The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

The IMMDS Review has continued to receive a number of emails from individuals and patient groups as part of our regular interaction. These have been carefully considered prior to the writing of the report. In this volume we publish further information the Review has requested following the Call for Evidence and Oral Hearings, and information we were previously unable to publish.

Published April 2020

Contents

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.

Association of Children Damaged by Hormone Pregnancy Tests

Provided the following documents in support of the Oral Hearings:

- CSD Minutes 19th December 1968, Appendix A – notes on Ovran; and [undated] notes on Ablacton

- A number of documents from the Landesarchiv, which are available in the annexes of the MHRA Expert Working Group on Hormone Pregnancy Tests

- A comparison of the EWG draft and final reports

The ACDHPT also provided further extensive written material. Where possible, references to publicly available sources for this material are included below:

Published articles and information

- Safety Testing of Drugs. Medical News. British Medical Journal 1963; 1:1619 doi: https://doi.org/10.1136/bmj.1.5345.1619
- Wheatley, D. Drugs and the Embryo. Br Med J 1964; 1:630 doi: https://doi.org/10.1136/bmj.1.5383.630-c
- Pregnancy test drug 'still prescribed after babies-at-risk warning'. Undated newspaper article.
- Bretherton RC. The indiscriminate use of hormone pregnancy tests. (Letter to the editor). Medical Journal of Australia. January 2, 1971; 1:48. https://www.popline.org/node/484982
- FDA Notices: Medroxyprogesterone acetate; norethindrone; norethindrone acetate; progesterone; dydrogesterone; and hydroxyprogesterone caproate. Federal Register 38(195):27947 Oct 10 1973. https://www.govinfo.gov/content/pkg/FR-1973-10-10/pdf/FR-1973-10-10.pdf
- WHO Drug Information No 150
- Greenberg et al. Hormonal pregnancy tests and congenital malformations. Br Med J 1975; 2:191 doi: https://doi.org/10.1136/bmj.2.5964.191-c
- FDA Drug Bulletin. December 1978 - January 1979. Patient Brochure for Progestins Warns Against Use in Pregnancy.
- World Health Organisation. Drug Information - July-September 1977. Hormonal exposure during early pregnancy - the danger of birth defects.

Material from the National Archives (copies of some of these files can be found in the annexes of the MHRA Expert Working Group on Hormone Pregnancy Tests)

- Correspondence between experts and the CSD/CSM
  - MH 149_1105 (p3, 7, 8, 9 62, 63, 64)
  - FD 23_127 (p2, 5, 6)
  - MH 171_39 (p24, 34, 43, 214)
  - MH 171_64 (p48, 74, 77)
  - MH 171_67 (p74)
- Publications, minutes and other reports related to the CSD/CSM

- MH 171_24
- CSD Dear Dr Letter 1964 - MH 171_26 (p147)
- MH 171_61. 1974. CSM/AR/48 (B) Maternal "Drug-Histories in Babies with Foetal Abnormality. Technique for Detection of Human Teratogens and some Preliminary Results.
- CSM/AR/159 Letter sharing Adverse Reaction Leaflet - Hormonal Pregnancy Tests
- CSM. Hormonal Pregnancy Tests and Congenital Abnormalities: A further statement. Adverse Reactions Series No 16
- Schering Dear Doctor letter - BN 116_24 (p6)
- CSM. Hormonal Pregnancy Tests: A possible association with congenital abnormalities. Adverse Reactions Series.

Material from the Landesarchiv

The following was also sent to the Review by the Association:

- *"Further to your request for documents referenced in the oral evidence session on Monday, please find the link to the Study which involved Prof. Hannaford, CHAIR of the ad hoc group. Prof Hannaford has produced extensive work on oral contraceptives and is the Guardian of the RCGP Oral Contraceptive study of 43 years ago. The above study from 2010 was financed by Schering AG, Schering Healthcare, Wyeth and Searle. All companies who are noted as conflicts of interest. For clarity, competing interests include: The Centre for Academic Primary Care received payment from Schering Plough, Wyeth and Searle, for lectures and* ***advisory*** *board work* ***by*** *Prof. Hannaford."*

  Hannaford Philip C, Iversen Lisa, Macfarlane Tatiana V, Elliott Alison M, Angus Valerie, Lee Amanda J et al. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study BMJ 2010; 340 :c927 doi: 10.1136/bmj.c927

- Information about Cumorit:

  - **Benin:** the following article mentions use in Benin **-** Boko et al. (2017) Interroger au Bénin les usages populaires d'un médicament abortif, le misoprostol. Rev. Méd. Périnat 9:20-24 (previously provided)

  - **Lebanon:** Cumorit was being distributed in Lebanon as recently as March 2017.

    This is a Lebanese drugs price list that was put up on 21st March 2017:

https://moph.gov.lb/userfiles/files/HealthCareSystem/Pharmaceuticals/DrugsPublicPriceList/21-3-2017/WebNonMarketed20170321.xls

- **India**: Also found other sources of the shipment from India (Mumbai area) to Turkey in 2015. It was £10,000 worth of pills.

  https://www.pharmacompass.com/detailed-india-export-price-data-finished-formulations/19-norethisterone

  https://www.eximpulse.com/export-product-Norethisterone-port-Nhava-Sheva-(JNPT)-SEA.htm

- **Peru**: Bonnema and Dalebout (1992) The abuse of high dose estrogen/progestin combination drugs in delay of menstruation: The assumptions and practices of doctors, midwives and pharmacists in a peruvian city. Social Science and Medicine 34(3):281-289 doi: 10.1016/0277-9536(92)90270-Z

- **Turkey**: Below is the link to Cumorit which shows it was exported to Turkey in July, 2015. The components are exactly the same as Primodos. https://www.zauba.com/export-cumorit-hs-code.html

- **Ireland:** Information regarding 1,000 packets of Duogynon provided to Ireland - Landesarchiv 13214, p126-129

Dr Wael Agur

Subspecialist and Lead Urogynaecologist | NHS Ayrshire & Arran Honorary Senior Clinical Lecturer | University of Glasgow | Scotland

Dr Agur shared the following documents with the Review:

- NICE patient decision aid for Surgery for stress urinary incontinence: https://www.nice.org.uk/guidance/ng123/resources/surgery-for-stress-urinary-incontinence-patient-decision-aid-pdf-6725286110

- Appraisal of four patient decision aids in use in the UK (follows)

- Management of Pelvic Mesh Complications in Scotland - Preliminary Results of a Service Evaluation Co-designed by Patients and Clinicians. Page 6 of The Petition to Scottish Parliament by Elaine Holmes and Olive McIlroy on behalf of Scottish Mesh Survivors (20 July 2019): https://www.parliament.scot/S5_PublicPetitionsCommittee/Submissions%202019/PE1517_HHHH_Comb.pdf

- What Matters to You in Choosing Treatment for Vaginal Mesh Complications? Patient-Decision Aid. Page 2 of The Petition to Scottish Parliament by Elaine Holmes and Olive McIlroy on behalf of Scottish Mesh Survivors (23 February 2020): http://www.parliament.scot/S5_PublicPetitionsCommittee/Submissions%202020/PE1517_KKKK.pdf

Wael Agur MB BCh MSc MD(res) FRCOG
Subspecialist and Lead Urogynaecologist | NHS Ayrshire & Arran
Honorary Senior Clinical Lecturer | University of Glasgow
30th September 2019

Baroness Cumberlege and The Review Team
Independent Medicines and Medical Devices Safety Review
King's College, London
Shepherd's House
Room 3.25b
London SE1 1UL

Dear Baroness Cumberlege and The Review Team

Re: Decision Aid for women considering SUI surgery

I would like to share with you some recent observations and thoughts with regards to the decision support needed by women considering surgery for stress urinary incontinence (SUI) and required by IMMDSR. Please find attached a critical appraisal of the four relevant Patient Decision Aids (PDAs) in current use in the UK.

Over the past 3 years, the Multi-Disciplinary Team (MDT) I belong to has been closely observing and documenting how women are making choices among the four procedures used in SUI surgery. We had developed the first UK PDA in the subject, the original SUI-PDA, and have been using it in our unit since September 2016. The PDA was published by our Health Board in Nov 2017 and its validation study was published in August 2019.

The attached appraisal suggests that a combination of **the four national leaflets** and **the original SUI-PDA** provides the current best available tool to reduce decisional conflict and to support women considering SUI surgery.

The original SUI-PDA is already in use in some UK hospitals. Our MDT will continue to use the combination of leaflets and SUI-PDA and will continue to promote their use in other units to facilitate patient choice and decision-making.

I would be grateful if the attached appraisal is considered and I do hope you will find it useful.

Kind regards

Wael Agur

Cc: Prof Kevin Harris, Programme director and clinical advisor, National Institute for Health & Care Excellence (NICE)

Critical Appraisal of Patient Decision Aids (PDAs) Currently Available in the UK

Dr Wael Agur MSc MD(res) FRCOG

Subspecialist and Lead Urogynaecologist | NHS Ayrshire & Arran

Honorary Senior Clinical Lecturer | University of Glasgow | Scotland

30 September 2019

The decision to be made by women considering SUI surgery

The choice facing women considering SUI surgery is not easy in the current circumstances.

The gold standard procedure for many years (**mesh tape**) is currently paused on safety grounds, while the original gold standard (**colposuspension**) is a major abdominal procedure and can cause pelvic organ prolapse.

The least invasive procedure (**bulking agent injection**) has relatively lower success rates, while the most effective procedure (**autologous fascial sling**) is also the most invasive - and is associated with a significant risk of voiding dysfunction and long-term self-catheterisation.

In addition, the generally low levels of technical skills in native tissue surgery appear to negatively affect surgeons' and patients' confidence in genuine shared-decision process. In the current climate, women are faced with a difficult choice of SUI surgery and their decisional conflict is inevitably high. The current rates of SUI surgical procedures are at all time low and many women appear to be already uncertain about whether to undergo any surgery at all.

The main purpose of a Patient Decision Aid (PDA) for women considering SUI surgery is to reduce their decisional conflict and enhance their confidence in the shared decision-making process.

This document characterises and appraises the four PDAs currently being used in the UK in this respect.

1- BAUS PDA

The PDA from the British Association of Urological Surgeons (BAUS) is comprised of a table that describes surgical and non-surgical options. The table imparts valuable information; however, it lacks the person-centred perspective of identifying individual values and what truly matters to the reader. In addition, while it prompts the reader to explore the reasons behind considering each option, it stops short of including a 'request-for-treatment'.

