcare by default, even where circumstances require or suggest differing approaches in implementation or operations.

Routine collection of Outcome Measures

Secondly, we believe that measures of improvement in health outcome, most commonly Patient Reported Outcome Measures (PROMs), should be collected much more widely and routinely as part of patient follow-up. PROMs consider the functional benefit of a procedure – was it effective and beneficial? - but can also help to identify problems at an early stage through structured data collections. For example, if an unusual number of patients were to experience a high degree of pain post-operatively that could quickly be seen in PROMs data, and would be especially useful where used in combination with a register of devices and/ or data describing clinical techniques or approaches.

Currently, PROMs collections are mandated for just two procedures at a national level (primary hip and knee replacements) although in practice there are many other outcome measure collections taking place in more-or-less nationally co-ordinated ways. The National Joint Registry, for example, supports routine collection of PROMs on hip, knee and shoulder replacements. For privately funded healthcare, PHIN is implementing a programme encompassing outcomes measures for 13 common procedures.

Measuring outcomes, which is fundamental to understanding both quality of care and value for money in care delivery, seems rather to have fallen off the national agenda.

GDPR and data protection

As with any healthcare data controller, PHIN takes our obligations under data protection and GDPR extremely seriously. The protection of personal data, particularly in relation to sensitive health data, should be of paramount importance to any data controller. However, as the seventh Caldicott Principle, added in 2013, specifically clarified, "the duty to share information can be as important as the duty to protect patient confidentiality."

Effective data sharing between care providers and/or relevant authorities is essential to tracking and managing the types of issues being examined by the IMMDS Review. The Review will be fully aware that problems can occur simultaneously across a range of device types, hospitals, clinicians, and funding sources, and it is vital that we establish processes to facilitate knowledge both at a local level and nationally.

Data protection considerations can, at times, present a barrier, particularly where people and their data move between organisations, and perhaps even more so where that involves moving between private care and the NHS. PHIN has spent several years trying to establish data flows that will enable the production of the performance measures we are legally mandated to publish. Despite the practical support of partners such as NHS Digital and strategic backing of clinicians and decision-makers at the highest levels, progress is hard to come by.

The CMA's Order explicitly compels private hospitals to send us data, and compels PHIN to publish it, and that provides both parties with a clear lawful basis for doing so. However, to produce the information we need to combine our data with data from NHS digital and give the consultants it describes an opportunity to validate the data and challenge our findings. Those needs are implicit rather than explicit in the CMA's Order, and as such present a greater challenge in terms of demonstrating a lawful basis.

Our learning is that the most reliable route to ensuring that good information is produced is to create a legal duty on the parties involved to produce it, co-operating and sharing data as required to do so. Not only does this require action, but it also provides a lawful basis for that action.

As such, whatever recommendations the IMMDS Review ultimately makes in terms of information, the use of registries and so on, you may wish to bear in mind that unless parties are positively obliged by law or regulation to participate in the solution, data protection law may inhibit genuine efforts to do the right thing.

Domestic law can and should facilitate, in compliance with the GDPR, the storage, management, and where necessary, the sharing of data for legitimate needs, rather than restrict it.

Recommendations:

1. Where PHIN has maintained a focus on quality and safety for the purpose of the CMA Order in the area of consumer rights, our data and the information we produce should be visible to wider healthcare reporting systems for the purpose of monitoring and regulation by the appropriate bodies. Formal recognition via a legal duty to cooperate with the CQC, GMC, NHS Digital and other reporting systems and regulators, will provide PHIN with legal basis to achieve this.

2. We commend the routine use of PROMs across clinical practice, where appropriate objective measures exist and the numbers of patients treated enable valid information to be produced. We would like NHS England, the CQC and the GMC to encourage better standardisation and wider use of these measures, to gain both a better understanding of the benefits (or not) brought by day-to-day clinical treatment and to build stronger 'objective assurance' of competent clinical practice.

3. We support the introduction of registries for implants and devices. However, we would prefer to see the development of a universal approach to the development of yet another bespoke response. All devices implanted should be recorded in a consistent fashion, across all types and clinical specialties, and be held centrally by the appropriate information authority.

4. In the longer term, we would welcome strong support for the Acute Data Alignment Programme (ADAPt) and developing a system-wide partnership to properly assess how to improve data quality and what additional data requirements would be needed to ensure a more comprehensive data-driven approach to clinical governance, reporting and regulation, across private and NHS care. We believe this partnership should consider the data that is currently available within the system, build on the current systems and consolidate current datasets, ensuring these are fit for purpose both for clinical governance and public reporting.

APPENDIX 1. QUESTIONS FROM THE IMMDS REVIEW FOR PHIN

1. Please detail any commercial, financial or legal connection or interest in the pharmaceutical and medical devices industry sector (including subsidiaries) or any other body or organisation of interest to the Review.

There are no further conflicts of interest between PHIN staff and any commercial, financial or legal connection in the pharmaceutical and medical devices industry.

Sir Cyril Chantler GBE, who is vice-chair of the Review team, is a Non-Executive Director of PHIN.

2. Please could you provide a timeline outlining your understanding and recognition of risks regarding the interventions covered by this Review. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

Although members of the PHIN Board and Team have been aware of the interventions covered by the review, as an organisation PHIN was made aware of the issues raised by the review through media reporting.

Our data collection started under the Order in 2016, after the interventions covered by the Review came to light.

3. If you have had any adverse events concerning the use of mesh in urogynaecological procedures reported directly to the Network, please provide an anonymised summary and indicate what actions were taken in response to these reports.

Adverse events would be potentially available within our data where patients were originally treated in the private sector and returned to the private sector for any revisions.

However, some adverse events by their nature are not 'reported', rather they can be identified within the data. For example, where a patient has the original treatment at one facility but is readmitted into another facility for further treatment or revisions, this may not be known to the original facility or consultant. In these situations, further methods are required, which we are currently developing. Routine use of PROMs to provide early warning on patients discharged from hospital may also be beneficial here. Once this data is complete and validated we will publish this on our website.

Currently linked adverse events would not be readily available to PHIN for activity in the NHS.

4. Are pelvic mesh procedures subcontracted from the NHS into the private sector? If so, what is the scale of this?

NHS Digital would be the appropriate body to answer this question.

5. Are you aware of the number of urogynaecological procedures using mesh carried out in the private sector for: a) implantation; b) corrective surgery; and c) removal from 1995 onwards.

Under PHIN's mandate from the CMA, we have only been collecting data in earnest since 2016, and the data is still maturing.

We are aware of more than 50 urogynaecological procedures using mesh carried out the private sector in 2017, according to the data submitted to PHIN. However, the true number is likely to be higher, and will be known as the data completeness matures. We are not able to provide a breakdown for implantation, corrective surgery, or removal, at this time.

6. Please provide details of valproate prescriptions and pregnancy-related adverse event numbers from 1971 to date among your members.

The prescription of valproates is not covered in the scope of PHIN's mandate. This may be held in NHS Digital's 'Prescribing Data' datasets. However, this is unlikely to include private prescriptions and we do not believe there is an equivalent national private dataset. We believe that consistent data standards and reporting systems across NHS and private is important for understanding and improving patient care and initiated the ADAPt programme with NHS Digital to begin addressing this very issue.

7. How are you working with NHS Digital to develop a holistic picture of patient safety, specifically in relation to mesh. What would need to be put in place for this to happen? What is the timeframe for delivery?

The Acute Data Alignment Programme (ADAPt) was instigated following a meeting with the Secretary of State for Health and Social Care and representatives from NHS Digital and the Private Healthcare Information Network (PHIN) on 9th January 2018.

The Programme is being jointly led by PHIN (appointed as the Information Organisation under the CMA Order) and NHS Digital, in partnership with stakeholders from the Department of Health and Social care (DHSC), NHS Improvement (NHSI), NHS England (NHSE), the Care Quality Commission (CQC) and other observer bodies.

The vision of the Programme is: "To bring about standardisation in data, measurement and reporting systems across NHS and private healthcare in order to enable greater transparency in quality and safety and to support patient choice and opportunities for improving patient care."

The programme is primarily concerned with episode records, and the foundation denominator dataset for all care provided. Additional datasets, including Adverse Events and measurements of health outcomes (PROMs), are not covered by the programme at this stage, but the programme will provide the foundations for further integration of datasets across NHS and private in the future, and we are actively pursuing this direction of travel.

8. Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated amongst your members.

9. In your view, where within the healthcare system does your responsibility for disseminating and responding to adverse event reporting begin and end?

Both of these questions related directly to PHIN's work with NHS Digital on the ADAPt programme.

PHIN has maintained a focus on quality and safety for the purpose of the CMA Order in the area of consumer rights, and surfacing case-mix adjusted adverse and never events rates to public scrutiny will have a positive impact. In addition, we play back the data to providers with national comparators and benchmarks, so that they may begin to identify trends in good and poor practice to aid service improvements. We also share aggregated data with the Care Quality Commission to support effective regulation.

We believe there is the potential for far greater utility of the data we hold within the healthcare system. Our data and the information we produce should be visible to wider healthcare reporting systems for the purpose of monitoring and regulation by the appropriate bodies at a national and local level. Formal recognition via a legal duty to cooperate with the CQC, GMC, NHS Digital and other reporting systems and regulators, will provide PHIN with an explicit legal basis to achieve this.

In the longer term, we would welcome a system-wide partnership to properly assess what additional data requirements would be to ensure a more comprehensive data-driven approach to clinical governance, regulation and reporting, across private and NHS care.

10. How do you see your members working with the NHS on health registries? Do you foresee any opportunities or obstacles?

A central issue which we are looking to address with NHS Digital in the ADAPt programme is the traditional separation between the private sector and NHS when it comes to regulation and data reporting. Policy initiative has tended to be NHS focused, leaving private providers excluded. The situation is improving, with CQC regulating private providers in the same way as the NHS, and more registries now open to private providers. However, registries are not compulsory (except for the NJR) and some still exclude private providers.

The direction of travel is to increasingly include private providers and to work towards mandatory reporting for all national audits and registries in due course, but there is some way to go.

Regulators

General Pharmaceutical Council (GPhC)

Following their attendance at the Oral Hearing session (10th January 2019), GPhC have provided the following documents and further information as requested by the Review.

General Pharmaceutical Council

The Independent Medicines and Medical Devices Safety Review Briefing from the General Pharmaceutical Council

About us

1. The General Pharmaceutical Council (GPhC) is the regulator for pharmacists, pharmacy technicians and registered pharmacy premises in Great Britain. We were established by the Pharmacy Order 2010 and came into operation in September 2010.
2. It is our job to protect, promote and maintain the health, safety and wellbeing of members of the public by upholding standards and public trust in pharmacy. Our main work includes:
   - setting standards for the education and training of pharmacists and pharmacy technicians, and approving and accrediting their qualifications and training
   - maintaining a register of pharmacists, pharmacy technicians and pharmacies
   - setting the standards that pharmacy professionals have to meet throughout their careers
   - investigating concerns that pharmacy professionals are not meeting our standards, and taking action to restrict their ability to practise when this is necessary to protect patients and the public
   - setting standards for registered pharmacies which require them to provide a safe and effective service to patients
   - inspecting registered pharmacies to check if they are meeting our standards.

Working effectively with other regulators and with representative bodies

3. We recognise that our role in relation to the areas being examined by the review is relatively limited but have provided evidence below in relation to our role and how we work with other organisations in relation to the safety of medicines and medical devices
4. We work closely where appropriate with other regulators with a more central role to play, including the Medicines and Healthcare Products Regulatory Authority (MHRA) as the regulator for medicines and medical devices.
5. We do not have a direct role in identifying risks and adverse events in relation to medicines and medical devices and in sending alerts to health professionals. We will however share any relevant intelligence or information we receive about medicines and medical devices through our work with the MHRA and other appropriate bodies, through the memoranda of understanding we have with them. You can see the Memoranda of Understanding we have with a range of organisations on our website.

- For example, in October 2018 we issued a statement and sent an email to all pharmacy professionals and pharmacy owners on our register to highlight the MHRA's Pregnancy Prevention Programme (PPP) for sodium valproate and to emphasise the responsibilities of pharmacy professionals and pharmacy owners to make sure they were meeting the requirements at all times when dispensing sodium valproate. This communication was in response to a direct request from the MHRA to support their efforts to promote the PPP to pharmacy professionals dispensing sodium valproate
- We are also currently working with the MHRA on an article for an upcoming edition of our e-newsletter reminding pharmacy professionals of their responsibilities to report any adverse drug reactions or other incidents via the MHRA's Yellow Card scheme. We are also considering what further steps we can take to remind pharmacy professionals and pharmacy owners of their important responsibilities in this area and are keen to use the findings of this review to inform our future work.

Setting and upholding standards and guidance

6. We set standards for pharmacy professionals, which all pharmacists and pharmacy technicians are accountable for meeting, and which describe how safe and effective care is delivered in pharmacy. We also set standards for registered pharmacies, which pharmacy owners are responsible for meeting and which are designed to create and maintain the right environment for the safe and effective practice of pharmacy and to improve the quality and safety of services provided to patients and the public.
7. The standards for registered pharmacies include a number of standards under principle 4 which set out how pharmacy services, including the management of medicines and medical devices. This includes standard 4.4 which puts a clear requirement on pharmacy owners to raise concerns about medicines or medical devices where appropriate; 'Concerns are raised when it is suspected that medicines or medical devices are not fit for purpose'.
8. We also produce a range of guidance to support pharmacy professionals and pharmacy owners to meet the standards that we set. This covers a range of topics, including consent and raising concerns. The full suite of guidance is available on our website.
9. We are currently developing new guidance on prescribing for pharmacy professionals, which we aim to consult on from Spring 2019. This guidance is being developed at a time when the number of pharmacist independent prescribers across Great Britain is growing and they are taking on new roles and responsibilities. Government policies and the changing demands from health services and patients across Great Britain suggest that the need for well-trained pharmacist independent prescribers will keep growing. We have also recently consulted on revised standards for the education and training of pharmacist independent prescribers, and expect the final standards to be published in the first quarter of 2019.

10. It is not within our remit to provide detailed guidance or standards on the prescribing or dispensing of particular medicines or medical devices; that is the role of other bodies, including the MHRA and NICE. In addition, the Royal Pharmaceutical Society, the professional body for pharmacists, provides professional standards that describe good practice, systems of care or working, including in relation to medicines.

11. We make clear in our standards for pharmacy professionals that pharmacy professionals are expected to consider their legal duties and any relevant guidance when making decisions. This includes guidance from the professional leadership bodies, other regulators, the NHS, National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network.

12. We also make clear to pharmacy owners in our standards for registered pharmacies that as well as meeting our standards, the pharmacy owner must make sure they comply with all legal requirements including those covering medicines legislation

13. We seek assurances that pharmacy professionals and registered pharmacies are upholding our standards and following our guidance, and the guidance of other organisations, in a range of ways. In 2018 we introduced revalidation for pharmacy professionals. The revalidation process helps pharmacists and pharmacy technicians to keep their professional skills and knowledge up to date, reflect on how to improve and show how they provide the safe and effective care patients and the public expect by meeting our standards. All pharmacy professionals now need to submit records to show how they have carried out and recorded revalidation activities on an annual basis, when renewing their registration. More information about revalidation for pharmacy professionals is available on our website.

14. We carry out inspections of registered pharmacies to seek assurances that they are meeting our standards. During these inspections, our inspectors will look for evidence that the pharmacy team has an effective process in place for monitoring for alerts relating to medicines or medical devices from the MHRA and any other relevant bodies and responding effectively to these alerts. As an example, our inspectors have been looking for evidence that pharmacies are complying with the Pregnancy Prevention Programme for Valproate since the new requirements came into effect. Since October 2018, following discussions with the MHRA, GPhC inspectors have been systematically checking compliance with the MHRA's Pregnancy Prevention Programme for valproate in all inspections of registered pharmacies.

15. Any pharmacy that is found not to be complying with the PPP for sodium valproate or other relevant medicines alerts would be required to complete an improvement action plan setting out the steps the pharmacy has taken to resolve this and to meet our standards going forward.

Responding effectively to concerns

16. We have a range of policies, formal criteria and operational procedures which are used to guide the way in which we investigate concerns that are raised with us or concerns that we identify through our inspections or other regulatory processes

17. We investigate concerns about pharmacy professionals that could suggest there is a risk to patient safety or could affect the public's confidence in pharmacy

18. We also investigate concerns raised with us relating to registered pharmacies. As an example, we have recently sought evidence from the MHRA and INFACT, a patient group campaigning on sodium valproate in pregnancy, in relation to reported cases of pharmacies not complying with the PPP. Our concerns team and inspectors are currently investigating these cases using the evidence shared with us and considering what actions to take.

19. A review of concerns raised with us has indicated that, with the exception of the cases referenced above, we have not received specific concerns in relation to the areas covered in this review.

Further information

20. Further information about our role and work is available on our website: www.pharmacyregulation.org

General Medical Council (GMC)

Following their attendance at the Oral Hearing sessions (10th January 2019, 14th March 2019), GMC have provided the following documents and further information as requested by the Review.

General Medical Council

Independent Medicines and Medical Devices Safety Review – GMC supplementary written evidence.

