COMMISSION ON HUMAN MEDICINES

AD HOC EXPERT GROUP ON SYSTEMATIC REVIEW AND META-ANALYSIS OF ORAL HORMONE PREGNANCY TESTS

Minutes of the meeting held on 18th March 2019 at 12:00 p.m. in the Round Room, 10th floor, 10 South Colonnade, Canary Wharf, London, E14 4PU

Participants Present

Members

Professor P Hannaford (Chair)
Professor J Higgins
Professor R Newbury-Ecob
Professor J Sterne

Invited Expert

Professor L Smeeth

Visiting Experts

Dr J K Aronson
Professor C Heneghan

Observers

Mr N Dobrik
Mrs M Lyon
Dr S Macleod
Ms L Pepper

Expert provided written comments

Dr Sarah Floud

Secretariat

Ms E Agca

MHRA Legal

Miss K Foster
Ms H Burrows

Professional Staff of MHRA Present

Supporting Specific Items

[redacted] – *VRMM*
Dr J Raine – *VRMM, Divisional Director*
Dr J Woolley – VRMM
Dr S Seabroke – VRMM

Observers

[redacted] – MHRA*, Public and Stakeholder engagement*
Mrs L Loughlin – *Head of Science Strategy*
Dr K Rantell – *Licensing Division*

VRMM - Vigilance and Risk Management of Medicines Division

1. Apologies and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 The Chair informed those present that the proceedings will be recorded for minute taking purposes. It was intended that the recording would be destroyed once the minutes of the meeting have been agreed.

1.3 All those present introduced themselves.

The Chair clarified that the meeting participation is divided into the following categories:

Chair & Members – are invited to attend for the whole meeting, receive all papers and are able to contribute to the conclusions and recommendations of the group.

Invited Expert – are invited to the meeting, receive all papers and are permitted to participate in discussions when invited by the Chair, but do not contribute to conclusions and advice of the Group.

Visiting Expert – receive all papers and are invited to present their work to the group for discussion, but do not contribute to the conclusions and recommendations of the Group.

Observers – receive all papers and are invited to attend the meeting, but do not contribute to the conclusions and recommendations of the Group. In her role as a member of The Independent Medicines and Medical Devices Safety Review Team, if she wishes, Dr Macleod may stay for the discussion of conclusions and recommendations. Dr MacLeod remained for these discussions.

1.4 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies:

Successors of the companies who originally marketed HPTs:

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The companies who originally marketed HPTs:

- Roussel Laboratories
- Parke Davis
- Wallace Manufacturing Chemists Ltd
- Schering
- Organon Laboratories
- Nicholas Laboratories Ltd
- Duncan Flockhart and Company Ltd.

The Chair reminded participants to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

The register of interests declared by participants was made available in advance of the meeting. The Chair informed those present that the declared interests had not been deemed to debar any participation. There were no concerns raised. No further interests were declared.

2. Matter Arising

2.1 The chair advised those present that should they be contacted by the media as a result of this meeting, they should refer the queries to the MHRA Press Office. Press office details were circulated to all participants.

3. Terms of Reference

The following Terms of Reference of the Group had been endorsed by the Commission on Human Medicines, to consider the paper by *Heneghan et al.*[1] on oral hormone pregnancy tests and the risks of congenital malformations and to consider:

- The suitability and robustness of the methodology, including the selection and application of the data quality score
- Any clinical implications

And to advise the CHM.

3.1 The meeting attendees noted the Terms of Reference and were asked if they had any comments. No comments were noted.

4. Key points for consideration

4.1 The MHRA presented the key points from their report for the Expert Group to consider, indicating areas that the Group might wish to focus on, including the:

- study design, method of data collection and statistical methods applied in the original studies conducted in the 1960s to 1980s
- potential biases and confounding that may have existed in the original studies
- utility of the Newcastle Ottawa Scale for assessing study quality
- use of meta-analysis to obtain summary effect sizes from combining these observational data.

4.2 The Chair asked if there were any points for clarification. Mr Dobrik commented that although the pitfalls of meta-analysis had been discussed by the original CHM Expert Working Group on HPTs (HPT EWG) it was helpful to go through these again.