2- BSUG PDA

The British Society of Urogynaecologists (BSUG) proposed an Updated Version of the Original SUI-PDA© in Spring 2018. The utility of the BSUG version was formally tested in clinical practice in Summer 2018 and the study conclusion confirmed a 'reduction' in decisional conflict (Jha et al, June 2019).

The BSUG PDA, however, appears to have attached less significance to the mesh-related adverse events. It included "mesh complications" as one of thirteen points for women to equally consider when making the decision. The weight attached to the potentially serious long-term mesh-related adverse events was similar to that attached to some of the mild transient complications. Therefore, the treatment-naïve PDA readers may not be able to distinguish the difference between the impact of the potentially serious long-term mesh-related risks from that of the short-term risks such as a perioperative bleeding or infection.

In addition, the BSUG PDA quoted the adverse event rate (3.3%) that relates only to complications where mesh removal surgery is required. The 3-times higher total rate of occurrence of mesh complications, requiring both surgical and non-surgical treatment, was not quoted.

Around 50% of women who read the BSUG Updated Version of SUI-PDA opted for mesh surgery. In contrast, 0% of women who read the original SUI-PDA© opted for mesh surgery (Ong et al, Aug 2019).

The difference between these results suggests the following:

1. Compared to the negative media stories, a PDA can have a higher impact on the choice made by treatment-naïve women. Had the media influence been higher than that of a PDA, similar proportions of women in the two studies would have opted for the mesh procedure.

2. When adequately highlighted and proportionately weighted in a PDA, the mesh complications are unacceptable to most, if not all, women. When communicated in a less obvious way, around a half of treatment-naïve PDA readers would opt for the mesh option.

The BSUG Updated Version of SUI-PDA could have done more to attach proportionate significance to the mesh-related risks, both in quantity and quality, to PDA readers. BSUG PDA is, therefore, unlikely to be suitable for use in the UK.

3- NICE PDA

The PDA from NICE had undergone a robust development process and the information were derived from the national guideline published in April 2019. In general, NICE PDAs are standalone documents as they contain the information patients need to decide on an investigation or treatment. NICE did not endorse or recommend the use of any SUI surgery patient information leaflets with its PDA.

There are some shortcomings that not only limit the ability of NICE PDA to reduce decisional conflict, but are likely to increase the level of such conflict in women considering SUI surgery. As NICE Evidence Review was limited to only comparative studies, there appears to be valuable information from non-comparative studies that did not make their way to the PDA. Such limitation appears to have led to the following conflicts:

- **Conflict with national leaflets on the risk of urinary retention following the autologous fascial sling (AFS) procedure**

  National patient information leaflets suggest a relatively higher risk of urinary retention and need for self-catheterisation following the AFS procedures. In contrast, NICE PDA communicates a similar risk of such adverse events for AFS, colposuspension and mesh tape. The PDA, therefore, does not warn women of the relatively higher risk of chronic retention and need for self-catheterisation, which could continue for life.

  Currently, as surgeons (re)start at the beginning of the learning curve with AFS procedure, the risk of chronic retention with long-term self-catheterisation is expected to be relatively higher. Such risk is increased with the inherently-tensioned AFS procedure, is well-established in current clinical thinking and is regularly communicated by most surgeons to their patients. The increase in the incidence of chronic retention with long-term self-catheterisation will be unacceptable to some women and, therefore, it should have been communicated on NICE PDA.

- **Conflict with the current most common first choice of SUI surgery by patients and clinicians**

Currently, bulking agent injections are the popular first choice by women and surgeons. The injections are currently the most commonly performed continence procedure in the UK. NICE PDA, however, removed the injections option from the main comparison tables and suggests to readers to consider the other three invasive procedures, including mesh tape, as first line and before considering the least invasive surgical option. This is likely due to the restriction to only comparative evidence, which is currently lacking, and not considering the significant body of non-comparative evidence. By minimising the least invasive SUI procedure chosen by many women who prioritise safety over efficacy, NICE PDA has come in conflict with the currently most common clinical practice in this respect.

- **Conflict on the type of anaesthesia for native tissue surgery**

  The PDA restricts the type of anaesthesia to only general anaesthesia for colposuspension and autologous fascial sling. In contrast, it offers the 3 types of anaesthesia (general, spinal and local) with the mesh tape option.

  This is inaccurate as open colposuspension and autologous fascial sling could also be performed under spinal anaesthesia. The relevant national leaflets clearly mention the spinal anaesthesia as on option with the two native tissue procedures. Women who wish a high efficacy procedure and wish to avoid general anaesthesia will find themselves being unnecessarily pushed towards the mesh option. The reason behind the removal of the spinal anaesthesia option with native tissue continence surgery in NICE PDA is unclear.

- **Unnecessarily repetitive confirmation of the scientific uncertainties**

  NICE PDA appears to struggle in striking a good balance between communicating scientific uncertainties and maintaining readers' confidence in its content. Instead of proportionately addressing the uncertainties to assist with patient choice, the PDA paradoxically adds to the decisional conflict to the patients. This is demonstrated by ***repeating negative statements*** and by ***persistently reminding the reader that NICE did not look at all the scientific studies*** in the subject matter.

- The phrase '***it is not possible***' is repeated ***21 times*** throughout NICE PDA document. Such repetition instils uncertainty about the safety and efficacy of the various SUI procedures.

- The phrase '***in the studies NICE looked at***' is repeated ***16 times*** throughout NICE PDA document. Such repetition instils doubt in the reader about the possible existence of valuable information in the ***studies that NICE did NOT look at***. Readers will wonder whether such absent information might be useful to their own individual decision-making.

The uncertainty and doubt would increase decisional conflict. Instead of addressing and resolving any potential conflict in the scientific literature, NICE-PDA appears to transfer such conflict to the consultation rooms. The outcome of individual conversations is likely to be solely or largely dependent on clinicians' interpretation, experiences and biases, rather than on patient empowerment with consistent and confident information provided by a decision aid.

A more detailed comparison of SUI-PDA and NICE PDA is in Table 1.

4- The original SUI-PDA©

The original SUI-PDA© appears the most suitable decision aid for use in the UK. This is because:

- Its content is based on a comprehensive literature review process that had considered all scientific evidence, including both comparative and non-comparative studies,
- It is designed in harmony with, and to be used in conjunction to, the national leaflets from NHS England, BAUS and BSUG,
- It details all the non-surgical alternatives on its pathway component,
- It attaches adequate significance and proportionate weight to the mesh-related adverse events,
- It clearly highlights to readers the relatively higher risk of urinary retention and need for self-catheterisation associated with the autologous fascial sling procedure,
- It reflects the current surgeons' and women's preference of safety over efficacy by offering bulking agent injections as one of the primary procedures considered in the comparison table, and
- It invites women to clearly document their reason(s) behind requesting a specific procedure and declining the other three.

Current developments in relation to the original SUI-PDA©:

- Our MDT continues to use the Decisional Conflict Scale (DCS) to **further validate SUI-PDA© in a larger group** of patients and to consolidate its usefulness in clinical practice.
- Our MDT started using the **DCS to make clinical assessments** on how confident women are in their decision following the administration of SUI-PDA©. MDT recognises high DCS scores as suggestive of a woman's need for additional information and/or support with decision-making prior to surgery. MDT suspects that high DCS scores prior to surgery may be associated with less favourable outcome afterwards.
- The SUI-PDA© development team is inviting patients to provide **postoperative reflections** using the Decisional Regret Scale (DRS); to compare to preoperative DCS scores.
- A scientific paper describing the **detailed impact of SUI-PDA© on the service** is in the pipeline.
- An **online version of SUI-PDA©** has been commissioned and the website www.sui-pda.com is under construction. Its use will be free of charge.

References:

1. **BAUS PDA** – Feb 2018
   Published by British Association of Urological Surgeons.
   https://www.baus.org.uk/_userfiles/pages/files/Patients/Leaflets/SUI%20options.pdf

2. **BSUG Updated Version of SUI-PDA©** – June 2019
   Published by Springer, for the International Urogynecology Journal.
   https://static-content.springer.com/esm/art%3A10.1007%2Fs00192-019-03982-1/MediaObjects/192_2019_3982_MOESM1_ESM.doc

3. **BSUG Updated Version of SUI-PDA© - Utility Paper**
   Jha, S., & Duckett, J. (2019). Utility of patient decision aids (PDA) in stress urinary incontinence surgery. International Urogynecology Journal. https://doi.org/10.1007/s00192-019-03982-1

4. **NICE PDA** - April 2019 (attached with highlights)
   Published by National Institute for Health & Care Excellence (NICE).

5. **The Original SUI-PDA©** – Nov 2017
   Published by NHS Ayrshire & Arran.
   https://www.nhsaaa.net/media/7598/mis17-214-gd-stress-incontinence-form.pdf

6. **The Original SUI-PDA© – Validation Paper**
   Ong, H.L., Sokolova, I., Bekarma, H. et al. Development, validation and initial evaluation of patient-decision aid (SUI-PDA©) for women considering stress urinary incontinence surgery. International Urogynecology Journal (2019).
   https://doi.org/10.1007/s00192-019-04047-z

Table 1 - Comparison between SUI-PDA and NICE PDA

	SUI-PDA	**NICE-PDA**
Number of pages?	12 pages	17 pages
Interactive pages	2/12	1/17
When was developed?	2016/17.	2018/19.
Scientific evidence upon which the PDA was based?	Literature Review Group of the Scottish Independent Review 2015. Included all scientific evidence, comparative and non-comparative.	NICE Guideline Development Group 2018. Included only comparative scientific evidence.
Were there any restrictions on the type of scientific evidence upon which the PDA was based?	No	Yes, only comparative studies, according to NICE methodology. The phrase '**In the studies NICE looked at**' is repeated 16 times in the PDA.
Does it list all non-surgical alternatives	Yes.	No. It does not mention continence pessaries or Duloxetine therapy.
Has it been validated for patient use in clinical practice?	Yes. Validation paper published in Int Urogynecol J Aug 2019.	No.
Is it a standalone document or dependent on other documents?	Dependent. SUI-PDA relies on the four national patient information leaflets provided to women prior to making their decision using the PDA.	Standalone. NICE suggests its PDA contains all the information required for decision-making. NICE did not endorse the use of any patient information leaflets with its PDA.
Information on type of anaesthesia	SUI-PDA depends on the national information leaflets.	NICE PDA restricts the type to only general anaesthesia for colposuspension and autologous fascial sling. It is well-known that

		colposuspension and autologous fascial sling can also be performed under spinal anaesthesia. In contrast, it offers the 3 types (general, spinal and local anaesthesia) with the mesh sling.
Comparative Efficacy of the procedures suggested on the PDA - From the most to the least effective:	1. Autologous fascial sling 2. Mesh Tape and Colposuspension 3. Bulking agent Injection	1. Mesh Tape and Autologous fascial sling 2. Colposuspension Bulking agent Injection, currently the most commonly performed SUI procedure in the UK, is not in the comparison table.
Does it contain information that are in conflict with the national Patient Information Leaflets?	No.	Yes. 1- Contrary to current practice in (most) units, where bulking agent injections are offered as one of the first line procedures, NICE PDA suggests they could be used only as second line. 2- Contrary to the national leaflets that confirms a higher risk of voiding dysfunction with autologous fascial sling option, NICE PDA suggests such risk is similar to colposuspension and mesh tape.
Likelihood of reducing decisional conflict and increasing confidence in women considering SUI surgery?	After using SUI-PDA©, women had an average Decisional Conflict Score of 9.29% (Ong et al, 2019).	There are no validation data for NICE PDA. The 21times repetition of the phrase ***'it is not possible'*** in NICE PDA is not expected to reduce decisional conflict.