Introduction

1 Thank you for the opportunity to provide further information to the review. Our overarching objective is to protect patients and we take the concerns that patients may have been harmed very seriously. Given our role in protecting patients and improving medical education and practice across the UK, we are keen to provide the Review panel with any assistance we can. We would also like to take this opportunity to express our sympathy for all those who have suffered, and continue to suffer, as a result of the interventions which are under consideration by the Review.

2 We have set out below our response to the specific questions on which the panel have asked for more information. In addition, we have also taken the opportunity to provide further information relevant to areas raised by the panel during our first oral evidence session.

Good Medical Practice

3 In our additional evidence, we make several references to our guidance – Good Medical Practice. It might be helpful if we first set out some general information on the status and scope of that guidance.

4 Good medical practice sets out the professional values and standards of competence and conduct expected of all registered doctors. It describes what makes a good doctor and can be seen as the foundation of the doctor and patient relationship. Good Medical Practice is supported by a range of explanatory guidance which provides more detailed advice on the application of the high level principles.

5 Taken together, Good Medical Practice and the explanatory guidance set normative standards for practice to which all registered doctors are expected to adhere. However, Good Medical Practice is not a statutory code, nor is it a set of rules, and doctors are expected to use their judgement about how to apply the principles to the particular situations they face in practice.

6 In all of our guidance we say that 'serious or persistent failure to follow this guidance will put your registration at risk'. Each case turns on its own facts and we will always carefully consider any complaint seriously to ascertain whether the breach of our guidance puts patients or the public confidence at risk. If it does we will take firm and proportionate action to protect patients and public confidence.

7 The threshold for undertaking an investigation is set out in statute and is whether the complaint or information raises a question about the doctor's fitness to practise. The Medical Act, which is our primary legislation, requires us to investigate such allegations. A doctor's fitness to practise can only be impaired by reason of misconduct, adverse health, deficient professional performance, a conviction or caution, a determination from another regulator or not having the necessary knowledge of English. The threshold is set out in rule 4 of the GMC (Fitness to Practise) Rules 2004.

8 The purpose of any action we take in relation to a doctor's registration is to protect the public by helping to make sure doctors on our register provide safe care and to uphold public confidence in doctors. In dealing with a concern, it is not our role to punish or discipline doctors for past events; we are bound in law to focus on current risk that the doctor may pose to patients or public confidence in the profession.

9 And we have provided an example of a case below to illustrate this point:

A GP saw an 8 year old child presenting with clear clinical signs of diabetes twice in a month. The GP did not document a thorough history or perform the necessary test to diagnose this. The child was later diagnosed with type 1 diabetes.

As part of our investigation, we commissioned an expert report which concluded that the care provided by the GP was seriously below the standard expected. However, the employer had no wider concerns about the doctor's practise and the doctor had both fully engaged with the significant event process (to understand how and why this happened and to identify learning points) and provided detailed reflection and evidence of remediation. Therefore, the case examiners decided that there was no ongoing risk to patients and closed the case.

10 While the missed diagnosis represents a serious concern and an issue that requires investigation, the low level of ongoing and future risk (due to the insight that the doctor has shown and the steps taken to remediate) means that further action is not necessary, on this occasion, to protect the public.

Additional evidence requested by the review team

Theme 1: What information do you have on 'alert fatigue' and what impact might this have on patient safety?

11 Our primary responsibilities in relation to complying with alerts and in relation to adverse event reporting are for the setting of professional standards. With regard to taking appropriate action in response to alerts, our prescribing guidance states that:

- you should make use of electronic and other systems that can improve the safety of your prescribing, for example by highlighting interactions and allergies and by ensuring consistency and compatibility of medicines prescribed, supplied and administered

- the Medicines and Healthcare Products Regulatory Agency's (MHRA) Drug Safety Update and the NHS Central Alert System provide information and advice to support the safer use of medicines relevant to your practice and alert you to safety information about medicines you prescribe.

12 And with regard to adverse event reporting, we say, within our guidance, that doctors must inform the Medicines and Healthcare products Regulatory Agency (MHRA) about:

- serious suspected adverse reactions to all medicines and all reactions to products marked with a Black Triangle in the British National Formulary and elsewhere using the Yellow Card Scheme

- adverse incidents involving medical devices, including those caused by human error that put, or have the potential to put, the safety of patients, healthcare professionals or others at risk. These incidents should also be reported to the medical device liaison officer within a doctor's organisation.

13 In addition, we say that doctors should:

- check that all serious patient safety incidents are reported to the National Reporting and Learning System (in England and Wales), especially if such incidents are not automatically reported through clinical governance arrangements where they work

- where appropriate, inform the patient's general practitioner, the pharmacy that supplied the medicine, the local controlled drugs accountable officer and the medicines manufacturers of relevant adverse drug reactions and patient safety incidents.

14 Although we don't have any evidential basis for assessing the effectiveness of, or compliance with, alert schemes, we recognise that alert fatigue is a multifaceted problem which will require concerted and coordinated action by a number of parties to address.

15 And while our complaints procedures provide a means through which non-compliance can be addressed (if this meets our threshold for investigation) they arguably offer a

blunt instrument for preventing non-compliance in the first place. They are clearly a part of the solution but not the solution.

16 We recognise that doctors face multiple messages from a variety of sources and think there may be scope for a more coordinated and streamlined effort across the system to ensure the right messages reach the relevant clinicians.

17 Increasing pressures associated with workload and work intensity further supports this belief. For example, in our 2018 State of Medical Education and Practice Report, we presented the findings of recently completed primary research exploring how doctors respond to increasing pressures. Our research found that doctors employed a number of strategies for doing so. In some cases, doctors reported that they prioritised immediate patient care and safety but potentially compromised longer term patient outcomes. This included making unnecessary referrals, not spending sufficient time with patients and bypassing the use of clinical checklists and protocols (with 27% doctors surveyed reporting that they had observed this at least weekly over a two year period). We have a programme of work underway to tackle the issues that have been raised about the environments in which doctors work, and the effects of systems pressures on medical practice under our 'Supporting a profession under pressure' work stream.

18 Part of the solution to alert fatigue may come from the way in which such information is cascaded. We are committed to working other agencies – such as the Medicines and Healthcare products Regulatory Agency – to raise awareness of risks associated with specific medicines and interventions. And we are considering how we can use our communication channels to raise awareness of specific alerts among the profession.

19 We are also discussing with patient safety experts at NHS Improvement, NHS Resolution and the Healthcare Safety Investigation Branch scope for developing and disseminating safety messages focused at particular medical specialties. We are committed to improving the ways safety messages reach and are acted on by doctors, but suspect there are not simple solutions given the breadth and complexity of medicine, and that an approach may need to be informed by insights from behavioural science, communications and medical education about what works in getting attention and ensuring action.

20 Given the complexity of the current process for cascading important safety information, the panel may wish to recommend that relevant parties (both those involved in currently cascading safety information and those that could further support this – including the GMC) collaborate on the production of a more streamlined system. Furthermore, the development of NHS Improvement's new Patient Safety strategy may provide a timely opportunity for progressing this.

Role of clinical governance

21 However, improved cascade of information will not by itself eliminate non-compliance. Effective systems of local clinical governance are critical to ensuring that alerts are appropriately disseminated, acted upon, and that care, treatment and support is delivered in line with legislation, standards and evidence-based guidance.

22 Although clinical governance is not a new concept, many Responsible Officers have commented that the introduction of revalidation has led to a strengthening of local clinical governance systems. And our recently published 'Effective clinical governance for the medical profession' handbook, aimed at organisations employing, contracting or overseeing the practice of doctors, provides boards with a description of the core principles underpinning effective clinical governance for doctors, focussing particularly on responsibilities outlined in the RO regulations.

23 The Responsible Officer Regulations (2010) support the ongoing evaluation of doctor performance. These regulations place specific duties and responsibilities on Designated Bodies (typically healthcare providers that doctors connect to for the purpose of revalidation), with Responsible Officers accountable for ensuring that these are delivered.

24 The introduction of the Responsible Officer role provides a more robust level of scrutiny and oversight by creating specific RO responsibilities for:

- monitoring the ongoing fitness to practise of doctors connected to them through a system of annual appraisals and a continuous review of clinical governance information including, for example, complaints, outcome data, hospital episode statistics, clinical audit data and incident reports
- communicating with the GMC through fitness to practise (FtP) referrals and revalidation recommendations, and monitoring conditions imposed by the GMC as part of individual fitness to practise procedures.
- ensuring effective systems of appraisal are in place.
- (within England only) ensuring that robust processes are in place for pre-employment checks of doctors (ensuring they have the required English language skills, have appropriate qualifications and experience, have their references checked and their identify verified).

25 It is the role of employers therefore to assure themselves that clinical governance systems and processes are in place and used effectively (which might include auditing prescribing practices to ensure standards of practice are being maintained – including complying with safety alerts) and the role of the systems regulator – the Care Quality Commission – to assess the robustness of such arrangements.

26 We also note the recent NHS Improvement consultation on their proposals for developing a patient safety strategy for the NHS. Referring to CQC's thematic review

of never events, NHSI highlighted the challenge that staff face in implementing risk reduction actions, and their struggle to prioritise and implement patient safety alerts designed to reduce risks. NHSI go on to say that Governance systems can be bureaucratic rather than responsive, too often focused on completing a process rather than supporting reduction of risk.

27 We firmly believe that all healthcare providers should explicitly designate an individual, at board level (or equivalent), with the responsibility of overseeing and quality assuring clinical governance systems more broadly (not just for doctors). This would also enable Responsible Officers to more effectively discharge their duties*. We have called for the RO regulations to be amended to this effect – to include an additional responsibility for Designated Bodies and Higher Level ROs to quality assure the governance processes underpinning revalidation.

Responding to emerging risks concerning the use of clinical treatments and procedures

28 Unless a concern is picked up during routine inspection (in the case of the CQC), regulators will typically intervene after something has gone wrong, usually in response to a concern that has been brought to our attention. By this point, the event may have occurred some time ago and in many cases, a patient has already suffered harm.

29 As we go onto discuss later, we believe that one of the best ways in which we can prevent this and protect patients is by supporting doctors in their commitment to deliver high quality care. And one of the ways in which we do this is through the development of guidance – as referred to above. But while it is our role to set normative standards for practice at the outset, and respond to concerns when things go wrong, it is not our role to monitor the use of new types of treatment, drug, or other clinical interventions (including compliance with patient safety alerts) in between. This is not something that we are set up to do.

30 Therefore and as a way of improving patient safety, the panel may wish to consider the processes for introducing new drugs and medical devices, monitoring their efficacy and use, and the process of audit and recall when things go wrong. This is something that both system and professional regulators can play a part in, but it

* Responsible Officer responsibilities include:

- Monitoring the ongoing fitness to practise of doctors connected to them through a system of annual appraisals and a continuous review of clinical governance information including, for example, complaints, outcome data, hospital episode statistics, clinical audit data and incident reports.
- Communicating with the GMC through fitness to practise (ftP) referrals and revalidation recommendations, and monitoring conditions imposed by the GMC as part of individual fitness to practise procedures.
- Ensuring effective systems of appraisal are in place.

must also include employers, providers and those responsible for commissioning services – so a whole system approach is required.

Theme 2: Issue of trust and conflicts of interest; what discussions have taken place within the GMC on establishing a register of interests for all registrants that is open and transparent and refreshed annually

31 We recognise that conflicts of interest are an issue that go to the heart of the trust between doctors and patients. In Good medical practice we set clear expectations in relation to doctors' honesty, openness about any conflicts of interest, and professional duty not to allow any interests they have to affect the way they prescribe for, treat, refer or commission services for patients. We expand on this in our guidance Financial and commercial arrangements and conflicts of interest (2013) – key paragraphs are cited below:

> 12 You should
>
> - use your professional judgement to identify when conflicts of interest arise
> - avoid conflicts of interest wherever possible
> - declare any conflict to anyone affected, formally and as early as possible, in line with the policies of their employer or the organisation contracting their services
> - get advice about the implications of any potential conflict of interest make sure that the conflict does not affect their decisions about patient care
>
> 13 If you are in doubt about whether there is a conflict of interest, act as though there is.

32 We take concerns about a breach of our guidance on conflicts of interest seriously and will take action where we identify that a serious or persistent breach by a doctor poses a risk to patients or to public confidence in doctors. The action we can take ranges from issuing a warning to a doctor to removing them from the medical register.

33 In August 2017, we published a joint statement from the Chief Executives of statutory regulators of health and care professionals reaffirming a shared understanding of our expectations of all healthcare professionals in relation to handling conflicts of interest. We also created and published a series of supporting joint case studies for this statement on our 'ethical hub' on the GMC website.

34 Furthermore, we have worked with the Association of the British Pharmaceutical Industry (ABPI) on how to encourage doctors working with pharmaceutical companies to consent to disclosing 'transfers of value' on Disclosure UK (an online

searchable database). And we have also supported the development of NHS England's guidance on *Managing Conflicts of Interest in the NHS*.

Doctors as dispensers

35 In relation to doctors also acting as dispensers, there are circumstances in which this is necessary to provide effective patient care, for example in rural areas where there are no or few pharmacies. It is not an issue that we cover specifically in our guidance, as the expected standards are set out in the Dispensary Services Quality Scheme established as part of the General Medical Services (GMS) Contract (England and Wales). We expect doctors to follow guidelines and regulations relevant to their work, and the principles in our guidance relating to conflicts of interest would also apply.

Establishing a register of interests

36 We note the panel's interest in a central register of interests. We share the opinion that more can be done to manage conflicts of interest, and in our view, this can be best achieved though promoting the need for openness, honesty, and transparency where such conflicts arise.

37 The appraisal process, which all doctors with a licence to practice are required to undergo on an annual basis, provides another platform for improved transparency. The general information required of all doctors for this appraisal includes a declaration of probity, which we are clear should include declarations of any conflict of interest. However, this does not of course mean that the doctor has told his or her patients about the conflict.

38 We understand the increasing arguments for a central register of interests. However, we need to recognise that the register will not by itself eradicate conflicts completely. The system would potentially be open to abuse from those deliberately intent on concealing an interest (which would of course represent a probity concern if it were to be referred to us). And secondly, whether or not an interest represents a potential conflict is dependent on the local context. The challenge of patients and the public interpreting this information and judging whether specific interests constitute a conflict in a given situation should not be underestimated.

39 Nevertheless, we are willing to work with the Inquiry, and Government, to develop a workable solution to this problem.

40 We would also encourage the Inquiry to consider how such a register could apply to all healthcare professions, recognising that this is not just an issue that applies to doctors. And for this reason, it may be that a separate organisation – rather than the GMC, as the regulator of doctors – is better placed to 'host' the register.

41 It is also important to recognise that there is considerable resistance to the GMC collecting and publishing additional information on our register (our List of Registered Medical Practitioners or LRMP). We consulted on this issue in 2016. Our intention was to expand the LRMP to be a more accessible and up-to-date record of doctors' current practice, rather than the largely historic record of qualifications it provides at present. The consultation sought views on whether or not to include information about doctors' conflicts of interest as part of this reform.

42 We received over 7,500 responses to our consultation – the biggest response ever to any GMC consultation. Overall, the consultation responses (the vast majority of which were from individual doctors) provided very little support for adding more information of any kind to LRMP, and most respondents were overwhelmingly against doing so.

43 Although we remain of the view that the register should be made much more accessible and useful, given the very negative response to the consultation we concluded it would not be appropriate to take the proposals any further at the present time. A paper summarising the responses to the consultation was taken to our Council in February 2017 and is accessible here.

44 In relation to the question of conflicts of interests, some common themes did emerge from the responses to the consultation. These were:

- respondents felt that publishing such information on LRMP was disproportionate. It was felt that no problem had been identified to justify this step; nor was the register the appropriate place to hold such information as it does not assist with its aim, which is to provide public assurance that an individual is properly qualified and fit to practise in the UK

- respondents argued that defining individual conflicts of interest and/or competing professional interests was inherently subjective and therefore any requirement to declare them would not be consistently complied with

- a number of respondents (both organisations and individuals) expressed concern over how any change to the register would be funded and about the additional organisational burden involved in ensuring that the LRMP was accurate and up-to-date.

45 The history of introducing revalidation tells us that to successfully introduce any major system change, three things are required. There needs to be appropriate legislative power to deliver the change, clarity of responsibility for enabling this, and critically, the support and acceptance of the broad mass of the profession

46 Therefore, taking into account the response to our 2016 consultation, if it was felt that the GMC was the most suitable organisation to host a register of interests, and if Government legislated to enable this, then we would work with the Inquiry and Government to persuade the profession of the value of collecting and publishing such

information. And in particular, emphasising the role that greater transparency can play in helping to restore public confidence in the profession.

Building trust in the profession

47 While we accept the argument for greater transparency over individual interests, it is important to recognise that public confidence (in the profession) remains generally high.

48 And we seek to further promote and uphold this through taking firm and fair action against those doctors whose fitness to practise is impaired, and through the guidance that we publish. However, we recognise that there is more that we can do to ensure that patients better understand the standards expected of doctors, so that they are empowered to challenge doctors when these standards are not met.

49 To address this, we are considering producing, collaboratively, a patient resource, such as a discussion aid or leaflet, to accompany our new guidance on consent which could, for example, help a patient prepare for a consultation with their doctor.

50 During our recent consultation on new guidance on consent we asked patients and carers to suggest specific topics that a patient resource might cover. We also asked for good practice examples of where a doctor has made the decision making process easier for the patient or carer. We are currently analysing the consultation responses but will aim to report on this later this year when plans for implementing the guidance will be underway.

Theme 3: How has the GMC responded to the Montgomery judgment in terms of guidance and the increased requirement to demonstrate informed consent

51 Good consent practice is at the heart of the doctor-patient relationship. It is important that doctors and patients make decisions together and that patients are given the information and support to do this. Again, we would take a breach of our guidance on consent seriously and would assess any concerns raised to determine whether we should take action.

52 How consent is expressed (that is, whether it is given orally or in writing) will vary depending on the situation. By law there must be written consent for certain treatments, such as fertility treatment and organ donation. Written consent should also be recorded if:

- the investigation or treatment is complex or involves significant risks (including risks to the patient's employment or personal life)
- providing clinical care is not the primary purpose of the investigation or treatment

- or the treatment is part of a research programme or is an innovative treatment designed specifically for their benefit.

53 However, simply having a signed form does not demonstrate sufficiently that the doctor has provided the patient with all of the relevant information or that the patient has understood it sufficiently to be able to make an informed choice. Our guidance emphasises the importance of giving patients the information they want or need, in a way they can understand, in order to support them in making decisions about their care. We also make clear that consent is an ongoing process and does not end when the patient signs a form.

54 Where there is no consent form, we say that doctors must record the key elements of their discussions with patient in the patient's medical record. This should include the information discussed, including any specific requests from the patient, any written, visual or audio information given to the patient, and details of any decisions that were made. We recognise that the best way to record information will vary depending on the nature of the information. In some cases, pre-printed checklists might be appropriate – but it is still important to tailor the discussion and record to the patient's individual needs. It should not be a tick box exercise.

55 We know that maintaining good practice in consent can be a huge challenge for doctors and that there are ever increasing pressures and demands on their time. To help in this, we advise doctors to consider the role that other members of the healthcare team might play and to consider the use of other sources of information and support which may include, for example, patient information leaflets, patient decision aids, advocacy services, expert patient programmes, or support groups for people with specific conditions.

56 The Supreme Court judgment in Montgomery has not altered the GMC's approach to consent and shared decision making. The GMC intervened in this case to explain the development and content of our guidance and make the case that the informed involvement of patients in their treatment, rather than their being passive and potentially reluctant recipients, can have therapeutic benefits, and is regarded as an integral aspect of professionalism in treatment. The court endorsed the position in GMC guidance and and in our view brought the law up to date with good medical practice.

57 We are however currently reviewing our guidance on consent, along with the range of supporting materials we provide to doctors and patients, to make it clearer and easier for doctors to apply in practice. The consultation on draft guidance has just closed and we hope to publish revised guidance in late 2019.

58 In our earlier response to the Review panel, we undertook to provide the outcome of our research into patient and public attitudes towards consent and decision making. This is available here.

Theme 4: Information about the accreditation of clinicians and any developments in our thinking around this

59 We are developing a process to provide additional regulatory oversight of high risk areas of practice (we are currently referring to this as our 'credentialing programme').

60 Credentialing would allow us to approve and recognise areas of practice outside of postgraduate training programmes which meet a risk threshold. Introducing a credential for cosmetic surgery for example would provide a recognised training route to enable doctors meeting the relevant entry criteria to gain an appropriate qualification. This would be visible to patients, so as they would be able to take an informed choice before deciding to have cosmetic surgery with a particular doctor.

61 We have been working with the RCS to evaluate their accreditation scheme for cosmetic surgery against our proposed model for credentials. We're looking at this scheme as a potential credential given it is an area with no governance and a high risk to patient safety.

62 Our Council will consider the framework for credentials soon, and there will then be an approvals process for potential credentials to be approved. We would be happy to share further details on our thinking with the panel once our Council have considered our proposals.

Theme 5: Please could you provide information on the following:

- **Number of referrals annually going back 10 years**
- **Number of those leading to sanction / impairment or erasure for each year**
- **Source of referrals annually resulting in impairment or erasure i.e. by employer / other clinicians / patients / other**
- **Annual total GMC income and proportion spent on FtP**
- **Further information on referrals focusing on informed consent**

63 This information can be found in Annex A.

Additional evidence for the areas of interest raised by the panel during the GMC's oral evidence session

64 The remainder of this note provides further evidence on several areas of interest for the panel including:

- our work to support individuals to raise and respond to concerns
- supporting whistle-blowers and complainants through this process
- using data to drive change and inform proactive regulation
- our response to the Paterson Inquiry.

Raising and acting on concerns

65 Within our guidance, we make clear that all doctors, whatever their role or level have a professional duty to promote and encourage a culture that allows all staff to raise concerns openly and safely. Prompt action must be taken if there are concerns that patients may be put at risk by the practice of colleagues, or as a result of any organisational systems, policies and procedures (Good medical practice (2013), paragraph 25, and Raising concerns (2012), paragraph 7).

66 In July 2015 we also launched joint guidance with the Nursing and Midwifery Council on the professional duty of candour, re-emphasising that doctors need to be open and honest with patients when things go wrong. This longstanding professional and ethical duty has since been reinforced by statutory organisational duties of candour, and the guidance provides links to the guidance provided by the CQC and equivalent bodies in the other UK countries.

67 We are taking forward work to reinforce this guidance through online resources, including an online decision support tool and workshops for the profession. For example, we are developing resources to support doctors to raise and act on concerns in systems under pressure, to form part of our 'ethical hub'. And in 2017, we developed, in collaboration with the Royal College of Physicians and academic partners, a series of 'Challenging Unprofessional Behaviour' workshops.

68 For 2019, through our Regional Liaison Service (introduced in 2012 to support doctors in providing good medical practice), we will be delivering the Professional Behaviours and Patient Safety Learning Series (developed in cooperation with specialists from Vanderbilt University) at a number of NHS Trusts and Health Boards, prioritising those institutions most likely to benefit from such interventions (drawing on GMC National Training Survey and NHS Staff Survey results to target these).

69 Lastly, we will be considering recommendations made by PSA for embedding candour, such as working with employers and system regulators to ensure positive reinforcement of skills learnt during practitioners' training are not negatively impacted by environments with poor records of candour.

Supporting whistle-blowers

70 If someone acting as a whistle-blower raises concerns with us in the public interest, we will assess whether there are issues which require us to take action.

71 We have taken a number of steps to support whistle-blowers in order to ensure that doctors who blow the whistle are not subject to retaliatory action through either a fitness to practise or revalidation recommendation. This includes commissioning Sir Anthony Hooper to examine our handling of cases involving whistle-blowers. The Hooper review made eight recommendations, including that the GMC should have a greater understanding of the circumstances surrounding a referral from an organisation and the timeline of events leading to this to make sure that referrals made to us are fair and accurate

72 As a result, we have been piloting a series of measures which are designed to provide us with a better understanding of these aspects. We have introduced a new referral form, in place since July 2016, which requires senior individuals acting on behalf of an organisation to:

- state whether the doctor has raised concerns about patient safety or systems. If so, supporting documents from the investigation can be attached. If the concerns were not investigated, an explanation should be provided
- confirm if they have made the doctor aware of their concerns about the doctor's practice and if so, when they did this.
- sign a statement to confirm that the referral has been made in good faith and that the doctor's RO has taken reasonable steps to make sure that the referral is fair and accurate.
- confirm whether they have approached our Employment Liaison Service for advice before making the referral.

73 If the referral involves a doctor who has raised concerns and the information provided does not contain objective evidence to support it, we will seek to gather more information about the complaint using our provisional enquiry process. This will help us to assess whether an investigation is necessary. This aims to avoid opening formal investigations on the basis of employer referrals in this context until the basis of the referral has been checked.

74 We have procedures in place to refer concerns to other bodies where they raise issues that may fall within their powers to take action to protect the public. Together with other regulators, we publish annually how many public interest concerns are raised with us and what action we take as a result. This legal duty came into force in April 2017, and we published our first annual report on whistleblowing disclosures in 2018 (in collaboration with the other healthcare professional regulators).

75 And in 2012 we introduced a confidential helpline for doctors so that doctors worried about the impact that raising concerns may have on their employment can raise concerns with us in confidence. Each year the National Training Survey, issued to all doctors in training, provides another channel for doctors to voice patient safety concerns about where they work.

Supporting complainants

76 As part of our major fitness to practise reform programme that began in 2011, we identified a need for patients to feel better supported and to more clearly understand our fitness to practise process and how we make decisions. We also identified that greater engagement with patients could help us to more fully understand the nature of their concerns and in turn improve our decision making. We therefore developed and piloted the Patient Liaison Service in 2012. The service was rolled out across the rest of the country by region on a phased basis starting in January 2015.

77 The patient meetings are intended to improve our communications with individuals (patients, relatives/friends of patients or members of the public) where we are investigating concerns they have raised about a doctor/s by ensuring we fully understand their concerns and by explaining our investigation process and subsequent decision. They can also help with discussing any concerns we cannot address and delivering signposting to other organisations (if they are better placed to respond to the complaint) as required.

78 They are either carried out face to face or over the telephone in Manchester, London or our Devolved Offices. The meetings are optional and informal and are offered during any initial provisional enquiries and at the initial and end stage of formal investigations.

79 This is just one of a number of initiatives aimed at placing patients at the heart of our fitness to practise process. Last year, we introduced a new policy and process to make sure that the patient's voice is heard in our processes even if they are unable to speak to us directly themselves. This approach ensures that we get in touch with family or those close to the care of a patient, where we are investigating concerns about a patient who would otherwise lack a voice because they lack capacity or because they have died. This means that we do not miss the valuable input that those close to them may be able to bring to our investigations.

80 A further example is our witness experience review. Having considered feedback received from witnesses involved in our fitness to practise processes, we carried out a survey in 2017 to gather detailed information about the witness experience and how we could improve it. Through 2018 we have worked to introduce improvements to ensure good witness care, contact and support throughout our processes. These include early assessments of each witness's needs and agreement with them of tailored communication plans, and signposting to other support services if necessary. We have also worked with the Medical Practitioner Tribunal Service to improve our

approach to witness care during hearings, including clear and frequent updates to witnesses and improved witness facilities at the hearing centre.

81 We know that our processes can be difficult to understand and can appear to patients and the public to be quite legalistic and remote. While we cannot completely avoid this, we have a continuous improvement approach to the tone and format of our communications. Last year for example, we completely redesigned our website in order to make it more accessible to the public and we regularly review our letters and publications to make sure they are as clear and relevant as possible.

82 We recognise that there will always be more that we can learn about how we can best support patients and the public, and we are committed to continuing to do so. And this is behind our decision to create a new patient champion role within the organisation to help embed that patient perspective into everything we do.

Supporting proactive regulation and the role of data in enabling this

83 We believe that the best way we can protect patients is by supporting doctors in their commitment to deliver high quality care. We ultimately take action against only a small proportion of doctors under our fitness to practise procedures, although our outdated legislation means that we end up investigating many more doctors that we would otherwise do. Where that happens, it is likely that harm to a patient or doctor has already occurred.

84 Ultimately, our effectiveness in realising this purpose will be assessed through our ability to meet four strategic objectives, as set out in our corporate strategy – that we:

- support doctors in delivering good medical practice – with our regulatory activities demonstrably supporting good medical practice and reducing harm to patients and doctors
- strengthen collaboration with our regulatory partners across the health services – leading to a more integrated approach to the identification and resolution of (emerging) concerns across the UK's health systems
- strengthen our relationship with the public and the profession - so that we are known as an independent and authoritative body that speaks and acts in the interests of patient safety and high quality care
- meeting the changing needs of the health services across the four countries of the UK – so that our approach to UK regulation is relevant and shaped to individual country specific needs.

85 Improving the use of our data and insights is critical to the success of a more proactive and preventative approach to regulation – and the following paragraphs illustrate how we use data to enable this.

86 Whenever we are reviewing our professional guidance for doctors we review a wide range of evidence to identify the issues that doctors, patients and others are asking us about, and the areas of practice where doctors may be struggling to understand or failing to follow our guidance. These sources include fitness to practise data, written enquiries to the GMC, and qualitative data captured by our liaison services during their meetings with doctors and medical students. We also commission literature reviews and primary research to fill gaps in our evidence.

87 Since 2018 we have also been reviewing the same qualitative data on a quarterly basis to identify emerging issues and areas of practice where the evidence suggests that we need to promote existing guidance to help doctors navigate to the relevant guidance and apply it to challenging, unfamiliar, complex or new subjects they're currently facing in practice. Our ethical hub provides additional resources on a range of ethical issues that our data has identified a need for. Examples of such issues include online prescribing, treating patients with learning disabilities, transgender healthcare and the care and treatment of older adults.

88 Furthermore, as we report in the 2018 State of Medical Education and Practice report, where concerns about a training environment are raised to us via our National Training Survey, we can institute a range of measures to help improve the quality of training. While we rely on postgraduate bodies to work with healthcare providers to ensure standards are met, we can take further action should this not suffice. This ranges from enhanced monitoring – where we proactively monitor problematic issues and work with organisations to alleviate these – to using statutory instruments such as conditions. To date, we have made use of our statutory actions at six organisations.

89 We are also exploring how we can better use our data to target our regulatory activities towards those areas where they add most value in supporting good practice. Our harms reduction programme is focused on using data to identify and understand specific risks that have the potential to result in harm to patients and/or doctors. As part of this programme, we are currently analysing our data to understand more about those concerns relating to poor communication – which can be a common theme for complaints relating to consent – in order to understand how and why these occur. Through analysing data in this way, and through sharing our insights with patients, doctors and key partners, we hope to explore whether further proactive action can and should be taken to improve communication practices more widely.

90 Our data and insight can also contribute to a fuller understanding of, and response to, risks and trends across the health systems. In 2017 we launched two major data products that aim to improve collaboration with our users and regulatory partners. GMC Data Explorer, available on our website, allows users to find answers to their

questions quickly and reliably without having to complete a request form or wait for a response. The new tool, which is updated daily, offers instant information on the makeup of the medical register, revalidation, doctors' training and fitness to practise.

91 We have also created data dashboards – offering information on a more restricted and confidential basis – for Responsible Officers and regulators. The designated body dashboard for Responsible Officers provides secure data on revalidation, fitness to practise and the national training survey within their own organisation. The dashboard for regulators and healthcare improvement organisations provides similar information for regulatory bodies within their area of responsibility.

Identifying and responding to emerging concerns

92 Recognising that the GMC may not always be best placed to identify or respond to a particular concern, we have supported the development of an Emerging concerns protocol.

93 This provides a clear mechanism for organisations with a role in the quality and safety of patient care to share information and intelligence that may indicate risks to patients, their carers, families, trainees or other healthcare professionals including doctors. It also establishes, for the first time, the ability for signatory organisations to trigger a multi-agency Regulatory Review Panel. At this panel, regulators can share early data or intelligence about emerging concerns regarding the quality or safety of care, the culture or behaviours of staff, or organisations which are beginning to provide cause for concern.

94 Concerns raised through this process may fall into three categories:

- concerns about individuals or groups of professionals
- concerns about healthcare systems and the healthcare environment (including the learning environments of professionals)
- concerns that might have an impact on trust and confidence in professionals or the professions overall.

95 To date, five RRP panels have been held in London and the Midlands. The first RRP was triggered after a senior NHS doctor flagged concerns about poor-quality theatre equipment; surgical packs were missing parts and contained instruments that broke during surgery. The supplier had also provided equipment to several other public and private care organisations.

96 The issue was escalated immediately within the GMC before the protocol was used to trigger one of the new Regulatory Review Panels (RRP) with the Care Quality Commission, Nursing and Midwifery Council, Health Education England, NHS Improvement and other partner organisations. We were able to agree a course of

action and referral to other non-signatory regulators. Between the CQC and these other organisations, steps to remove these items happened within hours, protecting both patients and staff.

97 Other situations where the protocol has already been used include a hospital with a lack of senior clinical supervision for trainee doctors out of hours; and concerns about the quality of care provided for patients on a particular treatment pathway in another organisation.

98 By using this protocol, we also hope to alleviate regulatory burden on employers and providers. By identifying shared concerns early, these can often be resolved locally, in partnership with those responsible, before a serious issue occurs and more formal (and burdensome) regulatory intervention is required.

99 Secondly, as part of our wider programme of work to proactively identify and respond to emerging concerns, we have a process in place for reviewing press publications to identify any potential fitness to practise concerns. Our Fitness to Practise Triage team and our media relations team have for some years shared monitoring and feedback on media news stories about doctors to ensure that any intelligence is assessed and acted upon as appropriate. This resulted in 161 investigations being proactively opened in the period 2011-2016 (1.1% of the total number of investigations opened during this period)

100 In addition, we now have an established news media intelligence sharing arrangement with the NMC and work is underway to enable greater analysis of the data and intelligence we receive from our media monitoring service so that we and other regulators can achieve the greatest collective effect from the data we hold.

101 Thirdly, to support the implementation of revalidation, we introduced the Employer Liaison Service (ELS) in 2012, changing the nature of our relationship with employers. The ELS meet regularly with the 600 plus Responsible Officers across the UK, providing advice regarding the local management of emerging concerns about doctors' fitness to practise. In this way, it has offered advice to Responsible Officers on about 1500 doctors. We believe that the 46% reduction in concerns raised to us by employers between 2012 and 2017 is partly a reflection of the positive impact of Responsible Officers working to resolve and prevent more issues locally and earlier, and the support they receive from the ELS. We believe that this engagement has also led to serious concerns being brought to our attention much more swiftly than before.