BPNA
British Paediatric Neurology Association

17th September 2019

Dr Valerie Brasse
Review Secretary
Review Team
Independent Medicines and Medical Devices Safety Review
King's College, London
Shepherd's House
Room 3.25b
London SE1 1UL

Dear Dr Brasse,

Re : In-utero exposure to sodium valproate

Thank for your enquiry relating to in-utero exposure to sodium valproate. You requested information about access to Child Development Units and the services offered as part of those units.

The BPNA is strongly committed to minimising the risk of in-utero exposure to valproate and, as you mentioned, we released joint guidance with the Royal College of Paediatrics and Child Health in April 2019. The guidance recommended a bespoke approach for each patient and family. The guidance recognised that in certain circumstances sodium valproate continues to be an important therapeutic option whilst strongly advocating measures to avoid in-utero exposure.

Most paediatric neurologists work in specialist children's hospitals and not in Child Development Units. Unfortunately, the BPNA does not hold information relating to the number and structure of these units across the country. Typically, community paediatricians are based in Child Development Units/Centres and the British Association for Community Child Health (BACCH) may be able to help with that aspect of your enquiry. The executive officer of BACCH is [redacted].

Our guidance states that sodium valproate should only be initiated in females by a Consultant with specialist training/expertise in epilepsy. As you mentioned, epilepsy specialist nurses are also an important part of the team caring for children with epilepsy and assist in advising female patients aged under 18 years on the Pregnancy Prevention Programme.

The BPNA is aware of a number of vacant consultant paediatric neurology posts across the UK. In addition, the RCPCH Epilepsy 12 audit (https://www.rcpch.ac.uk/work-we-do/quality-improvement-patient-safety/epilepsy12-audit) highlighted areas in need of considerable improvement. In particular, the audit recommended improvements in the numbers/provision of general paediatricians with expertise in epilepsy, epilepsy specialist nurses, and epilepsy clinic capacity. The latest round of the Epilepsy 12 Audit also includes metrics on transition. Our guidance makes clear reference to the Valproate Pregnancy Prevention Programme and advises on handover of care to specialist adult services. However, the BPNA is anecdotally aware that many of our members do not have dedicated capacity for transition work and, in particular, joint transition clinics with adult specialists.

We are grateful for the Independent Medicines and Medical Devices Safety Review's scrutiny of this important area and the BPNA would be very pleased to continue to assist with any further queries.

Yours sincerely,

Dr Andrew Mallick
Consultant Paediatric Neurologist
BPNA Secretary
[redacted]

British Association for Community Child Health

Note that child development centres/teams have been used as synonymous with 'child development units', which is not commonly used in the UK.

1. What changes have there been to the number and structure of Child Development Units across the country?

See attached table on the changes in proportion of units/centres delivering joint assessment (not necessarily in the same place at the same time but at least a coordinated approach with a timescale). These were increasing steadily, in response to Government policy like the National Service Framework, Together from the Start, Every Child Matters to a peak in 2013, then declined. The measures are not all exactly the same in the different reports but it gives an idea what's happened.

The Parr paper (attached) noted a decline in the members of the core team, particularly reductions in health visitor, social worker and teacher input. Psychology had remained steady but participation was already low. The Northampton CDC (Williams paper) has also noted a decline in members.

Table: Changes in proportion of units/centres delivering joint assessment:

	1998	2007	2010	2011	2013	2016
Respondents	307	396	225	142	127	83
No providing joint assessments	124	99		117	107	45
Percentage	40%	25%		82%	84%	54%
Based in CDC	79%		65%			
Source	McConachie	CHMapping	Parr	RCPCH census	RCPCH census	CAB survey

NOTE that not all the reports used the same questions so they may not be entirely comparable.

a. Is there national or regional variation?

Table 4 (P27) of Covering All Bases shows the geographical variation in service provision (General Development clinics/MDT we took to be equivalent Child development teams). Northern Ireland and the London area appear to have good representation)

b. What, if any, impact is this having on service provision and what alternatives have been put into place? Do you have any data on this relating to the group of children and young people affected?

This area of work in not well monitored by the NHS. It is also tricky as many of the consequences of poor provision are found in the long term or affect services/outcomes outside the NHS. However there is some evidence of the impact:

Waiting times for community paediatrics is much longer than the 18 weeks standard (Covering All Bases) and waits for children with neurodevelopmental conditions in CAMHS and community paediatrics are longer than any other mental health services (MHCYP 2017 P29).

CCH services cannot provide all medical reports for SEND/EHCP assessments on time (Covering All Bases)

A BACD study (Austerity) showed significant service funding cuts to disability services and the effect these were having.

A European study (Austerity Europe) has shown that services for disabled CYP have declined across many countries in the last decade.

BACCH recently pulled some evidence together on CCH services and what could be improved (Potential benefits of better CCH). Note that child development teams predominantly cater for CYP with SEND.

- Recognised Special Educational Needs and Disability (SEND) prevalence is increasing after 8 years of decline
- Pupils with SEN support had the highest permanent exclusion rate at 0.35 per cent. This was six times higher than the rate for pupils with no SEN (0.06 per cent).
- Pupils with identified SEND accounted for around half of all permanent exclusions (46.7 per cent) and fixed period exclusions (44.9 per cent)
- Pupils with an Education, Health and Care (EHC) plan or with a statement of SEN had the highest fixed period exclusion rate at 15.93 per cent - over five times higher than pupils with no SEN (3.06 per cent)

All four points above from
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726741/text_exc1617.pdf

https://learning.nspcc.org.uk/research-resources/statistics-briefings/looked-after-children/

https://learning.nspcc.org.uk/media/1185/child-protection-register-statistics-united-kingdom.pdf)

These figs suggest that the reduction in coordinated provision is associated with poorer outcomes for CYP with SEND at school. It is likely that poor/delayed assessment increase the demand for expensive residential services.

A recent OFSTED inspection report from Sefton (Sefton SEND) shows the impact of not getting provision right.

2. Have there been changes to the availability of trained specialist staff?

RCPCH/BACCH has estimated that there is a 25% shortfall in the community paediatrician needed to meet demand.

The Children's Commissioner has recently highlighted the ongoing postcode lottery in speech and Language therapy (SALT) funding (We Need to Talk 2019). This followed up on the Bercow report which showed poor access and provision for SALT.

NHS Benchmarking Network has shown a decrease in access, activity and investment in many children's services (NHS Benchmarking from slide 16 onwards)

3. Can you share any examples of systems of good practice which families and/or practitioners have found helpful?

The two Northampton papers attached show the provision in a particular area. The 2002 paper (Ni Bhrolchain) was able to correlate CDC provision with provision at school entry. It showed that the provision available at the time achieved almost complete ascertainment of children with early SEND before school entry. This involved close working with and training for health visitors and nurseries, and for general practitioners in child health surveillance. This meant that nearly all children had provision in place before starting school. We were also able to show that the diagnostic case mix was what one would expect, though this wasn't published. The more recent paper (Williams et al) established that referral rates of pre-school children plateau at about 6.5 per 1000 pre school children per annum although the case mix changed (probably more developmental delay now labelled as autism spectrum disorder).

Gray et al showed that being based in the same premises helped child development teams to meet quality standards. Better compliance was also linked with better funding.

There is also a Wirral report which looked at what parents wanted for Early Years services but it's not in the public domain. I might be able to get permission to share it if it was felt to be useful.

In summary, the services offered to disabled CYP – and CDCs/CDTs are a key part of that provision – have been reduced in the last decade and there is reasonable evidence that it is having a detrimental effect on them and their families by reducing their access to a range of services. These cuts are beginning to have an impact on educational provision and outcomes and is leading to parents protesting on the streets about lack of provision. The invisibility of services in NHS statistics and poor monitoring mean that these problems are not prioritised for NHS funding. Mental health services are currently getting a lot of attention but this doesn't include services for children with disability.

References attached:

BACCH. Potential benefits from improved CCH service and/or better staffed departments.

BACCH and RCPCH (2017) Covering all bases. Community Child Health: A paediatric workforce guide. September 2017. https://www.rcpch.ac.uk/sites/default/files/2018-03/covering_all_bases_community_child_health_-_a_paediatric_workforce_guide.pdf

BACD and BACCH (2015) Impact of Austerity Measures on families with Disabled Children: Survey of BACCH and BACD members and Child Development Team leads. November 2014 and January 2015.

Children's Commissioner (2019) We need to talk: Access to speech and language therapy. https://www.childrenscommissioner.gov.uk/wp-content/uploads/2019/06/cco-we-need-to-talk-june-2019.pdf

Gray, L et al (2015) Variable implementation of good practice recommendations for the assessment and management of UK children with neurodisability. Child: Care, Health and Development, 41: 938–946. doi: 10.1111/cch.12272.