Responding to the Paterson Inquiry – the GMC view

102 The panel also asked for our view on the Paterson Inquiry and how we are responding to this.

103 We recently provided written evidence to the Inquiry and attended an oral evidence hearing to expand on the points we made. In our view, the Ian Paterson case arose

as a result of wider failings in the system combined with inadequate local governance and poor clinical leadership.

104 However, it is important to note that since concerns over Ian Paterson were brought to our attention, a number of significant changes have been made to the way in which the practice of doctors is regulated and monitored, both to support licensed doctors to maintain and improve their practice, but also to help ensure that emerging concerns are identified in a timely manner.

105 One such change is revalidation. Introduced in December 2012, revalidation supports individual doctors to develop their practice, drives improvements in clinical governance and provides patients with the confidence that doctors are up to date and fit to practise.

106 We believe that the introduction of revalidation, coupled with the introduction of Responsible Officers, has made an important contribution to the oversight of doctors' clinical practice in the UK. It has also led to a significant strengthening of clinical governance systems across all sectors, embedding a comprehensive appraisal system for all doctors.

107 In addition to revalidation, we have strengthened our processes for identifying and responding to concerns – including the introduction of both the ELS and Emerging concerns protocol.

108 All of these steps collectively offer stronger safeguards to help reduce the risk of further 'rogue doctors' operating in a similar way to Ian Paterson without detection and action.

109 But we acknowledge that the system is certainly not perfect and the case of Ian Paterson provides an opportunity to further improve oversight of medical practice.

110 For example, for revalidation to be effective, it is critical that designated bodies support Responsible Officers to put in place robust clinical governance processes including annual appraisal, responding to concerns processes and pre-employment checks. Clinical Governance systems also provide key information about doctors that Responsible Officer use when making a revalidation recommendation to the GMC that a doctor is up to date and fit to practise.

111 It is important to note that Revalidation is an evaluation of a doctor's fitness to practise designed to:

- support doctors in regularly reflecting on how they can develop or improve their practice (informed by colleague and patient feedback)
- provide patients with confidence that doctors are up to date with their practice

- promote improved quality of care by driving improvements in clinical practice.

112 It is not designed to detect and address concerns over 'rogue doctors'. Concerns should be picked up through local clinical governance processes – and it is the Responsible Officer's responsibility to ensure that effective processes for raising concerns are put in place.

113 And despite the improvements in clinical governance that revalidation has led to, the robustness of such processes can be variable. For this reason, we believe that further action can be taken to strengthen these processes and enable Responsible Officers to discharge their statutory duties more effectively.

114 For example, we believe that the Responsible Officer regulations should be strengthened to create an additional responsibility for Designated Bodies to quality assure governance processes underpinning revalidation to ensure there is board level oversight of the Responsible Officer functions and associated systems.

115 Secondly, we believe that further action is required to promote information sharing between Responsible Officers.

116 Our information sharing principles, developed in response to Taking Revalidation Forward, establish a framework for improved information sharing between ROs and/or individuals with responsibilities for local systems of clinical governance. These principles also establish an expectation that the RO for a doctor is an information hub and should seek and receive information from other organisations where a doctor works about their practice. This should include receiving information from an independent organisation that a doctor has been appointed to and/or granted practising privileges to work in that organisation.

117 Our view is that this is so important that the RO regulations should place a statutory requirement on any given designated body to have in place the means to share key information (relating to revalidation and appraisal) with new employers and new designated bodies if the Doctor moves on. That is not the case today.

118 We believe that this statutory duty should require information to be shared in the following circumstances:

- when concerns arise about a doctor
- when local action is put in place for that doctor
- when a doctor moves to work in an organisation.

119 We have fed these suggestions in as amendments that we would like to see in the Responsible Officer regulations on which DHSC say they intend to consult later this year.

120 We also believe that there should be improved data on an individual doctor's scope of practice – primarily to assist those with responsibilities for monitoring and supporting medical practice. Put simply, there is lack of consistent and reliable data on what doctors are doing and we believe this needs to be addressed as a matter of urgency. There are potential benefits in here for appraisal, ensuring this takes into account whole scope of practice, and for awarding practising privileges.

Annex A – detailed fitness to practise information.

Number of referrals annually going back 10 years – including the number that led to sanctions / impairment or striking off for each year

(Source: Fitness to Practise Annual Stats 2008-2018)

Table 1 – Enquiries regarding a doctor's fitness to practise

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total Enquiries	**5,216**	**5,773**	**7,153**	**8,781**	**10,347**	**9,866**	**9,624**	**9,418**	**9,146**	**8,546**	**8,573**
Enquiries from PAPC (Person acting in a professional capacity)	628	1,030	1,395	1,481	2,003	1,316	1,200	1,105	744	807	815
Enquiries from members of public	3,569	3,689	4,525	5,665	6,154	6,475	6,572	6,547	6,688	5,714	5,677
Other enquiry sources	1,019	1,054	1,233	1,635	2,190	2,075	1,852	1,766	1,714	2,025	2,081

Table 2 – Case Examiner decisions

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Refer to Panel/Tribunal	359	319	314	212	216	258	218	279	200	200	280
Undertakings	110	95	102	148	143	173	136	144	144	106	93
Warning	169	212	183	199	182	154	110	135	95	117	69
Advice	326	428	458	736	844	208	257	373	333	225	66
Conclude	333	442	497	622	747	1,566	1,626	1,635	997	709	700

N.B. The table provides Case Examiner outcomes at the end of an investigation. It does not include any decisions to close with voluntary erasure. It relates to the count of decisions made and not the number of doctors or cases.

Table 3 – Fitness to practise panel outcomes

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Erasure	42	68	73	65	55	55	71	72	70	62	65
Suspension	75	77	106	93	64	86	86	95	93	76	101
Conditions	30	48	37	24	20	32	22	24	17	13	25
Undertakings	3	3	5	1	1	0	3	1	0	0	0
Warning	22	22	29	23	12	13	10	6	11	13	10
Reprimand	0	1	0	-	-	-	-	-	-	-	-
Impairment - NFA	4	4	4	2	6	1	4	2	2	4	2

No Impairment	28	44	65	33	48	38	37	38	34	27	40
Voluntary Erasure	0	3	7	1	2	4	4	1	2	0	3

N.B. NFA stands for no further action. Outcomes are based on first time (concluded) hearings at the end of investigations. It does not take into account the results of any appeals that may have taken place subsequent to the hearing. The figures also do not include the outcome of any review hearings for those doctors with suspension or conditions. The table relates to the count of outcomes not doctors or hearings

Source of referrals annually resulting in impairment or strike off i.e. by employer / other clinicians / patients / other

Table 4 – Percentage of cases heard at hearing resulting in sanction, by source of original enquiry

	% of cases heard at hearing resulting in sanction, by source of original enquiry							
Year Hearing End Date	1 Public	2 Employer	3 Other Doctor	4 Doctor self-referral	5 Police	6 GMC - Press Cuttings	7 GMC - Other	8 Other
2008	13%	44%	4%	4%	9%	1%	1%	24%
2009	14%	37%	8%	6%	11%	0%	0%	23%
2010	14%	42%	6%	6%	9%	1%	3%	19%

2011	9%	39%	9%	5%	9%	1%	3%	26%
2012	11%	44%	5%	7%	5%	1%	4%	23%
2013	9%	35%	9%	7%	9%	1%	8%	20%
2014	9%	34%	7%	6%	9%	2%	7%	27%
2015	13%	39%	8%	9%	11%	1%	5%	15%
2016	9%	39%	10%	9%	5%	3%	4%	21%
2017	11%	38%	9%	13%	6%	2%	3%	18%
2018	11%	33%	9%	15%	6%	2%	3%	21%

N.B. Source categories are more granular than those provided in Table 1. They translate to:
Member of the public = Public
Employer / Police = PAPC
Other Doctor / Self-referral / GMC / Other = Other

Number of cases with an allegation type or sub type relating to consent by year and by case outcome

Table 5 - cases involving consent

Case outcome	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
NFA before investigation (including provisional enquiry closures)	0	3	0	1	0	0	0	6	7	16	27

Closed during investigation	10	22	20	23	24	74	74	87	62	47	57
Closed during investigation – Advice	17	25	34	30	40	5	14	23	19	20	5
Referred to employer/Responsible Officer	3	14	24	22	34	15	15	32	24	12	12
Sanctions applied without a hearing – Warning	1	4	4	5	2	3	5	2	5	0	2
Sanctions applied without a hearing – Undertaking	0	3	1	0	1	5	0	3	4	3	3
Closed at hearing - No impairment	1	3	5	2	5	4	4	3	3	0	4
Sanction applied at hearing – Warning	1	1	3	2	1	2	1	0	2	0	0
Sanction applied at hearing – Condition	1	0	0	2	0	2	1	2	4	2	3
Sanctions applied at hearing – Suspension	0	1	5	1	2	0	0	0	5	3	3
Sanctions applied at hearing – Erasure	0	5	2	4	2	1	4	7	3	9	4
Totals	**34**	**81**	**98**	**92**	**111**	**111**	**118**	**165**	**138**	**112**	**120**

N.B. Results should be considered with caution as cases may consider multiple allegations against the doctor – including those unrelated to consent – which may have had an impact on the overall sanction. The data in the first row 'NFA before investigation (inc. PE closures)' should also be treated with caution as we did not collect allegation data for cases closed at triage (and therefore those cases we did not investigate) prior to 2017. This table also sets out cases that were closed during each year.

Does the GMC know what the single largest category of complaints refers to?

Table 6 – 2018 top 10 allegations total at triage

Allegation Type	Allegation Sub Type	Number of allegations
Knowledge & experience	Substandard treatment	1234
Knowledge & experience	Suitable action not taken	1122
Knowledge & experience	Inappropriate / irresponsible prescribing	855
Partnerships with patients	Rudeness to patient	800
Not about a doctor.	Other healthcare Professional	694
Not in GMP.	Issues cannot be identified	647
Not about a doctor.	System concern	582
Acting w. honesty/ integrity	Dishonesty with patient/colleague	551
Knowledge & experience	Misdiagnosis	456
Partnerships with patients	Failure to provide appropriate information	450

N.B. A single complaint may have multiple types of allegation attached to it. This table covers all complaints received during 2018.

Further information provided by the General Medical Council:

Fitness to Practise cases involving conflicts of interest

We can confirm that as of the 1 April 2019, we have erased 72 doctors (since 2007) where there has been a proven allegation of a conflict of interest.

However, it is important to note that in the majority of these cases, we will also have investigated other allegations (any one case may involve a number of different allegations). Therefore, it is not possible to say if the erasure was a direct response to the proven allegation of a conflict of interest, or one of the other allegations that was investigated as part of each case.

Consent

Our current guidance on consent (2008) sets out the following with respect to recording decisions:

51 *You must use the patient's medical records or a consent form to record the key elements of your discussion with the patient. This should include the information you discussed, any specific requests by the patient, any written, visual or audio information given to the patient, and details of any decisions that were made.*

Although patients have a right to access their medical records and can therefore access evidence of having provided their consent, our guidance does not currently require doctors to share this information with the patient. However, as we have noted previously, we are currently reviewing our guidance on consent. Our pre-consultation draft proposals included the following statements:

24 If a patient is likely to have difficulty retaining information, you should offer them a record of your discussions, detailing what decisions were made and why. For example, you could give them a written record, or you could suggest the patient makes an audio recording of the discussion.

58 You must record the discussion and any views or decisions the patient expresses. You should make sure a record of the plan is made available to the patient and others involved in their care, so everyone is clear about what has been agreed. [This is particularly important if the patient has made an advance decision to refuse treatment. You should bear in mind that care plans need to be reviewed and updated as the situation or the patient's views change].

We are currently reviewing the responses to the consultation and so are not able to confirm at this point whether these paragraphs will be included in full or in part in the final version – however, we wanted to share our developing thinking on these areas with you, given their relevance to the review.

Registries

The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

NCARDRS shared the following paper with the review:

- Stevens S, Miller N, Rashbass J. Development and progress of the National Congenital Anomaly and Rare Disease Registration Service *Archives of Disease in Childhood* Published Online First: 24 October 2017. doi: 10.1136/archdischild-2017-312833

National Joint Registry (NJR)

Following their attendance at the Oral Hearing session (5th March 2019), NJR have provided the following documents and further information as requested by the Review.

National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

National Joint Registry for England, Wales, Northern Ireland and the Isle of Man

National Joint Registry
www.njrcentre.org.uk

NJR Background

- Established by the Department of Health in 2002 following 3M Capital Hip Failure Report, 2001
- Data collection commenced April 2003 (now in 15th year) for hip and knee in England and Wales
- NJR submission of data has been mandatory for all NHS Trusts and NHS Foundation Trusts undertaking replacement surgery, since April 2011 – the actual compliance rate is around 95 per cent. The data reported increased significantly after 2011
- Extended to ankles (2010) elbows and shoulders (2012); Northern Ireland (2013) and the Isle of Man (2015)
- Largest database of its kind in the world, currently with c 2.5 M records (c 250k records submitted annually)

National Joint Registry
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Mission Statement

"To collect high quality, relevant data about joint replacement surgery in order to provide early warning of issues relating to patient safety, to improve quality of outcomes and ensure quality and cost effectiveness of joint replacement surgery, monitor and report on outcomes and enable related research."

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NJR Funding

- NJR is self-funded [No central government budget]

Pre 2014 income raised through:

- Hospital levy on sale of components
- Industry collected the levy on behalf of the NJR
- Manufacturers received all data free

Post 2014 New Economic Model:

- Hospital and industry subscription
- Aims: fairness and equity-reduce cost to hospitals
- NJR collects subscription charges
- Industry access data through NJR Supplier Feedback and bespoke supplier reports

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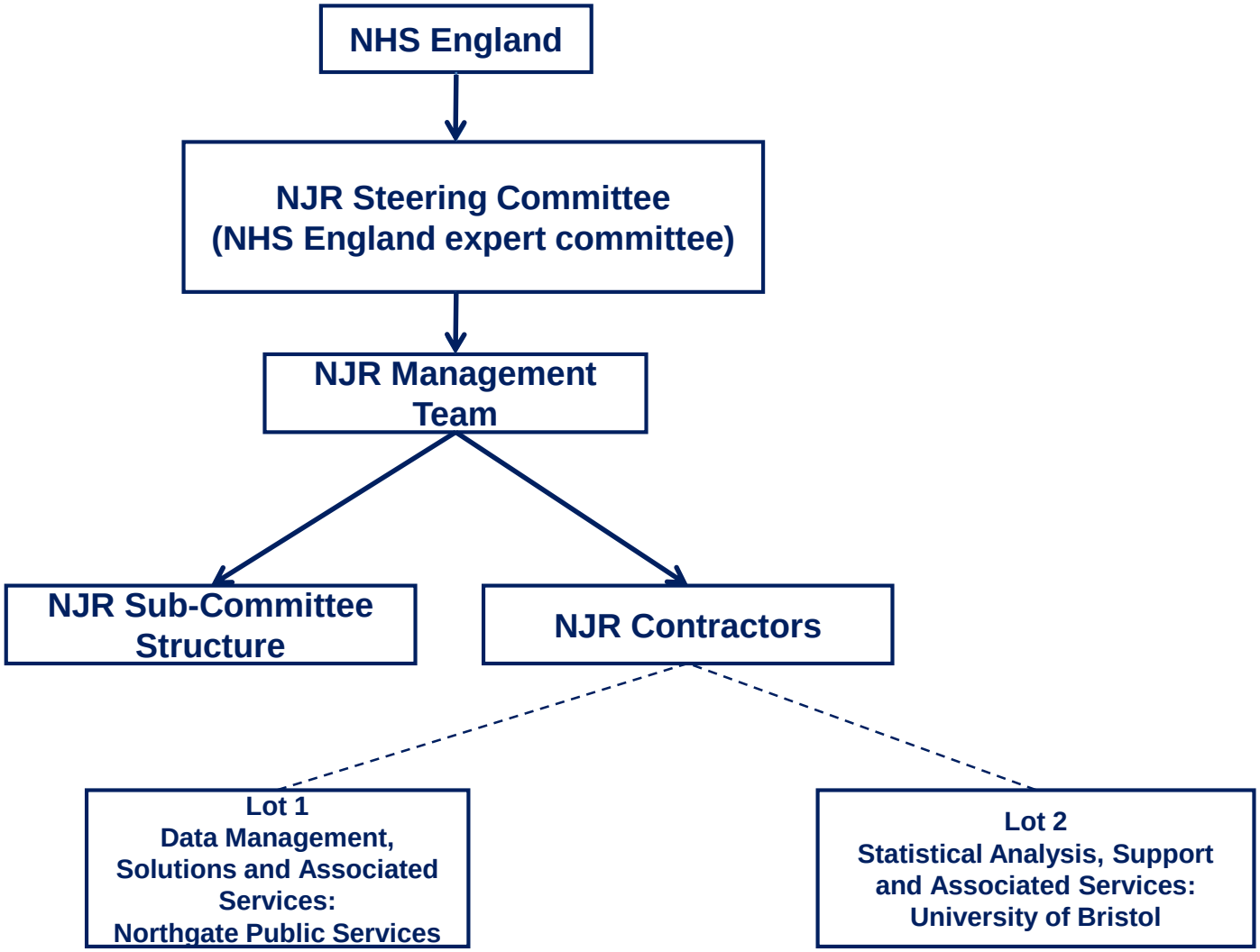
NJR Organisation Structure