Horridge, K. A., Dew, R. , Chatelin, A. , Seal, A. , Macias, L. M., Cioni, G. , Kachmar, O. , Wilkes, S. and , (2019), Austerity and families with disabled children: a European survey. Dev Med Child Neurol, 61: 329-336. doi:10.1111/dmcn.13978

NHS Benchmarking Network (2018) 2018 Children's Services benchmarking findings. Presentation given as part of the 2018 Community Services Conference.

NHS Digital (2018) Mental Health of Children and Young People in England, 2017. Webpage and Summary Document.

Ni Bhrolchain, CM (2002) Referral patterns to a district Child Development Centre: 25 years experience. Public Health 116: 300-303

Ofsted (2019) Letter to Sefton Children's Services. Available online: https://files.api.ofsted.gov.uk/v1/file/50085120

Parr, JR et al (2013) Twenty years of research shows UK child development team provision still varies widely for children with disability. Child: Care, health and development 39(6):903-907

Williams, AN, Mold, B, Kilbey, L, Naganna, P. Forty years of referrals and outcomes to a UK Child Development Centre (CDC): Has demand plateaued? Child Care Health Dev. 2018; 44: 364– 369. https://doi.org/10.1111/cch.12552

Department of Health

Baroness Blackwood
Parliamentary Under Secretary of State
Department of Health and Social Care

4 April 2019

Baroness Julia Cumberlege
Chair
Independent Medicines and Medical Devices Safety Review

Dear Baroness Cumberlege

I am writing following your letter to the Secretary of State to update you on recent action taken by the Department and its Arm's Length Bodies in relation to surgical mesh.

Thank you for all you and your team are doing to look at the issues relating to surgical mesh and other matters through your review. This work is invaluable.

Maintaining the 'pause' in the use of Surgical Mesh

Last July NHS England, with the support of the Department, implemented a pause on the use of Mesh for patients with stress urinary incontinence and pelvic organ prolapse, following a recommendation from your Review.

This pause was due to run until 1 April 2019, subject to an assessment by senior clinicians of the relevant issues. As you will be aware, Professor Steve Powis and Dr Kathy McLean, from NHS England and NHS Improvement respectively, wrote to all NHS Regional Directors and NHS Medical Directors on 29 March 2019,[1] to confirm that the pause would remain in place pending a further assessment later in the year.

As set out in the letter from Prof Powis and Dr McLean, there are a number of conditions that would need to be met before the current arrangements are changed.

Updated NICE Guidance on the use of Mesh

As you know, there has been significant interest in the development of updated NICE clinical guidelines on the management of urinary incontinence and pelvic organ prolapse in women. I am pleased that this work is now complete, and has been published.[2]

The new guidance is clear that there are a range of non-surgical options to treat stress urinary incontinence and pelvic organ prolapse that must be considered before surgery.

[1] https://improvement.nhs.uk/documents/5122/MESH_letter_-_Extension_of_pause_on_the_use_of_vaginal_mesh_29_March_2019.pdf
[2] https://www.nice.org.uk/guidance/NG123

If non-surgical options have not worked, or if the patient decides against them, they may wish to discuss a surgical option with their clinician, including, potentially, the use of Mesh. The guidance states that mesh surgery must only be performed by a specialist, and only following a very detailed discussion with their clinician of the potential risks. To support patients in making the most appropriate decision for them, NICE has also developed a series of decision aids for patients to use, to help inform their decision.

This guidance was developed following detailed consultation with patients, clinicians and expert surgical societies. It is entirely independent of, and does not pre-judge the outcomes of, your Review. NICE will, of course, be highly interested in the outcome of your work and will assess its implications for their guidance. The guidance seeks to reflect that while our understanding of the long term outcomes associated with mesh use are limited, and that many women have been profoundly harmed by its use, a patient may still decide, based on all available evidence, and following a detailed discussion with their clinician, that it is the appropriate option for them.

Next Steps

Safety is a key priority for the Department, and I hope you are assured by the progress outlined above. My officials would be pleased to provide any further information that would be helpful, and I look forward to receiving your full Report, and any further Interim Recommendations you wish to make, in the coming months.

Yours sincerely

Nicola Blackwood

General Medical Council

Further evidence for the Independent Medicines and Medical Devices Safety Review

February 2020

Q: Do we receive complaints from whistle-blowers and if so what happens to these in terms of outcomes?

1 We do receive complaints from whistle-blowers. As per our whistleblowing policy, any worker can raise concerns about a current or former employer, or in certain circumstances somewhere they have had a contractual arrangement to work or provide services. As set out within our additional written evidence, we introduced a confidential helpline in April 2012 to support individuals to raise concerns. This also allows doctors to raise concerns with us where they feel they cannot do so through local channels.

2 Furthermore, 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), with our second report published in September 2019.

3 Our most recent report shows that during the 12 month period from April 2018 to March 20109, the GMC received 35 whistleblowing disclosures, an increase on the previous year when 23 concerns were raised.

4 Of the 35 disclosures, the majority were made to the GMC's Fitness to Practise teams. Of these:

- 13 were concluded after an initial assessment (to consider whether it meets our threshold for investigation) was carried out.
- 15 were investigate either through our preliminary enquiry or full investigation process.
- Four were not progressed due to there being insufficient information to progress the case further

The GMC is a charity registered in England and Wales (1089278) and Scotland (SC037750)

- One was closed as the information was already under investigation.

5 Of the 35 disclosures, 13 were made by doctors, 10 by other healthcare professionals and 12 were anonymous.

Q: How do we support whistle-blowers?

6 As discussed, please refer to paragraphs 70 – 75 of our additional written evidence. Please advise if you require any further details on this.

Q: What are the outcomes for complaints that we receive from doctors about other doctors?

7 Please see Annex A

Q: Have any of our publications on raising concerns triggered spikes in activity (in terms of further concerns being raised to us)?

8 We have not undertaken analysis of this nature but we have commissioned research to understand the drivers of complaints among the public. This can be accessed here.

Q: What is our view on doctors using social media to criticise other doctors / healthcare professionals?

9 As discussed, our guidance on social media is located here. The key paragraphs are set out below:

5. The standards expected of doctors do not change because they are communicating through social media rather than face to face or through other traditional media.

And

15 *Good medical practice* says that doctors must treat colleagues fairly and with respect.[7] This covers all situations and all forms of interaction and communication. You must not bully, harass or make gratuitous, unsubstantiated or unsustainable comments about individuals online.

16 When interacting with or commenting about individuals or organisations online, you should be aware that postings online are subject to the same laws of copyright and defamation[8] as written or verbal communications, whether they are made in a personal or professional capacity.[9]

10 With regard to the complaints we have received about doctors misusing social media, we have considered 337 at the triage stage of our process where we assess whether the concerns reach the threshold for an investigation. These complaints were received during the period December 2016 to January 2020 – we did not routinely

'code' complaints closed at triage before this point, only those cases that went onto be investigated.

11 Each of these complaints related to an allegation of 'breach of confidentiality – social media' or 'fail to maintain trust – social media'.

12 Of these 337 considered at the triage stage,

- 272 were closed at triage as they did not meet the threshold for investigation
- 29 were referred to the doctor's employer
- 13 were closed after investigation as they did not meet the test for referral to a Tribunal
- 2 were closed with advice after investigation
- 2 were closed following a hearing with no further action
- 1 case resulted in suspension following hearing
- 1 case resulted in a warning following hearing
- 1 case resulted in undertakings following hearing
- 16 cases are currently under investigation

Q: How do we handle historical information about new and existing complaints? And what do we do with that information if we decide not to open a new case?

13 There are two routes through which we can use historical information (relating to events that occurred more than five years ago) within our fitness to practise procedures.

14 If the information relates to a case that we have previously closed within the last two years (unless exceptional circumstances apply) then we will review it under 'rule 12'. If the information relates to a new case that we have not investigated then we will apply the five year rule.

Rule 12

15 An overview of our powers under rule 12 of the Fitness to Practise Rules is available on our website. In summary, we can review the following decisions:

- Where we have decided to take no further action following an initial review of a complaint about a doctor

- Where we have decided not to refer a complaint about a doctor to a medical practitioners tribunal

- Where we have agreed undertakings with a doctor or given the doctor a warning.

16 Anyone with an interest in the decision can ask for a review. We can also decide ourselves that we need to consider a decision under our review process. However, we can only review a decision if:

- it may be materially flawed and / or there's new information which might have led to a different decision

- a review is necessary for the protection of the public, the prevention of injustice to the practitioner or necessary in the public interest, and

- the decision was taken less than two years previously, unless the circumstances are exceptional.

17 Although there is no definition of 'materially flawed' in the rules, the flaw must be something of real significance rather than a minor error. The key question we consider is whether, if any identified flaw were corrected, this might have led to a different decision.

18 New information can be anything that was not available to the decision maker when they made the original decision. However, it must be something completely novel and not a restatement of the original complaint. Importantly, it must also be information which if we had been aware of might have led to a different decision.

19 When deciding if a review is necessary we have to consider the wider public interest and the information and evidence available to us at the time the review is requested, not at the time of the original decision. We take into account factors such as the seriousness of the allegations, any evidence of the doctor having insight and remediated, the length of time since the incident giving rise to the allegation, whether any new complaints have arisen since the incident and whether the doctor has a fitness to practise history.

Five year rule

20 The current rule is that a complaint should not proceed to a full investigation if more than 5 years have elapsed between the most recent events giving rise to the complaint and the date the complaint comes to our attention. However, there is an exception to this in that we will proceed if it is in the public interest for us to do so.

21 However, there has to be a particular public interest to proceed. Therefore, the general public interest in the GMC investigating all complaints about doctors would not be sufficient in and of itself.

22 Prior to 1 January 2016, the five year rule test had an additional requirement. It had to be in the public interest **in the exceptional circumstances** of the case for the late allegation to proceed. So there had to be both a public interest and exceptional circumstances.

23 As you will be aware, the Paterson Inquiry identified a number of frustrations with regard to the five year rule. We recognise that this is an issue of significant public concern and support proposals to relax this restriction. We are currently engaging with the Department of Health and Social Care on proposals to change parts of the Medical Act so that we are able to carry out quicker and more efficient investigations. These discussions will provide a timely opportunity to review the purpose and future use of the five year rule (although it should be noted that any proposal to amend this rule would likely require full public consultation).

Fitness to practise history

24 We consider that a doctor's fitness to practise history should be taken into account when it is relevant to the current decision and fair in the circumstances for it to be considered. Decisions about whether to take a doctor's fitness to practise history into account are made in accordance with our Guidance for decision makers on when to take a doctor's fitness to practise history into account (see separate attachment). This guidance is for GMC decision makers during and at the end of investigations.

25 Every time we receive a complaint about a doctor it is formally recorded. We consider that a doctor's fitness to practise history can include closed enquiries in which the complaint has not been investigated, complaints that have been investigated but closed without formal action being taken, and complaints that have been investigated and conclude with some formal action. It is likely to be appropriate to take a doctor's previous history into account where current allegations are similar in nature or raise similar concerns. It will not be relevant where the factual allegations had been found not proven, which includes a formal finding at a tribunal hearing that the factual allegations made against the doctor following an investigation were not proven.

26 When we are deciding whether to investigate a complaint or deciding whether there is a realistic prospect that a tribunal will find that a doctor's fitness to practise is currently impaired, in most cases we will take a doctor's previous history into account, including closed enquiries, where the current allegations are similar in nature and / or indicate a pattern of concern. However, where a complaint was closed because there was insufficient evidence to support it, we would not take it into account without first re-opening the complaint under rule 12 of the Fitness to Practise Rules.

Q: We know from the patient stories we've heard that unless there is an agreed record of a consent conversation and of the basis on which the patient has given consent, then there is scope for misunderstanding, disagreement and unexpected/unwanted outcomes. On that basis a consent discussion and

decision should always be recorded and co-signed by the patient and clinician. The first of your seven principles of decision making and consent refers to patients having the right to be involved in decisions about their treatment. If the consent discussion and decision are recorded and co-signed by patient and clinician the 'right to be involved' becomes the 'right to co-own the decision' about future care and treatment.

Does the GMC have a view about this?

27 In our earlier response to you on this issue via email, we set out the following:

- An agreed record of a "consent conversation" – ie the dialogue between doctor and patient during which information is exchanged, and on the basis of which the patient is consenting to treatment – is certainly an example of good practice. While this would be appropriate for complex decisions, or decisions about an intervention that could have a significant impact on a patient's circumstances, it would not be proportionate to require this for every healthcare decision.

- Our guidance is relevant to every decision that doctors support patients to make, including decisions about examinations, investigations and referrals. We take the view that the quality of the conversation leading to a decision is of paramount importance, and we would be concerned that a focus on documenting the conversation might detract from the conversation itself and could be perceived as practising defensively.

- We've tried to move away from the idea of consent being a signature on a form at a particular point in time, towards the idea of an ongoing process of decision making. We absolutely agree about the importance of doctors aim to reach a shared understanding with patients about the expectations and limitations of the available options (see paragraph 9) and want to support doctors to have better conversations with patients to help them make the right decisions for them.

- We intend to collaborate on resources, including case studies, to illustrate how doctors can apply our guidance in proportion to the complexity, urgency etc (para 5) of the decision to be made. One or more of these case studies could address how to take a proportionate approach to the level of detail recorded in patient's notes (para 50-51), and could include the suggestion of an agreed (by patient and doctor) record of the discussion as an example of good practice.

- Finally, in relation to the first principle, you suggest that rather than the right to "be involved" patients have the right to "co-own" decisions about future care and treatment. In the majority of cases, where patients have capacity to make decisions, we would argue that the decision is owned entirely by the patient: while the doctor and patient "co-own" the decision-making *process*, the decision itself is the patient's. In circumstances where patients lack capacity, and where patients' right to consent is affected by law, while these patients may not be able (or

permitted) to make these decisions, we believe they have the right to *be involved*. I hope this helps to explain the wording of the principle.

And in our subsequent exchange:

- Firstly, there are many reasons why a consent conversation should be recorded and agreed and it may well be the case that for any O&G procedure – even those perceived to be simple and uncontroversial – consent should be recorded and agreed, perhaps because of the intimate nature of any O&G procedure.

- We will be collaborating with the RCOG on materials for their members (with the help of their Women's Network as well as doctors from the RCOG) which help to illustrate how our guidance applies in practice for doctors working in O&G specialties. We will raise this issue with them and suggest we consider including a good practice example in which doctor and patient agree a record of the discussion leading to consent for a simple/uncontroversial procedure.

- We'd be happy to keep you updated as to progress – if that would be helpful - or consider any further suggestions for materials to accompany the guidance. For the reasons given in our first email we don't feel that the guidance itself requires amendment.

- Secondly, on the specific points you raise below, I wonder if there are perhaps two issues here that require separating out. Clearly if the risks and concerns surrounding the use of a procedure were known but were not communicated as part of the consent seeking process then that would represent a failure to seek informed consent. However, as you observe, if this was considered, at the time, a routine task with low level risk and therefore information on potential harms was not disclosed (as these were not widely known or understood) then further tightening up the consent process through recording conversations would not have addressed this. In which case the issue is more about ensuring that there is appropriate approval and surveillance of new procedures to ensure that those risks are identified and understood by clinicians and then subsequently communicated through conversations on consent.

- What would address this issue in the updated guidance is the section on reviewing decisions (paragraphs 54-57) which states that *reviewing a decision is particularly important if new information has become available about the potential benefits or risks of harm of any of the options that might make the patient choose differently.*

28 We would like to make the following points in addition to this:

- With regard to the issue of documenting and sharing an agreed record of the consent conversation, we would also like to draw your attention to paragraph 27 d) and e) of the new guidance in which we set out:

- 27. Patients need relevant information (see paragraph 10) to be shared in a way they can understand and retain, so they can use it to make a decision. To help patients understand and retain relevant information you should:

    d) share it in a format they prefer - written, audio, translated, pictures or other media or methods

    e) give them time and opportunity to consider it before and after making a decision

- To support the implementation of the guidance, we are exploring ways to help patients make the most of their conversations with doctors. We hope to collaborate with a patient organisation to develop a resource that could help patients know what information their doctor should be giving them, and key questions to ask, as part of any conversation on consent.

- Finally, as you will be aware, the Paterson Inquiry have made a specific recommendation regarding consent, and as with the concerns raised over the five year rule noted above, we will need to reflect on the implications of this for the forthcoming publication of our revised guidance on consent.

Annex A – Data on complaints referred to the GMC from doctors

Please note:

- this excludes complaints from Responsible Officers, Persons Acting in a Public Capacity e.g. employers or other authorised public bodies
- we did not routinely code allegation type for complaints received at triage before 2017. Prior to that we only recorded the allegation type for those complaints that were taken forward for investigation
- the data is restricted to complaints where the complainant is identified as a doctor (subject to the exclusions above)
- a 'triage' refers to a complaint about a doctor from one complainant in an enquiry shared with us. An enquiry may have more than one triage and more than one allegation.

Table 1: The outcome of complaints closed at triage (N.B. NCM = non clinical matter unrelated to professional capacity)

	# Triages																					**# Triages**
	Closed at Triage Outcomes																				In Progress	
	Closed																		Referred	Unregistered Doctor	Unspecified	
Enquiry Year	5 year rule	<6 months delay for report	Already Investigated locally	Anon complaint: no danger	Conflicting diagnosis	Demanding drugs/treatment	Disagreement with Med Report	Dr's profession is incidental	Exercising legal/human rights	Fees for private treatment	Intervention in treatment	Issues cannot be identified	Licensing issue res by Reg	NCM unrelated to prof cap	Practice/dept dispute	Refer to Mental Health Org	Removal from GP list	Side effects of treatment	Vexatious complaint			
2010	5		4				4	16				125		8	19		1			7	3		**192**
2011	10		9		3		5	6			5	134		3	55				11	5	1		**247**
2012	5				6		10	5	3	1	1	200		5	45					1	1		**283**
2013	5			1	9		8	4	3		1	245			99					6	2		**383**
2014	4				10	1	3	6	17	1	5	259		3	80					1	1		**391**
2015	5				3		9	8	1			292		5	48	3				1			**375**
2016	3				3		7	11	3			439		4	14		4		1		1		**490**
2017	1	1			2	2	2	3	3			425			15	2					2		**458**
2018	2	1					9	3	1			433			22			1			1		**473**
2019	3						5	4	1			329	2	1	7					1	2	62	**417**
Grand Total	**43**	**2**	**13**	**1**	**36**	**3**	**62**	**66**	**32**	**2**	**12**	**2881**	**2**	**29**	**404**	**5**	**5**	**1**	**12**	**22**	**14**	**62**	**3709**

Table 2 – allegations of complaint closed at triage

	# Allegations																		**# Allegations**
Enquiry Year	Acting w. honesty/ integrity	Communicating effectively	Continuity, coordination of care	Fairness and discrimination	Knowledge & experience	Not about a doctor.	Not in GMP.	Partnerships with patients	Probity - criminality	Probity - criminality (NFA)	Professional performance	Recording work	Respect for patients	Responding to risks to safety	Risks imposed by health	Systems to protect patients	Teaching, training, assessing	Working with colleagues	No allegation recorded	
2010																			0	**0**
2011																			0	**0**
2012																			0	**0**
2013																			0	**0**
2014																			0	**0**
2015	3				1				1										0	**5**
2016	19	1	2	4	15	1	8	4		1	15	4		19	1	6	5	33	0	**138**
2017	207	12	13	43	204	7	72	38	1	8	55	58	3	29	11	5	26	179		**971**
2018	303	10	8	39	194	10	73	25	4		107	36	7	23	15	15	40	204		**1113**

2019	229	15	5	54	86	7	85	21	12	14	83	9	6	27	12	14	24	152	0	**855**
Grand Total	**761**	**38**	**28**	**140**	**500**	**25**	**238**	**88**	**18**	**23**	**260**	**107**	**16**	**98**	**39**	**40**	**95**	**568**	**0**	**3082**

Table 3 – outcomes of cases investigated

	# Cases										**# Cases**
Enquiry Year	Sanctions applied at Hearing - Erasure	Sanctions applied at Hearing - Suspension	Sanctions applied at Hearing - Condition	Sanctions applied at Hearing - Warning	Sanctions applied without a Hearing - Undertaking	Sanctions applied without a Hearing - Warning	Not impaired after Hearing	Advice following Investigation	NFA following Investigation	Case in Progress	
2010		2	3	1	4	3	5	52	93		**163**
2011	3	4			15	5	4	65	75		**171**
2012	4	5			8	3	4	34	131		**189**
2013	3	4		1	7	1	4	16	136		**172**
2014	2		1		4	3	3	12	97	1	**123**
2015	4	6			9	2	2	16	100	1	**140**