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Governance Structure
NJR Steering Committee

Classification: NHS England Expert Committee

Chairman reports to NHS England Medical Director

NJR is hosted by the Healthcare Quality Improvement Partnership (HQIP)

NJR Steering Committee Membership:

- Chairman
- Medical Director / Vice Chair
- 3 surgeon members
- 2 patient representatives
- 2 orthopaedic implant supplier representatives
- 1 public health and epidemiology representative
- 1 practitioner with special interest in orthopaedics
- 1 NHS Trust management representative
- 1 independent healthcare sector representative

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NJRSC Governance Structure

- **Co-opted members:**
  - BOA President
  - National Director of Clinical Improvement (GIRFT)
  - Welsh Government representative
  - NJR Regional Clinical Coordinator Committee Chair
  - MHRA
  - Procurement

- **Attendees:**
  - NJR/HQIP Management Team Representatives
  - Lot 1 Contract (Northgate) representatives
  - Lot 2 Contract (UoB/Oxford) representatives

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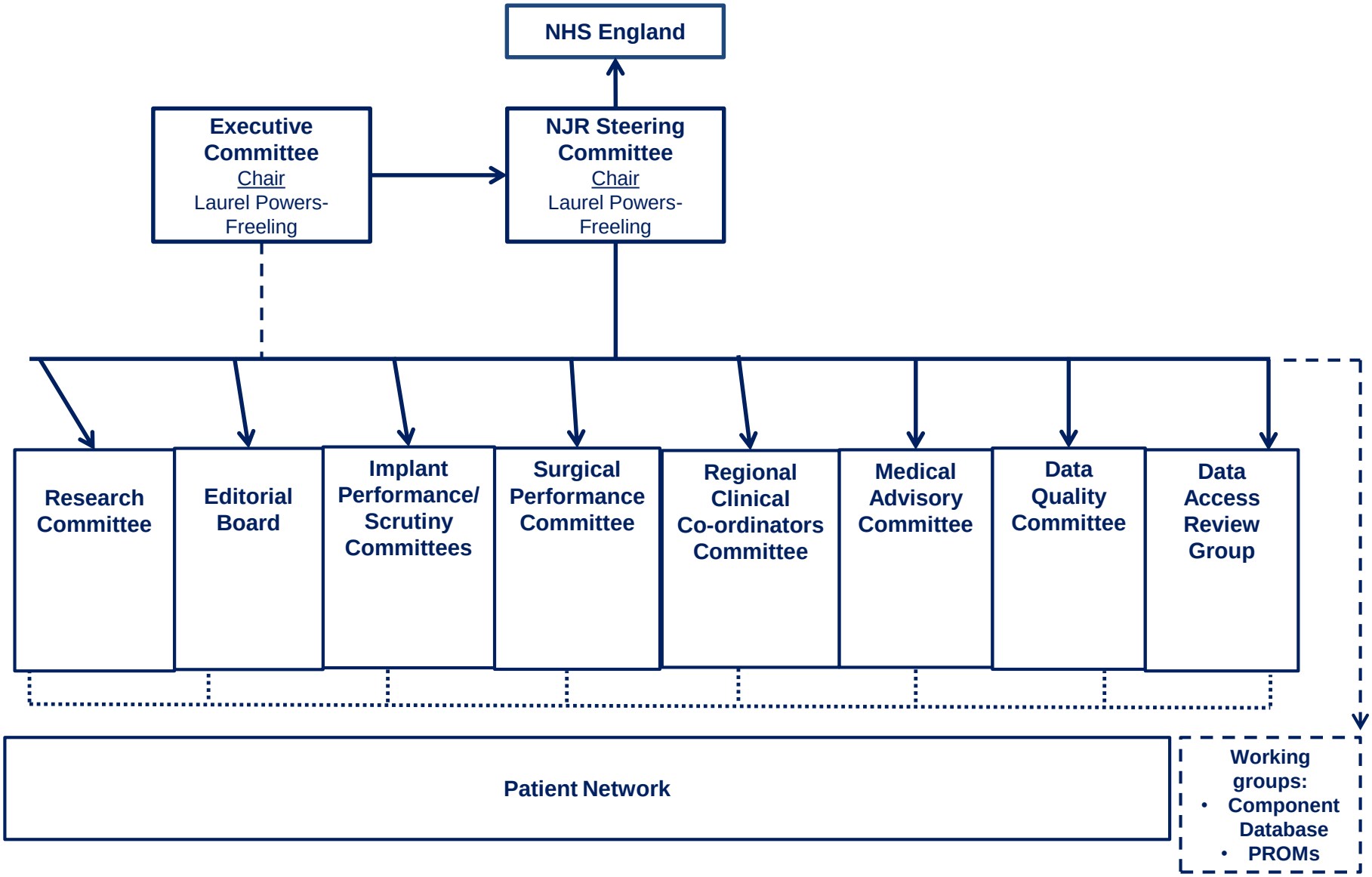
NJR Committee Structure



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NJR Governance Structure

Support Structure

- NJR Helpdesk ©5,000 calls per year
- 8 NJR Regional Coordinators
- 28 NJR Regional Clinical Coordinators
- 66 NJR Clinical Leads
- 2 NJR Research Fellows

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NJR Strategic Documents

Key Strategy Documents:

- Strategic Plan 2018-2021
- Annual Work Plan
- Research Strategy
- Communications Strategy
- Supporting Data Quality Strategy
- How NJR Data are Made Available

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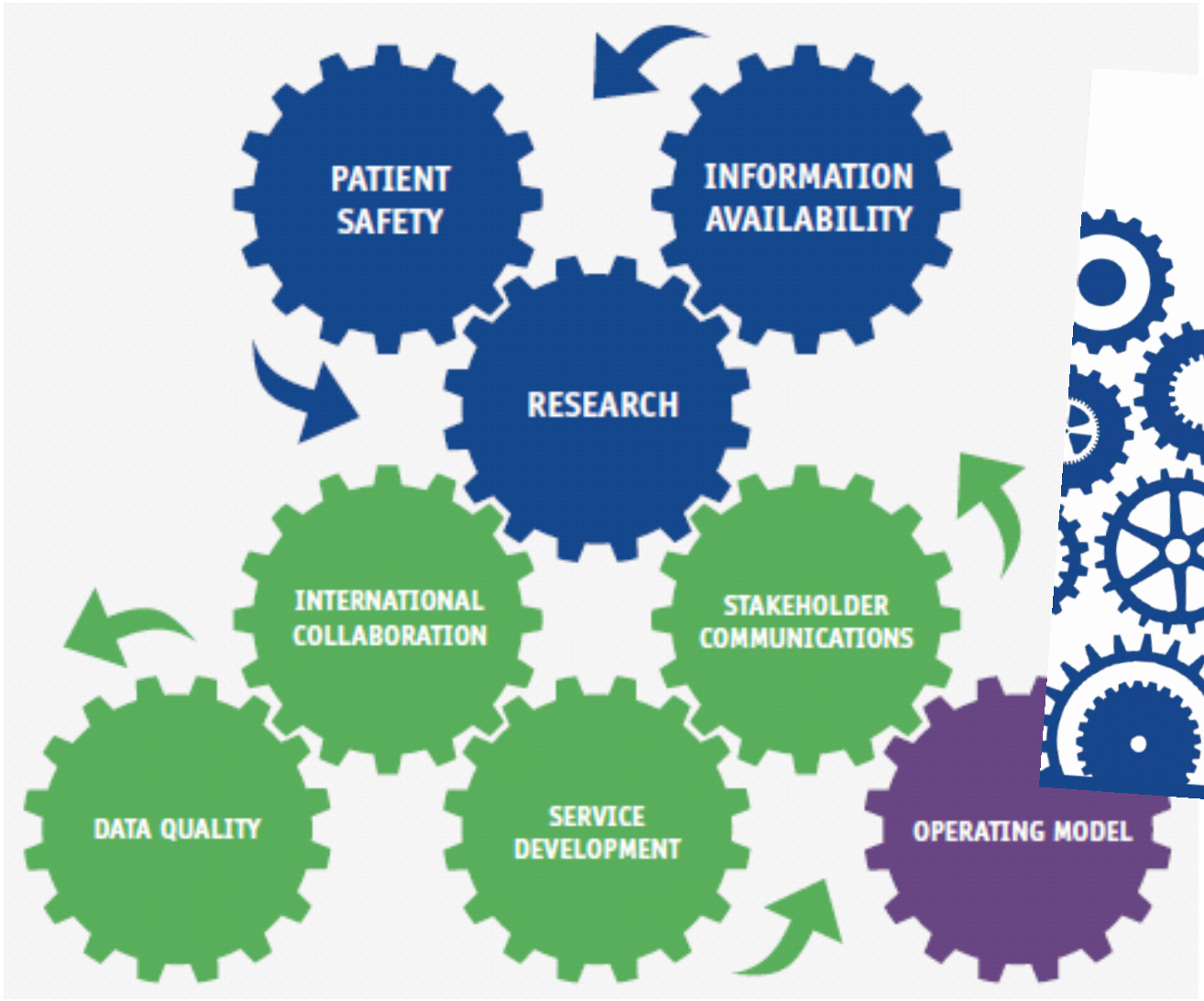
NJR Strategic Plan 2018 - 2021



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How is the Data collected?

Hospitals

Patient Consent

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Online Data Entry

Patients

Outcome Questionnaires

Industry

Input to Component Database

Data Validation
Data Quality
Assurance

Secure Data
Management

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NJR Data Validation

- NJR's Data Quality Audit involves hospitals, both in the NHS and independent sector, providing extracts of data from their local Patient Administration System (PAS) relating to hip and knee primary and revision procedures, which is checked against the NJR data submitted and vice-versa.

- This retrospective data audit enables the NJR to compare patient records for procedures recorded in a local hospital's database to those within the registry, with the aim of investigating the accuracy of number of arthroplasty procedures submitted, compared to the number carried out.

- The audit of 2017/18 data is the fourth year of the audit in NHS hospitals and the third year independent organisations reporting data into the NJR have been included in the audit.

- **NJR Annual Data Quality Award**
  To achieve an NJR Data Quality Provider Award, hospitals are required to meet a series of six ambitious targets, including 95% or above, hip and knee data compliance.

- The scheme embeds NJR's mission in ensuring quality data and also benefits hospitals by:
  - recognising and rewarding best practice
  - increasing engagement and awareness of the importance in quality data collection
  - embedding the ethos that better data ultimately ensures improvement in quality of care for all our patients.

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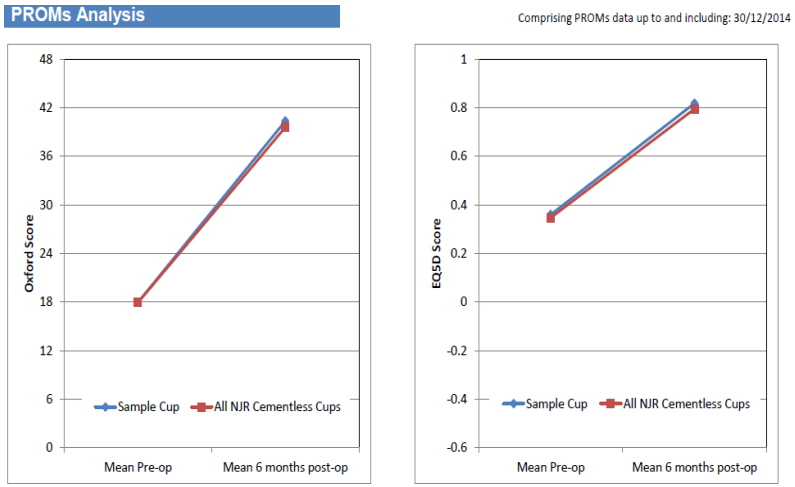
NJR PROMs

NJR PROMs:

- Started 2010 with cohort of 50,000 patients
- Five year analysis due for publication shortly

- Shoulder PROMs Post-op follow up
  - six months
  - three years



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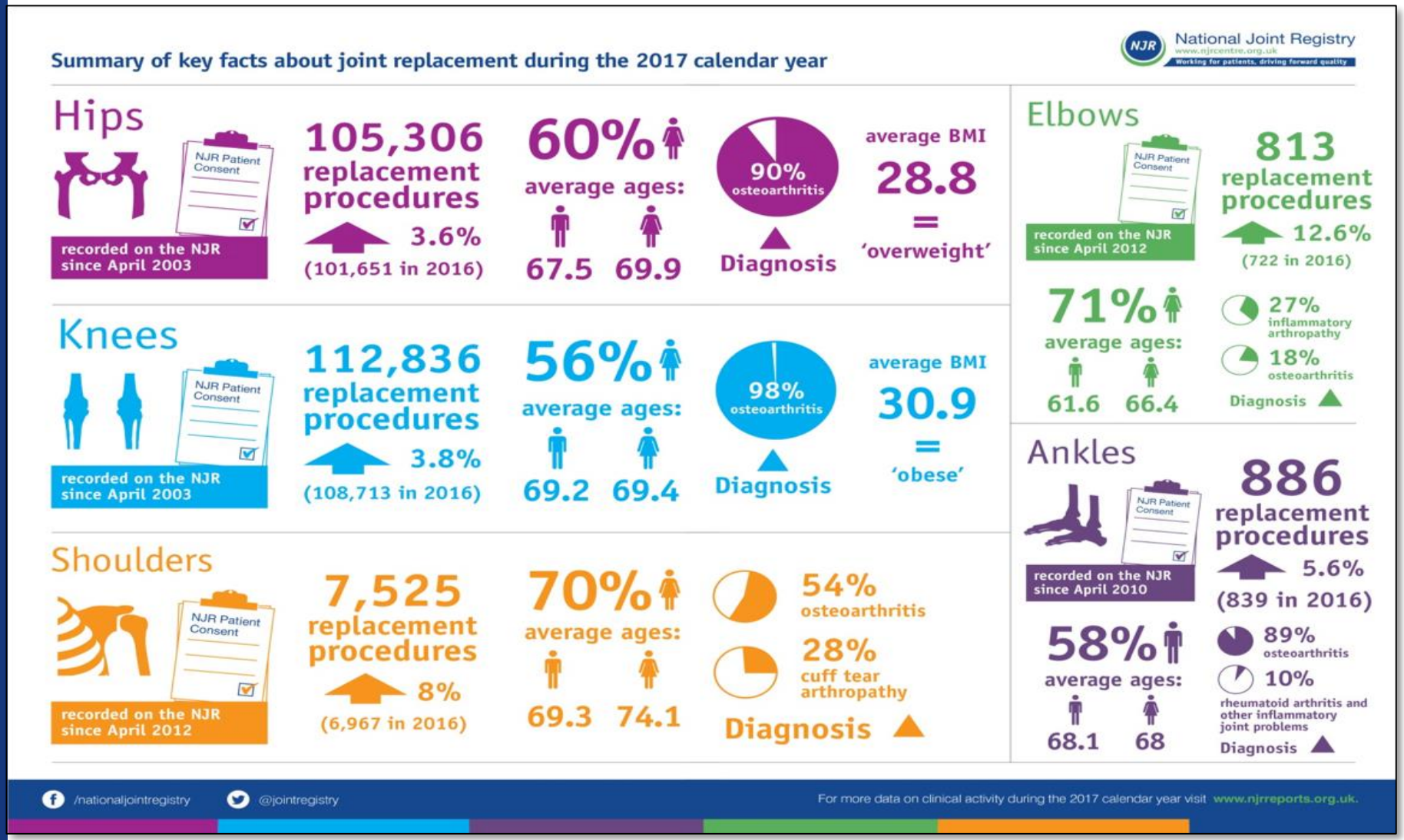
Data shows increasing numbers Year-on-Year



NJR works collaboratively with a number of key stakeholders to ensure and further develop robust processes which are underpinned by agreed roles and responsibilities.