2016		9	1		6	2	4	10	59	8	**99**
2017	2	7		1	7	1		3	62	16	**99**
2018	1	1		1	2	5	2		62	41	**115**
2019					2				22	99	**123**
Grand Total	**19**	**38**	**5**	**4**	**64**	**25**	**28**	**208**	**837**	**166**	**1394**

Table 4 – allegation category of investigations (using category allegation types drawn from our publication – the State of Medical Education and Practice)

	# of Allegations (SoMEP)										**# of Allegations (SoMEP)**
Enquiry Year	Clinical competence (only)	Clinical competence and communication or respect for patients	Communication or respect for patients (only)	Doctors health	Honesty or fairness (only)	Honesty or fairness and clinical competence	Honesty or fairness, but not health, probity, criminality or clinical competence	Other types of allegation	Probity or criminality, but not health	Professional performance, not included elsewhere	
2010	26	22	4	56	72	14	58	61	10	105	**428**
2011	52	28	7	49	42	8	76	207	13	113	**595**

2012	34	44	10	51	28	30	80	136	17	178	**608**
2013	70	50	4	67	35	25	101	88	1	130	**571**
2014	19	38	2	38	31	20	40	138	4	144	**474**
2015	38	24	3	42	50	7	57	65	21	175	**482**
2016	21	18	5	72	24	10	55	109	15	113	**442**
2017	15	27	1	34	18	15	47	100	33	67	**357**
2018	27	12	1	70	22	33	57	140	9	95	**466**
2019	17	23	3	42	37	17	66	100	23	71	**399**
Grand Total	**319**	**286**	**40**	**521**	**359**	**179**	**637**	**1144**	**146**	**1191**	**4822**

HealthWatch

Susan Bewley, Chair of HealthWatch provided the following statement:

I have no commercial, financial or legal connection or interest in the pharmaceutical and medical devices industry sector or any other body or organisation of interest to the Review. I am the chair of the charity HealthWatch.

Susan Bewley provided the following:

- Letter to the Review (see next page)
- Braillon, A and Bewley, S. Medical device postmarket clinical follow-up in Europe: Getting priorities right. Pharmacoepidemiology and Drug Safety. February 2020: 29(2): 226-227 doi: 10.1002/pds.4935

HealthWatch

for science and integrity in healthcare

Registered Charity No 1003392

Please reply to:
Susan Bewley
sbewley@doctors.org.uk
Mobile: 07984 907548

The Baroness Cumberlege,
Chair,
The Independent Medicines & Medical Devices Safety Review,
King's College London,
Guy's Campus,
London,
SE1 1UL

6th November 2019

Dear Julia,

I write on behalf of HealthWatch UK, a registered charity founded in 1988 which campaigns for science and integrity in healthcare, in the hope of contributing to your work.

Healthwatch held a symposium in June 2019 on the subject of medical devices and their regulation informed by a commissioned background paper. This was attended by many UK experts in the field of evidence-based medicine (including Carl Heneghan, Director of the Centre for Evidence-Based Medicine in Oxford), professionals working in the area of healthcare products regulation (including two members of staff from the MHRA), as well as the Chair of the IDEAL Collaboration, (Peter McCulloch Professor of Surgical Science and Practice, Oxford University), representatives from public health organisations and a variety of other stakeholders including, most importantly, patients, including from "Sling the Mesh". The symposium and its working groups discussed a variety of topics connected to medical devices, the current state of their regulation and possible ways of improving device regulation and approval (particularly, but not exclusively focusing on implantable devices).

In brief, our conclusions were as follows:

- The 'equivalence' system of device approval using Notified Bodies has failed and device approval has been a technical rather than a medical process. We feel that implant approval should be graduated, and supported by step-by-step evidence.
- Using and recording all device serial numbers would be a simple first step.
- Those who implant a device must know (and be able to explain to the patient):
  - what it is and what its constituents are;
  - how it is identified and tracked;
  - how the evidence shows that it works;
  - what risks are involved;
  - what to do if things go wrong.

- The IDEAL-D framework described in 2016 (BMJ 2016;353:i2372) provides for evidence-based implant development.
- Databases are not enough; adequately funded registries are also needed, with compliance monitoring.
- Political action will be required to influence the developing rules, to draw agencies together and consider funding, e.g. via pooled levies.
- There are academic responsibilities: early reporting; development of evidential standards; guidelines for data reporting and appropriate data amalgamation procedures.
- Putting the issues into simple statements will be a powerful aid to progress.

We hope our work is of interest to you, especially the symposium outcomes. We would very much like to see our recommendations incorporated into your final report. A fuller account of the symposium and its discussions can be found here: https://www.healthwatch-uk.org/images/Projects/Medical_devices/HealthWatch_Symposium_Report_2019_-_Evidence_Healthcare_and_Medical_Devices__Implants.pdf

If we can do anything further to assist the work of your committee we would be very happy to contribute.

Yours sincerely,

Susan Bewley MD FRCOG MA
Chair, HealthWatch UK

Chair of Trustees, HealthWatch
sbewley@doctors.org.uk
www.healthwatch-uk.org
skype sjbewley
@susan_bewley

Registered Charity No 1003392

for Science and Integrity in Healthcare

Professor Carl Heneghan

Professor of Evidence-Based Medicine, University of Oxford

Professor Heneghan provided to following to the Review:

- Carl Heneghan. Australian judge finds mesh manufacturer negligent: here's why. BMJ Opinion December 4 2019. https://blogs.bmj.com/bmj/2019/12/04/carl-heneghan-australian-judge-finds-mesh-manufacturer-negligent-heres-why/

MHRA

Review question:

We have recently been told that the ANSM requested that the following wording be added to the licence variation, which was approved in France in January 2006 "Furthermore, a few isolated cases of autism and related disorders have been reported in children exposed to sodium valproate in utero. Additional studies are necessary in order to confirm or disprove all of these results". The supposed background to this was that at a meeting of the EMA Pharmacovigilance Working Party in July 2005, the French Ad Hoc Pregnancy Expert Working group presented their conclusions that a warning should be added to the SmPC for sodium valproate and carbamazepine regarding the risk of developmental delay and autism. We were also told that MHRA were present at this meeting.

This does not appear to be in the valproate timeline provided by the MHRA. Can you confirm if MHRA were present, and provide any reasoning to not include a similar warning at this time (this was not added until 2010 in the UK).

MHRA response:

I can confirm that the UK was represented at the July 2005 meeting of the Pharmacovigilance Working Party (PhVWP). The PhVWP was a forum for discussion of pharmacovigilance and was replaced by the Pharmacovigilance Risk Assessment Committee (PRAC) in July 2012. Unlike the PRAC, the PhVWP had no legal basis and its recommendations had no legal force, although member states were encouraged to implement nationally the output of the PhVWP.

We have looked back at the papers that we hold from PhVWP meetings at that time. At the February 2004 meeting of the PhVWP key principles for the Summaries of Product Characteristics (SPCs, as then abbreviated) for valproate (a set of warnings agreed by consensus by PhVWP) which should be included in all valproate SPCs had been agreed (see attached). The PhVWP key principles did not include the warnings about developmental delay present at that time in the UK SPCs. [*"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."].*

At the July 2005 PhVWP meeting, the French fed back from their national expert meeting which had considered the issue of developmental delay in children exposed to valproate in utero and concluded that there should be warnings in the valproate product information as follows:

"*Available Epidemiological data did not show a decrease of total IQ in children exposed in utero to sodium valproate. However a slight decrease of verbal capacities (verbal IQ) and / or an increase of additional educational needs or speech therapy have been reported in this group of children.*

Moreover, isolated cases of autism or related disorders have been reported in children exposed in utero to sodium valproate. Additional studies are necessary to confirm or rule out this risk."

The item was on the agenda of the PhVWP for information and the PhVWP key principles for valproate SPCs were not updated in response to the information shared about the

recommendations from the French expert group. Under these circumstances there would have been no EU agreement to implement the same warning in all member states and no requirement for the Marketing Authorisation Holder to submit variations to other member states. No variation was requested to amend the UK SPC as the warnings in the UK product information were considered to reflect the available data. Following consultation with the EMA, I attach the relevant extract from the minutes of the July 2005 meeting of the PhVWP.

Attachment included below, individuals names have been redacted in line with Review policy.

C.5 Valproate q (also other antiepileptic drugs: carbamazepine and phenytoin):

- Use during pregnancy: risk of developmental delay (children with lower IQ) and congenital malformations (NL) – French expert meeting feedback (FR)
  - *Feedback from the French Ad Hoc Pregnancy Expert Working group meeting held on 21 June 2005 (FR) dated 21 July 2005 (circ 21 Jul 05 and tabled 25 Jul 05)*

Status: for discussion

In February 2004 the PhVWP agreed Key Principles for SPC Wording for antiepileptics in general and for sodium valproate in relation to use during pregnancy and increased risk of congenital malformations.

In October 2004 [redacted] (NL) informed the PhVWP of media attention in the NL because of a publication in the BBC News regarding lower IQs in children exposed in uterus to sodium valproate.

In November 2004, [redacted] informed the PhVWP that a French expert group would review the issue in the following months (carbamazepine and phenytoin would also be included in the review).

At the current meeting, [redacted] (FR) reported the French Ad Hoc Pregnancy Expert Working group meeting held on 21 June 2005, who reviewed the risk of developmental delay and autism after in-utero exposure to sodium valproate or carbamazepine. Their conclusion was to implement a warning in the section 4.6 of the SPC for sodium valproate and carbamazepine, which is being implemented in FR (the SPC wording is very close to the one agreed by the PhVWP in February 2004, but a little bit broader as it refers to the risk of developmental delay as well). [redacted] (UK) pointed out that MSs might need additional time to specifically look at the issue of developmental delay. The PhVWP will come back to this issue as necessary.

Review question:

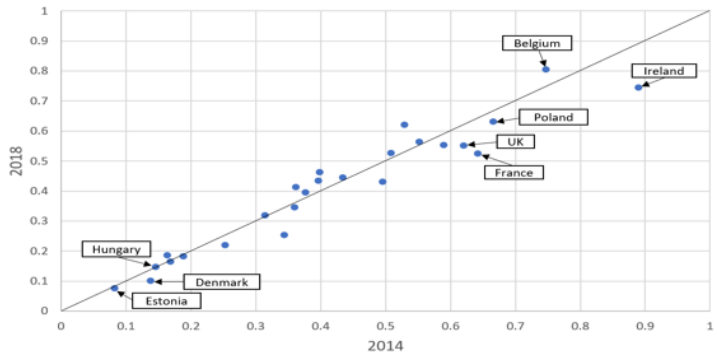
[In a meeting with MHRA] mentioned using the Danish prescribing practice data to estimate what might be the irreducible minimum number of women on valproate in the UK (something like 2-3000, rather than 18,000). Would you be able to provide us with a firm estimate?