1. Extensive stakeholder engagement
2. Defined Roles and Responsibilities
3. Agreed MOUs and data sharing agreements

Patient Safety – Performance Monitoring

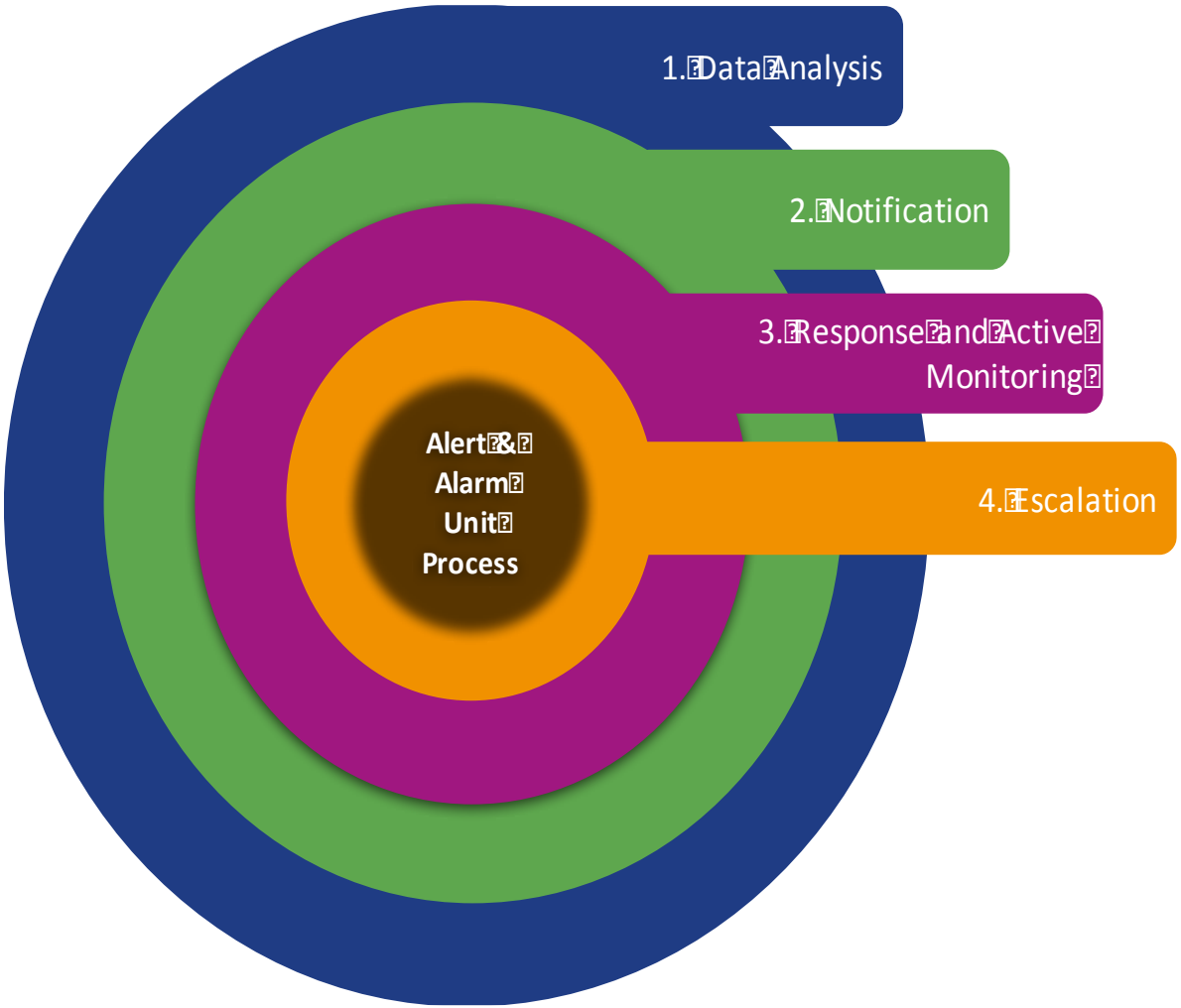
OBJECTIVES - public and patient reassurance in:

- ✓ The value of National Audit data and patient registries
- ✓ The NJR's monitoring processes making joint replacement surgery safer
- ✓ The transparent approach by National Audit, regulators and the profession

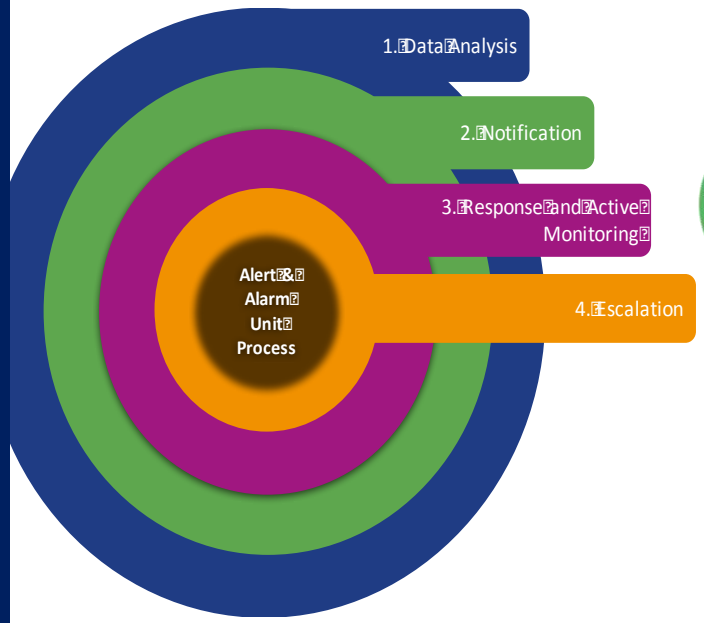
OBJECTIVES - direct stakeholder groups engagement:

- ✓ Surgeons greater insight how the NJR is supporting them to practice safely
- ✓ Surgeons greater insight how to reflect on own practice and performance data
- ✓ An increased number of surgeons downloading their data for appraisal
- ✓ For hospital management to place a stronger focus on National Audit data
- ✓ Maintain and develop strong, cooperative relationships with the key stakeholders

Alert and Alarm Unit Process for Hip and Knee - Overview



The Alert and Alarm Unit Process – Key Stakeholder Roles and Responsibilities



NJR Lot 1 & 2 contractors

NJR Lot 1 contractors are responsible and accountable for provision of data extracts
NJR Lot 2 contractors are responsible and accountable for analysis of the data and sharing results with SPC

NJR Surgical Performance Committee (SPC)

Responsible for monitoring performance and communicating directly with Units; collaborates with CQC and NHSI by informing of concerns

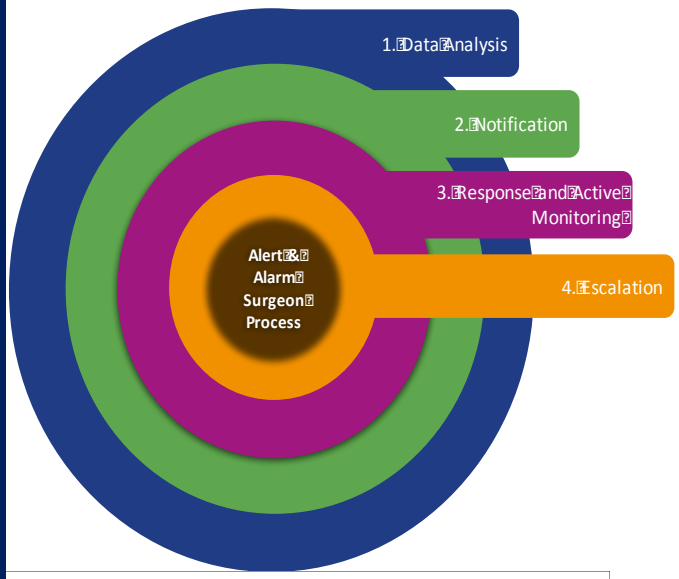
CQC & NHSI

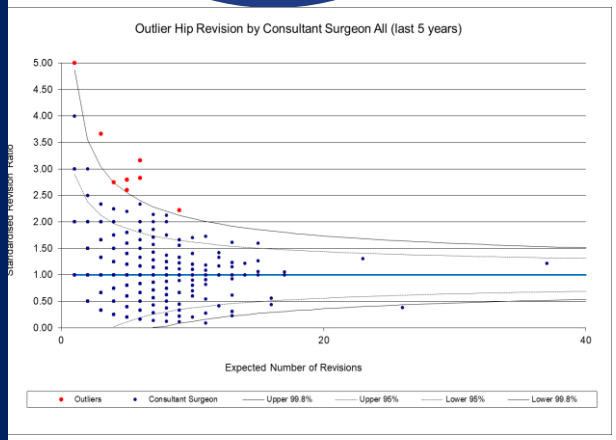
- Responsible and accountable for escalation management

BOA

- Responsible and accountable for carrying out an independent Elective Care Review when this is recommended by NJR and has been agreed by the unit

The Alert and Alarm Surgeon Process - Key Stakeholder Roles and Responsibilities





NJR Lot 1 & 2 contractors

- NJR Lot 1 contractors are responsible and accountable for provision of data extracts
- NJR Lot 2 contractors are responsible for data analysis and sharing results with the SPC

NJR Surgical Performance Committee (SPC)

- Responsible and accountable for monitoring performance and communicating with surgeons

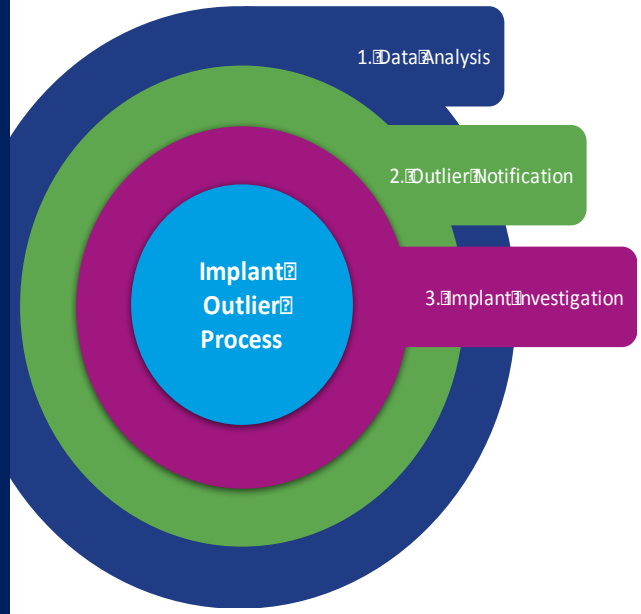
CQC

- Informed by the SPC when there are concerns with adequate trust intervention when dealing with performance issues and internally agreeing next steps

BOA

Supporting NJR with communication of messages and best practices to members

Implant Outlier Process - Key Stakeholder Roles and Responsibilities



NJR Lot 1 & 2 contractors

- NJR Lot 1 contractors responsible and accountable for the provision of data extracts
- NJR Lot 2 contractors responsible and accountable for data analysis and sharing results with the ISC

NJR & Implant Surgical Committee

- ISC are responsible for managing the end to end outlier process, formally notifying the MHRA of Level 1 implants and advising manufacturers of Level 1 & 2 implants
- The NJR OMT are responsible and accountable for sharing Level 1 implant details for the Annual Report

Manufacturer

- Responsible for receiving (and internally managing) Level 1 status notifications
- Responsible for responding to the ISC within 3 months with an action plan for Level 2 implant outliers

MHRA

Responsible and accountable for undertaking investigations of Level 1 implants

National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

NJR Data - Metal on Metal Hips

- Key aim of the NJR is to identify any brand of prosthesis showing high failure rates and recommend prompt removal from the market.
- In 2010 NJR data identified higher than expected revision rates for the metal-on-metal implants, immediately informing the MHRA, who thereafter issued an alert.
- ASR implants were withdrawn by the manufacturer (DePuy) in 2010 following the publication of NJR statistics.
- Patients with any metal-on-metal implant who have consented to their data being registered with the NJR, have all been identified and recalled for monitoring.
- Without NJR data hospitals would have been unable to identify which patients had these specific implants.

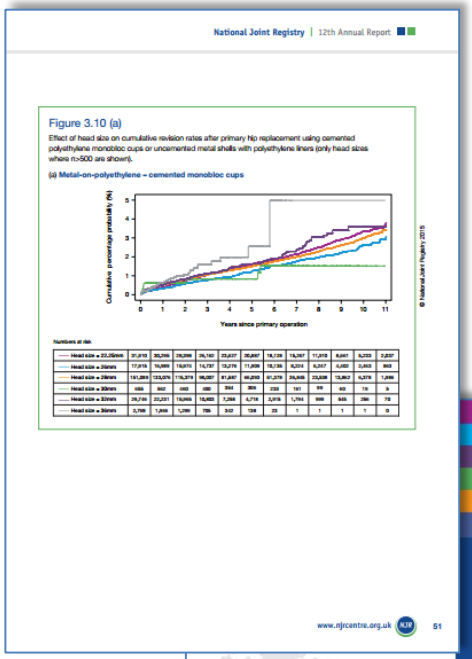
National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

How NJR data are made available

NJR Annual Report

Purpose:

- Report published in September each year.
- Presents analysis of data submitted to the NJR, highlighting aims and achievements of the NJR its Steering Committee and sub-committees.
- Identifies key trends in surgical practice, activity levels, implant usage and patient demographics are presented, also chosen specialist research topics.



National Joint Registry
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How NJR data are made available

NJR Annual Report Online

Purpose:

- Provides interactive access to content from the NJR Annual Report, providing visitors with ability to analyse and compare data across years, and to filter and segment results to a greater extent than that available through the printed report.

- Aims to reduce the growing size of the printed Annual Report, through dynamic, interactive web content.

National Joint Registry
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NJR Patient Information

NJR Public and Patient Guides

Available for each joint type and reflecting the level of information available for patients within the NJR.

National Joint Registry
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How NJR data are made available

Clinician Feedback

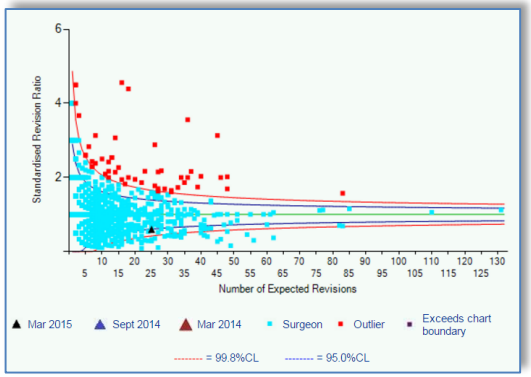
Purpose:

Enables clinicians:

- to review their data captured within the NJR through a series of interactive graphs, charts, reports and data tabulations which are updated quarterly.

- to review their outcomes data, to assess whether this is within the expected range.

- to preview their data and results prior to publication on the NJR Surgeon Hospital Profile website.



National Joint Registry
www.njrcentre.org.uk
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How NJR data are made available

Consultant Level Report

Purpose:

Accessed through Clinician Feedback, provides clinicians with an annual downloadable PDF Report summarising their activity and outcomes.

The report has been designed specifically to support use in consultant appraisal / revalidation.

National Joint Registry
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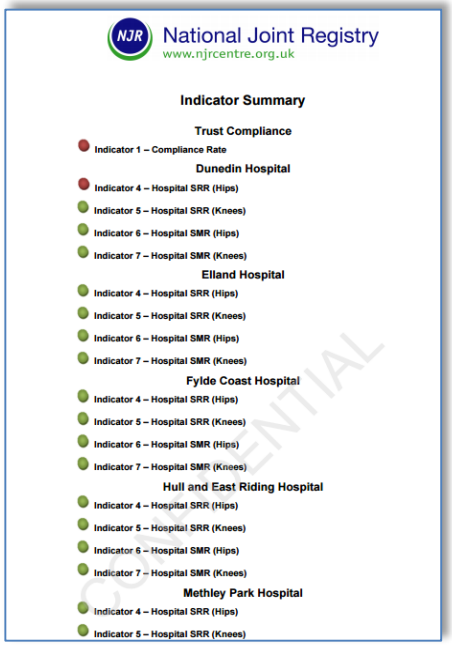
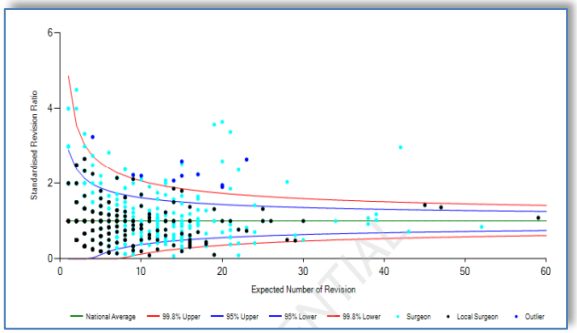
How NJR data are made available

Management Feedback:
Annual Clinical Reports



Purpose:

- An annual report enabling trusts / hospitals / hospital groups to review their activity and outcome data recorded on the NJR through a downloadable report.



National Joint Registry
www.njrcentre.org.uk
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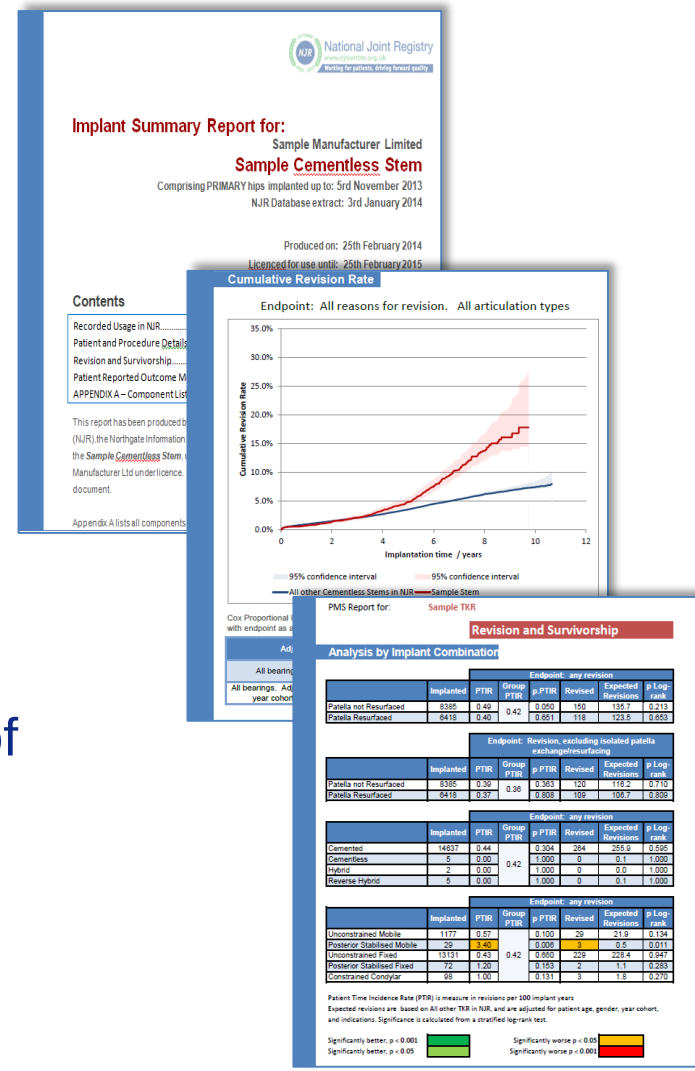
How NJR data are made available

Supplier and Regulator Feedback

Purpose:

- Provides medical device suppliers and also the MHRA access to data and reports on the use of their implants, and outcomes for patients receiving their implants.