MHRA response:

The 18500 referred to overall prescribing/dispensing in England and Wales from the most recent NHS Business Services Authority data. The 20% figure corresponds to the data in the slide attached which shows Denmark with roughly 1/5 of UK estimated patients years of treatment.

Sanofi Valproate Sales data

Estimated patient years of treatment with valproate / 1000 people per quarter in 2014 and 2018



1

NHS England and NHS Improvement
Skipton House
80 London Road
SE1 6LH

By email: reviewteam@kcl.ac.uk

9 July 2019

Dear Baroness Cumberlege,

Thank you for your email concerning the numbers of pelvic procedures involving the use of surgical mesh that have taken place since the national pause began on 20 July 2018.

Firstly, you asked when the provisional HES data would be confirmed as accurate and complete. Finalised HES data is generally published in the October or November following the end of the financial year. The provisional publication date for the 2018-19 data is 17 October 2019.

Secondly, you asked whether we have been able to satisfy ourselves that procedures since the pause have been carried out in line with the requirements of high vigilance regime Kathy McLean and I outlined in our letter. This letter firmly placed the onus on NHS Trust medical directors to put appropriate measures in place based on their clinical and operational experience. The number of procedures has fallen dramatically. There have been just 31 procedures during the eight months from August 2018 to March 2019 according to the provisional data (July data needs treating with caution because the pause began two thirds of the way through the month), whereas in the twelve month 2017-18 period there were 3,893. We will write to Medical Directors and ask them to confirm whether any such mesh procedures that have been carried out during the period since July 2018 have been done in compliance with the high vigilance conditions.

Yours sincerely,

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement

Professor Stephen Powis
National Medical Director
Skipton House
80 London Road
SE1 6LH

Baroness Julia Cumberlege CBE DL
By email: reviewteam@kcl.ac.uk

28th August 2019

Dear Baroness Cumberlege,

RE: Mesh response

I wrote to you initially on 9 July 2019 in response to your concerns over the numbers of pelvic procedures involving the use of surgical mesh that have taken place since the national pause began on 20 July 2018. I have included a copy of this correspondence, for reference, stating that 31 mesh procedures had been carried out between August 2018 and March 2019.

I am now writing to you to clarify that we have received responses from Medical Directors in Trusts to our survey exploring the effects of the national pause on mesh surgery on patients, surgeons and organisations. In particular, one question relating to your previous enquiry asked Trusts whether any mesh procedures that have been carried out since the start of the national pause have been performed in compliance with its conditions. All but one Trust confirmed that they had fulfilled all the requirements of the NHSE/I guidance published at the start of the pause. The respondent who confirmed that they had not, stated that they had fulfilled the majority of the clinical requirements, but were awaiting appropriate administrative support and infrastructure to allow databasing of all patients pre and post operatively.

I have provided a summary of all the results of the survey, below. For most questions, Trusts were asked to provide a scaled response ranging from 1 – 5 where 1 indicates minimal adverse impact and 5 indicates major adverse impact. Below, I have described scores of between 3 – 5 as having a 'significant' adverse impact:

- The survey did not request exact figures of patients on waiting lists, however the responses indicate that between 265-800 patients are currently on waiting lists for mesh or tape implant surgery as a result of the pause. These operations will not proceed during the pause.
- 66% reported that the pause had a significant adverse impact on patient's understanding of treatment options. These operations will not proceed during the pause.
- 70% reported that the pause had a significant adverse impact on patient waiting time for surgery.
- 64% reported that the pause had a significant adverse impact on surgeons' levels of confidence in performing the alternative surgical options.
- 78% reported that the pause had a significant adverse impact on surgeons' satisfaction with outcomes from alternative treatment methods.
- 72% reported that the pause had a significant adverse impact on patients' satisfaction with outcomes of alternative treatments

- 49% of respondents indicated that there had been unforeseen implications of the pause on the organisation
- 94% reported that they had not had difficulty procuring devices for patients that meet the criteria and need an operation
- There were a further 12 written comments from Trusts indicating a significant adverse impact caused by the pause. Some of these comments included references to patients' inability to access any form of alternative treatment or opting not to have alternative treatment, increased length of stay in hospitals due to alternative surgeries, and patients opting to go ahead with alternative treatments with more associated morbidities.

I hope that this provides the necessary reassurance that Trusts are complying with the conditions of the pause as far as possible. However, these results do also show that the majority of trusts believe the lack of access to mesh procedures is having a significant adverse impact on patients as well as damaging surgeons' confidence in their ability to offer effective treatment for women with urinary incontinence and pelvic organ prolapse. It may be helpful to know that NHS England and NHS Improvement are progressing work on the creation of a national registry for vaginal mesh procedures, in order to help satisfy the data related conditions of the pause, as well as NICE guidance NG123 which outlines recommendations for a national mesh registry. We recognise that there is a wider need for a comprehensive registry for implantable devices but are conscious that the solution for this lies in the longer-term. We have taken a decision to progress with a solution for vaginal mesh in the short-medium term in order to address the relevant conditions and recommendations.

We look forward to the findings of the Independent Review in order to address any further action that is needed in regarding complaints on the use of mesh.

Yours sincerely,

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement

OACS Ireland

OACS Ireland have provided the IMMDS Review with a substantial number of documents, which we have been unable to list in full here. These documents include:

- Journal articles, books and other academic literature relating the use of sodium valproate in pregnancy and the wider teratogenicity of antiepileptic drugs
- Articles in other professional publications related to sodium valproate
- Datasheets, summary of product characteristics, and patient information leaflets related to sodium valproate and related products used in Ireland and France
- Product license applications for sodium valproate
- Documents produced by public bodies in the USA, Ireland and France in relation to sodium valproate and teratology of antiepileptic drugs, such as reports of side effects to the National Drugs Advisory Board (Ireland)
- Newspaper and other media publications related to the use of sodium valproate in pregnancy

OACS Ireland Progress Update to the UK Independent Medicines and Medical Devices Safety Review

1. Introduction

Concerns relating to Anti Epilepsy Drugs (AED's) and Foetal Anti-Convulsant Syndrome (FACS) have been growing steadily in recent years in many countries including in the UK and in Ireland. The Irish campaign which includes OACS Ireland and Epilepsy Ireland have been working to highlight the issue regarding the use of sodium valproate in women since 2013.

2. OACS Ireland

OACS Ireland is a voluntary group, predominantly made up of mothers and fathers of children who have been affected. In 2019, OACS Ireland received full charity status in Ireland from the Charities Regulatory Authority. Many families in our organisation have received invaluable support from OACS UK over the years and they have been instrumental with their ongoing encouragement in developing OACS Ireland. In addition to our work in Ireland, OACS Ireland is also a stakeholder in the MHRA Valproate Stakeholders' Network (VSN), a relationship which has helped inform progress and practice in Ireland in recent years.

3. Valproate in Ireland

Sodium Valproate (Epilim) is a drug licenced in Ireland for the treatments of epilepsy and bi-polar disorder. Developed in the 1960s, it has been authorised in Ireland since 1975. For many people, Sodium Valproate can be a very effective drug.

However, the teratogenic effects of Valproate have been accepted since the mid-1990s, while effects on development were highlighted for over a decade prior to the publication of the NEAD studies from 2008. Despite these risks, many parents involved with the OACS Ireland organisation and many more over the past 40 years were not informed of the risks. Risk-reduction measures were not put in place and Valproate treatment continued as normal during pregnancy.

4. FACS Campaign in Ireland

Over the last 6 years, the Irish campaign has centred on three main aspects:

1) Working with relevant authorities including the Health Service Executive, Department of Health, the Health Products Regulatory Authority and the Pharmaceutical Society of Ireland to reduce the risks for current and future generations of children being born with severe physical and developmental disabilities associated with FACS.
2) Seeking adequate supports for those already affected by FACS.
3) Campaigning for an independent investigation/ inquiry on the historical use of Valproate including issues of accountability and redress.

While there has been significant progress on point 1 and limited progress on point 2, there has been no significant progress with regard to point 3.

4.1 Progress achieved

We have brought this issue into the public domain. We have spoken out in the media, met with countless political representatives and officials - including the Minister for Health**.** We have spoken publicly at the Oireachtas Health Committee and the European Medicines Agency. We secured important regulatory changes (including important packaging changes) via the Health Products Regulatory Authority, practice changes via the Pharmaceutical Society and brought about the creation of the Health Service Executive (HSE) Valproate Response Project Group, which OACS Ireland and Epilepsy Ireland have participated in over the past year.

4.2 HSE Valproate Response Project

The Project was established under the Office of the Chief Clinical Officer with the aim of ensuring *"the safe prescribing of Epilim (Valproate) treatment in women with Epilepsy, Bi Polar and other conditions, preventing current and future harm to women of childbearing age who are pregnant or who could get pregnant while taking Epilim (Valproate) and to develop a pathway of care for diagnosis and therapy for those who think they or their offspring may have been affected by past exposure to Valproate while pregnant".* Seven work streams were established to achieve these aims.

The work of the Project group has ensured that all women currently on valproate and their GPs received direct letters from the HSE informing them of the risks along with details of a temporary helpline and a new HSE website. It has worked to put in place measures to support families affected through a package of community supports and has secured approval for important new personnel in the areas of epilepsy, paediatrics and clinical genetics to ensure a longer-term effective response. Funding has also been secured to support the Epilepsy Pregnancy Register. The HSE, Epilepsy Ireland and OACS Ireland also came together to organise the first National Conference on the effects of Sodium Valproate in March 2019.