- Enables suppliers and MHRA to assure on-going safety, quality and appropriate usage of implants, as well as tracking product sales within the market.



National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

How NJR data are made available

Surgeon Hospital Profile

Purpose:

- Public website profiling surgeon and hospital activity and outcomes data based on NJR Data.
- Enables patients and public to look up hospitals or surgeons and review the number and type of cases performed and outcomes achieved.
- Website developed as part of the NHS England Consultant Outcomes Publication initiative.

National Joint Registry
www.njrcentre.org.uk
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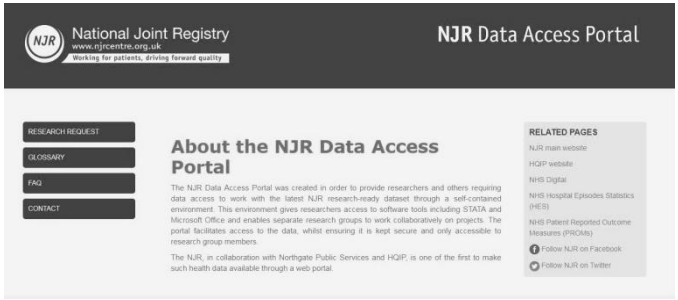
How NJR data are made available

Research

Purpose:

- NJR is a resource made available to external researchers conducting new and clinically relevant research related to joint replacement.
- Research projects wishing to use NJR data are classified as external, independent, or internal or collaborative projects (NJR Partnership Projects).
- All applications for research projects are managed by the NJR Research Committee.
- NJR Data Access Portal has recently gone live.
- NJR Research often gets published in journals including the BMJ, and The Lancet.



THE LANCET

thebmj

National Joint Registry
www.njrcentre.org.uk
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How NJR data are made available

Recent Research

- NJR-funded research - recent publication.
  'How long do hip and knee replacements last?'

THE LANCET

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31665-9/fulltext

- This research gained national and international coverage in many journals and newspapers and featured on national BBC TV 6pm and 10pm news on 15th February.

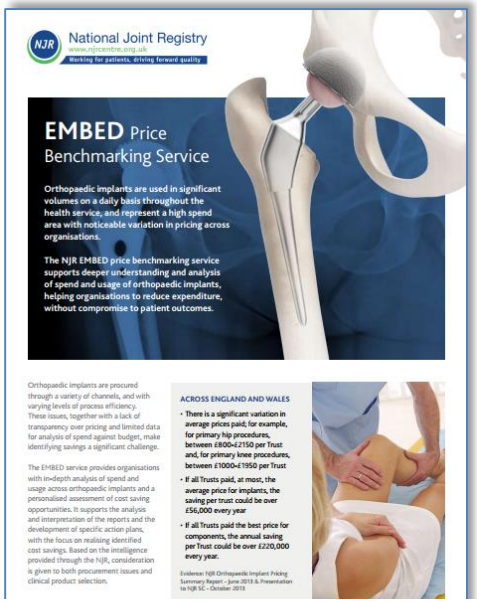
National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

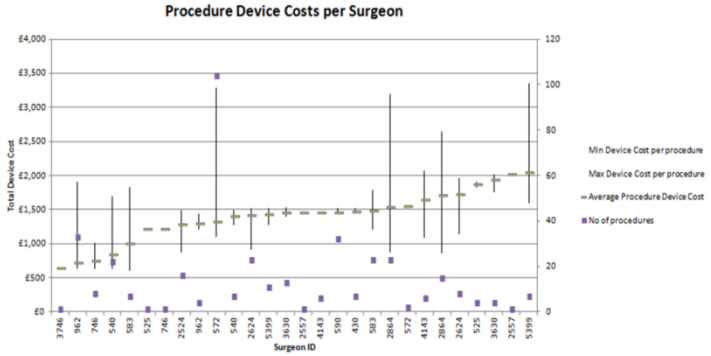
How NJR data are made available

Price Benchmarking

Purpose:

- Trusts and hospital groups able to submit pricing catalogues for implants to the NJR.
- Price benchmarking reports produced comparing local implant costs with national average, best quartile, and best pricing.
- Option to subscribe to enhanced service ‘Embed’ providing additional analysis, including provision of surgeon level data packs, feeding back implant costs to each surgeon within the trust or group.





National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

How NJR data are made available

Third Party Usage

Examples:

- NHS Choices
- NHS Improvement
- Care Quality Commission [Hospital Regulator]
- MHRA [Device Regulator]
- Beyond Compliance
- ODEP

National Joint Registry
www.njrcentre.org.uk
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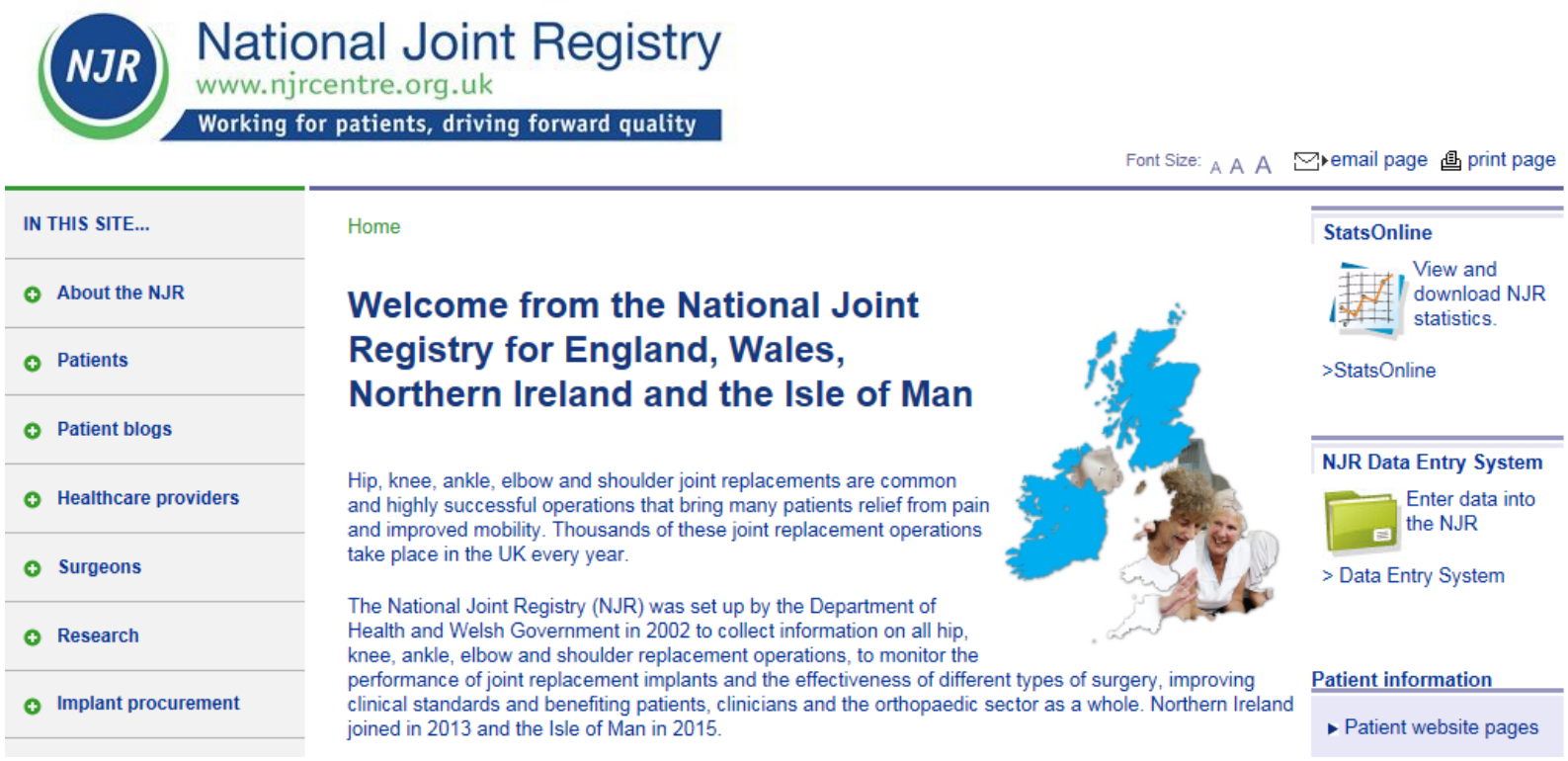
NJR Patient Decision-making Aid going live this year

- Online NJR tool which will enable patients to input their own personal details to assess the potential benefits of having a procedure.

National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

NJR Website

http://www.njrcentre.org.uk



National Joint Registry
www.njrcentre.org.uk
Working for patients, driving forward quality

Thank you

Other organisations

Drug Safety Research Unit (DSRU)

The DSRU shared the following papers with the Review:

- McNaughton R, Huet G, Shakir S. An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making. BMJ Open 2014;4:e004221. doi:10.1136/bmjopen-2013-004221

- Lane S, Lynn E, Shakir S. Investigation assessing the publicly available evidence supporting postmarketing withdrawals, revocations and suspensions of marketing authorisations in the EU since 2012. BMJ Open 2018;8:e019759. doi:10.1136/bmjopen-2017-019759

ISCAS

ISCAS shared the following evidence with the Review:

ISCAS
INDEPENDENT HEALTHCARE SECTOR
COMPLAINTS ADJUDICATION SERVICE

Evidence from the Independent Complaints Adjudication Service (ISCAS) with regards the **Evidence session PHIN, AvMA and NHS Resolution** session
http://immdsreview.org.uk/index.html

Background:

The evidence is provided by the ISCAS Chair Baroness (Fiona) Hodgson CBE and Sally Taber ISCAS Director for Baroness Cumberlege, DSG, DL and Professor Sir Cyril Chantler, FRCP, FRCPCH FMedSci.

This evidence sets out the role of ISCAS in providing an independent complaints service in the private health sector and aims to correct the information provided to the Review at the beginning of Session 2 held on January 10th, 2019. The legislation relevant to Independent Healthcare is explained, in particular with regards to Practising Privileges.

Executive Summary:

The Independent Sector Complaints Adjudication Service (ISCAS) sets out the following key points:

- In England the escalation of complaints by dissatisfied patients to the Parliamentary Health Service Ombudsman (PHSO) is only permitted for NHS treatments.
- ISCAS is a complaints process for the independent sector that aligns with the NHS system. ISCAS is a not-for-profit, values-based organisation that has operated in the independent sector scheme for nearly 20 years.
- The Care Quality Commission (CQC) register, monitor and inspect NHS and independent sector organisations against the same regulation with reference to complaints (Regulation 16).
- ISCAS and its Code of Conduct are recognised by regulators and patient groups, and the majority of independent sector providers subscribe to the scheme.
- ISCAS is independent of any trade body or other organisation and is now hosted by the Centre for Effective Dispute Resolution (CEDR).
- ISCAS has a three-stage process that reflects that there are differences in the structures in the independent sector. The third stage is independent adjudication, which is transparent for patients in terms of scope, outcomes and level of any award.
- ISCAS is able to award goodwill payments up to £5,000 but is not the mechanism to pursue clinical negligence damages.
- NHS Private Patient Units (NHS PPUs) have been slow to subscribe to the scheme leaving their patients without access to the recognised independent review stage in private healthcare.
- ISCAS shares information with relevant bodies including the CQC. There is formal information sharing agreement with CQC which is listed on the website along with other organisations such as Health Quality Improvement Partnership (HQIP),
- ISCAS engages in training from induction of new subscribers through to continuing professional development in complaints management events to ensure lessons learned are incorporated into the development of staff in subscribing organisations.

Context - ISCAS vision, mission and values:

ISCAS exists to ensure there is an alternative dispute resolution process where the Parliamentary and Health Service Ombudsman (PHSO - and related in other home countries) is unable act.

Our vision, mission and values frame our activity in continual improvement in complaint handling.

- **Our vision** is creating the environment in which all patients have access to high quality complaints systems.

- **Our mission** is to provide access to independent adjudication and promote compliance to the ISCAS Code of Practice as the recognised industry standard for complaints handling, wherever patients are treated in independent healthcare and NHS PPU's

- **Our Values**
  - Compassionate – we are empathetic, understanding and attentive to people's concerns. We resolve concerns appropriately.
  - Fair – we treat people, both patients and subscribers, fairly, proportionately and according to the evidence.
  - Responsive – We ensure that patient concerns are addressed swiftly according to the ISCAS Code of Practice and resolution is found.
  - Improving – we use feedback and lessons learned from complaints in training and updating resources to continually improve people's experience of the complaints process in the independent healthcare sector.

Context - Regulatory Framework:

The devolved governments in the UK each have differences in their regulatory systems although the approach to complaints is broadly similar. In England the relevant fundamental standard is the Regulation 16 of the Health and Social Care Act 2008 (Regulated Activities) Regulations 2014, which covers receiving and acting on complaints. This regulation applies to all organisations undertaking regulated activity, whether in the NHS or the independent sector. The intention of Regulation 16 is to make sure that people can make a complaint about their care and treatment. To meet this regulation providers must have an effective and accessible system for identifying, receiving, handling and responding to complaints from patients using the service.

CQC guidance under Regulation 16 is clear that all staff must know how to respond when they receive a complaint, this includes self-employed Consultants and General Practitioners. CQC glossary states that the meaning of 'staff' is the entire group of people employed for the purposes of carrying on a regulated activity. The Care Quality Commission (Registration) Regulations 2009 (see Appendix 2) and the Health and Social Care Act 2008 (Regulated Activities) Regulations 2014 define employment to include:

- *Practising privileges granted to a medical practitioner, which give permission to practise as a medical practitioner in a hospital managed by the service provider.*

On inspection the CQC uses key lines of enquiry (KLOE) to look to see how people's concerns and complaints are listened and responded to, and how this is used to improve the quality of care. The CQC inspection framework for independent healthcare identifies ISCAS as the professional standard that inspectors should look for during inspection of complaints management in independent healthcare.

However, ISCAS is concerned that on inspection of NHS Private Patient Units (NHS PPUs) CQC utilises NHS inspection frameworks and therefore there is no prompt for inspectors to check that the NHS PPUs subscribe to ISCAS. Private patients treated in NHS PPUs are not entitled to escalate their complaint to PHSO and at the moment very few NHS PPUs subscribe to ISCAS thereby leaving the patient without access to an independent review stage.

Overview of ISCAS:

Patient-centred: ISCAS considers that handling complaints to the satisfaction of patients is the litmus test of a caring organisation. Issues of perception, courtesy, informed consent and realised risk can make complaints hard to bring to mutually agreed termination. ISCAS gives independent healthcare providers the tools and training to handle complaints well. ISCAS is a supporter of the Patients Association, helping them to continue to listen to patients and speak up for change: https://www.patients-association.org.uk/our-supporters

Responsive: in 2017/18 all of the 101 relevant complaints (consisting 279 heads of complaint) were subject to independent adjudication resulting in 28% of heads of complaint being fully upheld, 35% partially upheld and 37% not upheld. A goodwill payment was made in 80% of stage three complaints, with an average award of £813.

Governance: ISCAS is a not-for-profit organisation overseen by a Board of Directors with an independent Chair, Baroness (Fiona) Hodgson CBE. ISCAS receives advice from the ISCAS Governance Advisory Board made up of subscribers and patient groups. ISCAS is hosted by the Centre for Effective Dispute Resolution (CEDR). CEDR brings experience of operating a variety of alternative dispute resolution schemes – see https://www.cedr.com. The combined healthcare experience of ISCAS Directors, patient representatives and the consumer experience of CEDR ensures that the scheme remains relevant to the independent sector.

Code of Conduct: ISCAS provides the only agreed set of standards and Code of Conduct for handling patient complaints in the UK independent healthcare sector. Subscribers abide by the ISCAS Complaints Code of Practice; the latest version of the "Code" is June 2017. There is a companion publication, the 'Patients Guide" to the Code, which is endorsed by the Patients Association.

Recognition: ISCAS is the complaints management framework in the independent healthcare sector that is recognised by the Parliamentary and Health Service Ombudsman

(PHSO), system regulators including the Care Quality Commission (CQC), the Patients Association, Action against Medical Accidents (AvMA) and others (see Appendix 1). It provides patients with an independent adjudication and a final decision on their complaint.