4.3 The HSE Rapid Assessment Report 2018

The Valproate Response Project also undertook a rapid assessment report estimating the scale of the issue in Ireland. The HSE Rapid Assessment Report of the number of women and children exposed to sodium valproate in Ireland 1975-2015 was completed in August 2018. It estimated that between 1975 and 2015, between 153 and 341 children will have experienced a major congenital malformation and up to 1,250 children will have experienced some form of neurodevelopmental delay. Of children born since 2000, it is estimated that between 43 and 95 will have experienced a major congenital malformation and 349 will have experienced some form of neurodevelopmental delay; a similar number of children, born between 2002 and 2017 and currently aged 0-16, are likely to have experienced such a malformation and/or delay. These figures represent the best data available at present and reinforce the need for an independent investigation as called for by the Irish campaign.

4.4 Key outstanding issues of concern

These have all been positive developments, but a number of important outstanding issues remain:

- Staffing positions promised have not all yet been delivered on including the provision of four Epilepsy Nurse Specialists with responsibilities for supporting women with epilepsy and ensuring annual risk reviews are undertaken. As a result, implementation of annual risk reviews is behind schedule.
- The package of community supports proposed by the HSE falls well short of the service provision required by those affected by FACS. While there are some positives in the plan, such as the proposed appointment of a National Specialist Needs Assessment Team and Valproate Specific Officers at national and local level, the proposal, in the main, does little more than restate what services exist already and attempt to 'shoe horn' our members needs into existing services. The proposed package also refers only to HSE health services and does not identify other government departments which need to take action in regard to services for those affected e.g. housing, education.
- No efforts have been made to directly contact women who were taking valproate in the past but who no longer do so. Awareness-raising campaigns have remained the responsibility of Epilepsy Ireland and OACS Ireland, with little support from the State.

4.5 Valproate Response Project Final Report

The HSE's Valproate Project final report has recently (October 2019) been sent to the Minister by HSE officials. The report consists only of a summary of the actions undertaken by the HSE over the past 18 months. It is now our intention to meet again with the Minister on the findings of this report and on the outstanding issues relating to FACS in Ireland. We will also be pursuing this with the Oireachtas Health Committee to seek a follow-on meeting to review this report against their 12 recommendations published last year.

5. Addressing issues of accountability and recompense

The Irish Campaign is concerned that in Ireland, few efforts have been made by the State to investigate the reasons behind the tragedy of valproate or deal with issues of accountability. This is in contrast with other jurisdictions including the UK and France.

The Irish campaign has called for the establishment of an independent investigation and/or inquiry into the historical use of Valproate, addressing:

- If and how existing cases of FACS could have been prevented.
- Whether or not appropriate and timely information was provided to healthcare professionals and to patients in line with knowledge at the time.
- Whether or not appropriate decision-making processes were in place concerning the treatment of women taking Valproate in line with knowledge at the time.
- Whether or not appropriate regulatory steps have been taken over time to ensure patient safety.
- How a system of redress should be established to meet the lifelong care needs of children and the impact of diagnosis on families.

These concerns were acknowledged in 2018 by the Oireachtas Committee on Health which included the following two recommendations in its "Report on Foetal Anti-Convulsant Syndrome" following a debate on the matter:

> *"The Committee recommends the establishment of an independent investigation to examine the historical use of valproate medicines in Ireland and into the ongoing effects of valproate medicines".*
>
> *"The Committee recommends that further consideration and examination is undertaken with regard to compensating FACS patients".*

To date, no progress has been made by the Department of Health on these parliamentary committee recommendations. Families need to know how so many cases of FACS were allowed to happen. The Irish public deserve answers too, so that changes can be put in place to avoid similar occurrences in future. A full investigation needs to take place so that the families can move forward knowing the truth. Families also need a system of redress established so that they can ensure that their children have the best of care and when families are no longer around to see their loved ones. Some of the complexities that arise in relation to the issue of compensation would also be best addressed via an investigation. The Minister for Health has promised to consider these requests but there has been no significant progress since our last meeting in March 2018.

Sanofi

Sanofi provided additional evidence as requested by the Review.

Q: The Rhone-Alps study was a pivotal point in the recognition of the impact that in utero exposure to valproate could have on an unborn child. We would like to have a fuller understanding of how this study impacted on contemporaneous perceptions of the risks associated with valproate use during pregnancy. If you have any further information, including communications or correspondence that Sanofi had with UK regulators, based on this study we greatly appreciate if you would share them with the IMMDS Review.

It is difficult, in 2019, to provide an accurate picture of the contemporaneous interpretation of the Rhône-Alps data in 1982, in view of the fact that more than 35 years have passed since the data were published in the Lancet and our current understanding is influenced by later studies and reports. Furthermore, in view of the period that has elapsed since 1982, substantial documentation from this period, including material correspondence between Sanofi and the UK regulatory authority, is not now available.

However, we understand from publications at around that time that interpretation of the Rhône-Alps data was complicated by the possibility of confounding and the fact that the results were not replicated in other studies. We refer in this context to correspondence in the Lancet, which followed the publication of the letter from Robert et al and to a multi-institutional study from Japan; copies of these papers/ correspondence are attached. The conclusions of these studies and commentators are consistent with those of the CSM's Current Problems, dated January 1983, which referred to the increased incidence of congenital malformations in babies born to mothers with epilepsy and the difficulty in determining whether such abnormalities were related to the disease itself or to the medication used to treat the condition. The Rhône-Alps data, published in the Lancet, were referred to in Current Problems as a single study which reported on potential problems following use of valproate . Current Problems concluded "*there is no clear evidence that any one anticonvulsant drug is any safer or more dangerous than any other*". The January 1983 version of Current Problems appears to provide a fair reflection of contemporaneous views at that time, including in the context of the Rhône-Alps data.

Attachments:

- CSM. Sodium Valproate (Epilim) and Congenital Abnormalities. Current Problems January 1983 No. 9 Link here
- Nakane, Y et al. Multi-institutional Study on the Teratogenicity and Fetal Toxicity of Antiepileptic Drugs: A Report of a Collaborative Study Group in Japan. Epilepsia,1980: 21: 663-680. doi:10.1111/j.1528-1157.1980.tb04320.x
- Stanley, OH and Chambers, TL; Jeavons, PM; Macrae, KD. Sodium valproate and neural tube defects. The Lancet. Letters to the Editor 04 December 1982: 320(8310): 1282-1283 , december 04, 1982 doi: 10.1016/S0140-6736(82)90141-6

The company core safety information (CCSI) first referred to developmental delay in August 2002, when the following statement was included: "*Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment".*

A variation application to add this statement to the UK SmPC was submitted to the MHRA during January 2003, and the MHRA approved the following revised wording in April 2003: *"Developmental delay has been reported in children born to mothers with epilepsy."*

An application to make a similar variation was also submitted in France but refused by the French Authorities in June 2004.

The CCSI was further updated on 15 October 2004, to include the following statement: *"Some data have suggested an association between in-utero valproate exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ."*

A variation application to include the wording from the October 2004 version of the CCSI in the French SmPC was subsequently submitted to the French Authorities. During the assessment of that variation,the following statement concerning autism was introduced at the request of the ANSM: "Furthermore, a few isolated cases of autism and related disorders have been reported in children exposed to sodium valproate in utero. Additional studies are necessary in order to confirm or disprove all of these results".

This variation was subsequently approved by the ANSM on 25 January 2006.

The background to the ANSM's addition of the statement around autism to the French SmPC seems to be related to discussions that had been ongoing at the EMA Pharmacovigilance Working Party meetings.

At a meeting of the PhVWP in July 2005, the French representative reported that a French Ad Hoc Pregnancy Expert Working group meeting had been held on 21 June 2005, and this had reviewed the risk of developmental delay and autism after in-utero exposure to sodium valproate or carbamazepine. The conclusion of the French Ad Hoc Pregnancy Expert Working group was that a warning should be included in section 4.6 of the French SmPC for sodium valproate and carbamazepine. The UK PHVWP representative from the MHRA pointed out at that time that Member States might need additional time to specifically look at the issue of developmental delay.

The MHRA were therefore aware of the review of the French Ad Hoc Pregnancy Expert Working group, but it seems they did not consider at that time that autism should be added to the UK SmPC.

A variation application submitted in the UK to implement the October 2004 version of the CCSI was approved by the MHRA in October 2005. The MHRA's approval of this variation, therefore, occurred after the discussion by the PhVWP referenced above. The data then available in relation

to autism were limited. Autism was not mentioned in the CCSI at that time and no information on autism was proposed by Sanofi as part of that variation.

However, Sanofi continued to monitor signals for autistic spectrum disorders.

In July 2008 Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2006 – 31 January 2007. This was a routine submission in respect of the valproate marketing authorisations. A cumulative review of autism, autism spectrum disorders (ASD) and Asperger's syndrome was carried out, based on reports of exposure during pregnancy. The conclusions were:

> "*According to the National Center for Health Statistics, the prevalence of autism ranges from around 10 to 15 cases per 10,000 populations. It is noteworthy that a statement is present in the CSI, regarding the potential association between in utero valproate exposure and a risk of developmental delay, particularly of verbal intelligence quotient. No conclusion can be drawn regarding a causal role of valproate in the development of autism in these children exposed in utero or orally to valproate. This topic will remain under surveillance by the company*".

In December of 2008, publication of a paper (Bromley et al) reported the preliminary results of a prospective study being undertaken by the Liverpool Group. These data suggested an increased incidence of autism spectrum disorders in children who had been exposed to valproate in utero as compared with a control group.

This led to a further cumulative review of the safety data collected in Sanofi's global electronic pharmacovigilance database and a review of the scientific literature. The conclusion of the review was that some data were available on autism in children after maternal exposure to valproate but there was currently limited information in relation to a causal relationship.

Autism spectrum disorders were first listed in the CCSI dated December 2008 where the following statement was added: *"Autism spectrum disorders have also been reported in children exposed to valproate in utero". A* variation application to include this wording in the UK SmPC was submitted to the MHRA in April 2009 and approved in October 2010.

Sanofi France also submitted a variation to ANSM in April 2009 where they asked for a modification of the sentence related to autism added by ANSM in January 2006, to what was proposed in the company core safety information of December 2008. During the variation review, ANSM changed Sanofi's proposal and the sentence below was approved by ANSM on 08 June 2010.

> "Increase in the frequency of pervasive developmental disorders (autism spectrum disorders) have also been reported in children exposed to valproate in utero".

This sentence replaced the January 2006 sentence regarding autism in the French SmPC.

Subsequently, following implementation of the conclusions of Article 31 EMEA/H/A-31/1387 (PRAC review) approved on 17 April 2015, the statement regarding autism was harmonized in all EU member states, as follows:

"Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population."