Independent: ISCAS is objective and non-partisan, an independent but well-informed partner to both complainant and complained-about. ISCAS is always empathetic, reasonable and fair to both patients and subscribers. ISCAS has no commercial connections with legal, insurance or other interests and the subscribers to ISCAS are not its owners. ISCAS engages through CEDR Independent Adjudicators to undertake adjudications.

Funding: ISCAS is funded in a similar to the way in which the independent sector funds the Private Healthcare Information Network (PHIN). Subscribers pay an annual subscription of a size related to their private patient turnover and number of Hospitals/Clinics. The cost of each Independent Adjudication is borne by the subscriber. Assurance is given to the Complainant (Patient) that this is the case.

Subscribers: ISCAS is a voluntary subscription scheme that serves the majority of independent healthcare providers (subscribers) in the UK. These include charities, not-for-profit and for-profit organisations from large hospital groups such as HCA, BMI, Spire, Ramsay, Priory and Nuffield Health, as well as standalone or smaller organisations such King Edward VII Hospital, KIMS Hospital and New Victoria Hospital. In addition, ISCAS subscribers include diagnostic providers such as In-Health, Alliance Medical and other single specialty organisations such as Marie Stopes as well as new entrants to the UK healthcare market including Babylon and Schoen Clinic London. A full list of subscribing organisations can be found on our website and in Appendix 3.

Website: ISCAS is currently updating the website which will result in links changing. It is anticipated that the new website, including a new training portal to support continuing improvement and learning by subscribers, will be launched in late Spring 2019. In the interim the ISCAS Code, Patients' Guide, Goodwill Payments Guide, Position Statements and Annual Reports can all be accessed from: https://www.iscas.org.uk. The ISCAS Annual Report includes analysed anonymised data on Independent Adjudications and is both published on the ISCAS website and sent to our partner organisations.

ISCAS Independent Adjudication process.

The ISCAS Code has three stages: the first two stages are internal designed to give the subscriber a chance to respond to a complaint and, where appropriate, to put things right. The stages reflect the structures in the large independent acute providers, who make up the majority of private provision.

- Stage 1: Local Resolution – Hospital Director / Registered Manager+
- Stage 2: Review by corporate CEO / Nominated Individual (NI)^

+The manager in the independent sector registered by CQC and who is accountable for operating an effective complaints process

.^ The NI is the person nominated to supervise the regulated activity provided

The ISCAS Code includes the seven steps to good complaint handling, which supports subscribers in resolving complaints at stage 1 and 2. It is estimated that 90% of complaints are resolved during these two stages. Where the patient declares dissatisfaction with the provider's decision, the third and final stage of the process is Independent Adjudication.

The Patient's Guide to the ISCAS Code clearly defines what the ISCAS Code covers, and what it does not cover. As is the case with the PHSO, ISCAS is not the mechanism for patients to pursue clinical negligence claims. ISCAS is able to offer goodwill payments and sets a limit of £5000, which is clearly stated in the Patients' Guide. The methodology that the independent adjudicators use for goodwill payments is transparent in the Goodwill Payments Guide and covers the following points:

- Nature of complaint
- Quality of investigation
- Tone of response
- Attempts to remedy
- Timeliness of responses
- Compliance with Code
- Impact on complainant
- Adjudication decision

A team of five Adjudicators is sourced and managed independently of the independent healthcare sector by CEDR, with the healthcare support and experience of the ISCAS Directors. ISCAS uses independent, specially trained, and skilled Adjudicators in the final third stage of its route to objective resolution of a complaint. These adjudicators are advised of the statutory and regulatory facts that may bear upon their work. The Adjudicators are professional and accountable for their own self-development process to maintain competence in the area of independent sector complaints management. The Independent Adjudicators speak together in a bi-monthly forum, facilitated by ISCAS, to exchange experience.

In a similar manner to the processes used by the PHSO, the Adjudicators will utilise independent clinical experts, where the complaint requires such an intervention. The Independent Adjudication is sent to the CEO of the organisation, personally addressed, and to the patient. The CEO letter has a section for action containing the learning that should come out of the Adjudication.

As identified in the last ISCAS Annual Report, in 2017/18 the greatest percentage* of categories of heads of complaint were:

- Complaints Handling – 80%
- Consultant medical care – 52%
- Administration / information – 32%
- Discharge / aftercare – 24%
- Clinical outcomes – 23%

** Greater than 100% as one complaint can have several heads of complaint / category*

Within the complaints handling category (80%), the most common area of breach of the ISCAS Code is failure by the provider to signpost the dissatisfied complainant to the next stage of the ISCAS process.

Trends identified by the independent adjudications, which are specific to the independent sector, include Consultants with Practising Privileges engaging with the ISCAS Code and issues with transparency of fees.

Concerns about Private Patients in NHS units (PPUs)

ISCAS sets standards for handling complaints from patients in the independent healthcare sector. But not every UK patient with a complaint is able to rely upon those standards being applied. One such group are those treated in the many Private Patient Units (PPUs) of NHS hospitals, who fall outside the Health Ombudsman's remit and previously could not belong to ISCAS.

Over 10 years ISCAS has persistently represented the need to fill this gap, and in 2017, after a particularly concerning example of poor patient care was escalated to Ministers by ISCAS, NHS Trusts were, for the first time, given permission by the Department of Health to subscribe to ISCAS' Code.

The first to do so was Imperial College Healthcare NHS Trust, however take-up has been extremely slow. With approximately ninety NHS Hospital Trusts managing PPUs, there are substantial numbers of patients without access to an independent complaint review stage. ISCAS continues to receive inquiries from patients treated in NHS PPUs who, because the NHS Trust does not subscribe to ISCAS, are left with no access to independent review.

Unfortunately, many NHS Trusts do not understand the issue and continue to use the NHS complaints leaflet for private patients, even though any dissatisfied patients will ultimately be refused access to the PHSO. ISCAS considers this is misleading for patients and continues to raise the matter with various bodies including PHSO and CQC. Specifically, ISCAS has recently raised with CQC that using the NHS inspection framework for NHS PPUs means that inspectors are not addressing the requirement to follow the ISCAS Code as the 'professional standard' referenced by CQC for the independent sector. We understand that CQC are reviewing the approach to inspections of NHS PPUs.

Sharing information and acting on learning:

ISCAS utilises the learning from the outcomes of independent adjudications in a variety of ways to continually improve standards in complaint management. ISCAS shares information with key organisations to support the intelligence to improve patient safety.

Our Information Sharing Agreement (ISA) with CQC is key to supporting the system regulator gain intelligence about how independent healthcare providers are managing complaints. https://www.cqc.org.uk/about-us/our-partnerships/joint-working-agreements#hide3

ISCAS has shared anonymised independent adjudication reports with CQC since 2009. As part of CQC's revised approach to intelligence monitoring, ISCAS has worked through a pilot and at the end of 2018 has refined the information shared.

The table below provides an extract from our ISA with CQC:

Data topic:	**Detailed ISCAS adjudication decisions/ broader information updates**

Item	Data period	Data sub-topic/ element
1	Ongoing: as and when produced following adjudication decisions	a) All upheld or partially upheld stage 3 adjudication decisions regarding ISCAS subscribing organisations (with the complainant's details anonymised); and b) For above, accompanying written communication to the provider organisation (with complainant's details anonymised). This will be sent initially as part of a 3-month trial to understand its usefulness as well as to consider its replacing (a) above.
2	Ongoing	c) The names of any provider without an independent adjudication process in place and where ISCAS has advised complainants to contact CQC directly.
3	Monthly/ quarterly updates as stipulated	d) A report in an agreed format that summarises the adjudication decisions (three to four times per year, following each ISCAS Advisory Board meeting); e) An up-to-date report listing the names of all ISCAS subscribing organisations, three to four times per year, following each ISCAS Advisory Board meeting.

ISCAS and CQC also share poor practice which affects patient's safety and in particular involves the Fit and Proper Person Regulation. ISCAS has two concerning organisations at present which have been submitted to the CQC.

The Private Medical Insurers (PMIs) collect data to inform them of the quality and cost-effectiveness of service delivery. In 2018 CQC signed Memorandum of Understanding with four of the large PMIs in order to act in the public interest by sharing data and information of concern relating to patient safety and quality of services, and to inform the regulatory functions of CQC through its inspection and monitoring of providers of independent healthcare. ISCAS has written to the relevant Medical Directors of these larger insurers about how lessons learned from ISCAS adjudications could be used to inform discussions on quality and safety. Meetings are being scheduled with the PMI Medical Directors, beginning in Spring 2019.

ISCAS continues to revise ISA and maintains discussions with the system regulators – in Scotland (Health Improvement Scotland – HIS), Wales (Healthcare Inspectorate Wales - HIW) and Northern Ireland (Regulation and Quality Improvement Authority - RQIA). ISCAS also liaises closely with the professional regulators (e.g., GMC, GDC, NMC, etc,)

ISCAS has an open dialogue with the relevant Ombudsman. This includes a good relationship with the PHSO and sharing information on Goodwill payment guidance and mediation skills, and input into consultations in Wales on the role of the Ombudsman in independent healthcare complaints.

Continual improvement and training:

ISCAS considers an approach to continual improvement to be core to the provision of high quality services. We are reviewing how quality accreditation might be an effective approach for ISCAS subscription. This methodology underpins commissioning in the NHS: https://www.ukas.com/sectors/healthcare/accreditation-underpinning-quality-healthcare-commissioning/. This is being reviewed as a potential long-term ambition for ISCAS but in the interim ISCAS has introduced a Quality Assurance Framework for subscribers to use as a self-assessment tool to monitor compliance against the ISCAS Code.

The ISCAS Code is regularly updated to reflect learning from complaints and changes in regulation and standards. In the intervening periods between ratification of an updated ISCAS Code, 'position statements' are issued to ensure that learning can be rapidly disseminated. ISCAS position statements are on our website and include:

- Practising Privileges: This statement outlines the meaning of practising privileges within the context of 'staff' within the regulations in each of the four home countries. It emphasises the requirements of all 'staff' to be engaged in the complaints process. The position statement makes it clear to all subscribers, that they are required to provide a single response to a complaint and that it is not acceptable for the independent provider and Consultants with practising privileges to write separate responses to complainants.

- Fees: This statement addresses the identified theme regarding lack of transparency on the fees charged separately by the provider and those levied by those granted practising privileges. The statement clearly sets out the requirements for terms and conditions with reference to the Care Quality Commission (Registration) Regulations 2009 Regulation 19 and also refers to new powers given to the Private Healthcare Information Network (PHIN) on transparency of fees.

These statements align with CQC Scope of Registration, which states that for practising privileges to apply:

- *…….. it means that all aspects of the consultation must be carried out under the hospital's management and policies. For example, being subject to the hospital's requirements for clinical governance and audit, and the hospital's policies and systems for complaints and for records (with the hospital owning the records).*

ISCAS recognises that handling complaints equitably is a skill not always understood by those newly designated to this duty in their hospital. A good quality learning and training package is therefore a primary building-block in the ISCAS agenda. Newly appointed local managers were individually briefed by ISCAS; however, this approach has been hard to sustain with the growing number of subscribers.

New for 2019, ISCAS has developed an **online tool** that introduces the Code and the associated guidance and thereby setting staff on the right direction. In order to continue to develop skills for staff in subscribing organisations ISCAS has also developed an online training tool based on the ISCAS seven steps to good complaint handling. This training has been developed with the Patients Association and utilises learning material focusing on the experience of patients.

A key event in the ISCAS calendar is the **annual training event**. This enables staff from existing and potential subscribers to hear from a range of speakers with experience of patient complaints. Peter Walsh, CEO AvMA, has attended in the past to present the Duty of Candour.

The 2016 and 2017 events for 80 attendees received very good reviews. The June 2018 programme *Quality in Complaints – Listening and Learning* was attended by 74 delegates included presentations by the:

- CEO of the Patients Association (*Working with the Patients Association)*;
- Parliamentary and Health Service Ombudsman (*Working in partnership to improve frontline complaints handling);*

In addition, the event included an opportunity to share lessons learned from the regulator, independent adjudicators and solicitors involved in the Paterson litigation case. CEDR also facilitated a workshop at the event on the introduction of mediation skills and process. Planning is already underway for the 2019 event, which is scheduled to take place on June 11th.

Appendix 1: Examples of organisations that signpost to ISCAS

Parliamentary and Healthcare Service Ombudsman (PHSO): https://www.ombudsman.org.uk/making-complaint/if-we-cant-help/private-healthcare

Patients Association: https://www.patients-association.org.uk/private-healthcare

Care Quality Commission (CQC): https://www.cqc.org.uk/sites/default/files/20171128_6642_cqc_how_to_complain_leaflet_final_web.pdf

Actions against Medical Accidents (AvMA): https://www.avma.org.uk/?download_protected_attachment=Complaining-about-private-healthcare-2016.pdf

Private Healthcare Information Network (PHIN): https://www.phin.org.uk/find-out-more/useful-information-sources

Appendix 2 – Regulations defining 'employed staff' with respect to regulated activity

Regulation 4 - The Care Quality Commission (Registration) Regulations 2009: http://www.legislation.gov.uk/uksi/2009/3112/made

Persons to be regarded as the person carrying on a regulated activity

4.— *(1) For the purposes of Chapter 2 of Part 1 of the Act (registration in respect of the provision of health or social care), the following provisions apply.*

(2) Where a regulated activity is carried on by a person (A) and one or more other persons who are—

(a)individuals; and

(b)employees of A for the purpose of carrying on the regulated activity,

A is to be regarded as the person who carries on the regulated activity.

(3) For the purposes of paragraph (2), a person is an employee of A where that person—

(a)is employed by A under a contract of service, an apprenticeship, a contract for services or otherwise than under a contract (including under a carer agreement); or

(b)has been granted practising privileges by A.

Health and Social Care Act 2008 (Regulated Activities) Regulations 2014: http://www.legislation.gov.uk/uksi/2014/2936/contents/made

The key part here is the definition of employment for the purposes of the regulations which set out the fundamental standards that registered providers must meet when providing care and treatment: -

"employment" means—

(a) employment under a contract of service, an apprenticeship, a contract for services or otherwise than under a contract, and

(b) the grant of practising privileges by a service provider to a medical practitioner, giving permission to practice as a medical practitioner in a hospital managed by the service provider,

and "employed" and "employer" is to be construed accordingly

Appendix 3 – Subscribers

Aesthetic Beauty Centre
Alliance Medical
Ascot Rehabilitation Centre
Aspen Healthcare
Nova Healthcare
Babylon Partners Limited
Baddow
Bella Vou
Benenden Healthcare
BMI Healthcare
British Hair Clinic
Bupa Cromwell Hospital
Burrswood Health and Wellbeing
Care Oncology Clinic
Care UK
Castle Craig Hospital
CC Kat Aesthetics
Centre for Reproductive Immunology and Pregnancy (Miscarriage Clinic)
Centre for Sight
Circle Health
Clinical Partners
Cobalt Health
Cosmetic Surgery Partners
Custom Vision Clinic
Elanic
Epsomedical
Fairfield Independent Hospital
Fortius Clinic
Foscote Court (Banbury) Limited
Genesis Cancer Care UK Ltd
Glenside Manor Healthcare
Harley Street ENT Clinic
HCA International
Hearts First Ambulance Service
Heathrow Medical Services LLP
Horder Healthcare
McIndoe Surgical Centre (now in Horder Healthcare)
Imperial Private Healthcare
Independent Doctors Federation
InHealth
Japan Green Medical Centre Ltd
KIMS Hospital Limited
King Edward VII Hospital Sister Agnes
La Belle Forme
Linia Cosmetic Surgery aka Harley Health village
London Claremont Clinic
London Doctors Clinic
London Medical
London Wellbeck Hospital

Manchester Private Hospital
Marie Stopes International
ME Clinic
Medical Equipment Solutions Ltd
MET Medical Ltd
Mills Medical Services
My Aesthetics/My Breast
MYA Cosmetic Surgery
MyBreast
National Migraine Centre
Nature Consultancy Ltd (Emotions Clinic)
NES Healthcare
New Medica
North West Independent Hospital
Nuffield Health
One Health Group
One Healthcare
One Stop Doctors
Optegra
Ramsay Health Care
Randox Health
Regent's Park Heart Clinics Ltd
Royal Free PPU
Rushcliffe Independent Hospitals
Sancta Maria Hospital
Scheon Clinic UK
Sk:n Clinics Ltd
Spencer Private Hospitals
Spire Healthcare Ltd
St Hugh's Hospital
St. Joseph's Private Hospital
TAC Healthcare Group Ltd
The French Cosmetic Medical Company
The GP Surgery Ltd
The Harley Medical Group
The Harley Street Hospital
The Hospital of St John and St Elizabeth
The London Clinic
The Manchester Clinic
The Mole Clinic
The New Victoria Hospital
The Nightingale Hospital
The Priory Group Ltd
The Private Clinic
The Raphael Medical Centre
The Sefton Suite
The Standing CT Company
The Ulster Independent Clinic
THFC and Combine Op Co
The Hospital Group
UK Birth Centres T/A Private Midwives
UME Diagnostics

Weymouth Street Hospital
Wimbledon Neuro-Care
ZoomDoc Ltd