4.3 Mrs Lyon asked the MHRA to confirm that the original HPT EWG had not conducted a meta-analysis. The MHRA confirmed that the original EWG had not conducted a meta-analysis. As the Group had had no involvement in the previous HPT EWG review, MHRA provided some context on this point.

4.4 As the MHRA mentioned the ROBINS-I tool for assessing bias in the meta-analysis of observational data, Professor Sterne clarified that he had co-developed the ROBINS-I tool with Professor Higgins, who was also co-editor of the Cochrane Handbook.

[1] https://f1000research.com/articles/7-1725/v2

5. Professor Heneghan and Professor Aronson's Presentations

5.1 The Chair welcomed Professor Heneghan and Professor Aronson to the meeting and invited them to give their presentations. Professor Heneghan said they had not prepared a formal presentation but would explain why they conducted the meta-analysis, how they conducted it and describe events since it was published.

5.2 Professor Heneghan stated that the decision to conduct a meta-analysis was based on a discussion with the Chair of the Association for Children Damaged by HPTs in November 2017 and concerns about certain aspects of the report of the CHM Expert Working Group on HPTs (HPT EWG) published in November 2017, including whether the HPT EWG had meta-analysed the observational data. The MHRA clarified that the EWG had not done a meta-analysis but had presented the data visually by way of forest plots.

5.3 Professor Heneghan briefly outlined how his meta-analysis had been conducted. He emphasised the importance of transparency and explained that because some data extraction was conducted before applying to register the protocol, the International Prospective Register of Systematic Reviews (PROSPERO) had not accepted it. Some changes had since been made to the protocol, but Professor Heneghan considered these would make no difference to the outcome of the study.

5.4 Referring to the MHRA's in-house report, which had been sent to Professor Heneghan and all members on 5th March to support preparation for the meeting, Professor Heneghan said it would have been helpful to have been sent questions in advance of the meeting so that a response could have been submitted prior to the meeting. Nevertheless, he said he would be content to respond to questions.

5.5 Professor Aronson referred to the CSM 'Adverse Reaction' publications which stated in 1977 that the study by Greenberg et al. had confirmed an association between HPTs and congenital anomalies. He referred to questions over the terminology used and phrasing of the conclusion of the HPT EWG Group and to the possible mechanisms of action that had been considered. Professor Aronson noted that association does not imply causation and stated that relatively few safety signals are ever proved to be causally associated.

5.6 The Chair reminded the Group that the purpose of today's meeting was the meta-analysis by *Heneghan et al.*[1], that to ensure independence, none of the experts present were part of the previous review, and that any comments on the HPT EWG report could be handled through a different mechanism.

5.7 The Chair asked if the Group had any points for clarification. Mr Dobrik asked whether Professor Heneghan had been provided with enough information from the MHRA to be able to duplicate the work of the HPT EWG. Professor Heneghan confirmed that a random effects meta-analysis of the data provided by the MHRA had been performed and was consistent with the findings of his own meta-analysis; these data would be made available once checked. Professor Heneghan went on to say that they would next be evaluating whether there was an association between HPTs and spontaneous abortion.

6. Discussion of the data presented and questions to Professor Heneghan and Professor Aronson

6.1 The Group discussed the issue of multiplicity and noted that in assembling data for a meta-analysis it may be necessary to select from among a number of eligible results, for example when a case control study had more than one control group. However, the reason for making such choices did not appear to be documented in the publication by *Heneghan et al*.[1] One example where it was not clear why different control groups had been selected in the assessment of different outcomes was in the study by *Torfs et al*.[2] The Group commented that ideally, a clear rationale for selecting from among multiple results should be documented prospectively within the protocol.

6.2 Professor Heneghan considered it would be unrealistic to pre-specify such decisions in advance of data extraction and commented that only one or two studies had used more than one control group and, furthermore, whatever control group had been selected would not have impacted on the observed effect estimates. He stated that the protocol could be published retrospectively on F1000 but would not be time or date stamped.

6.3 The Group highlighted examples where there was a difference of opinion with Professor Heneghan over the numbers that had been selected for inputting into the meta-analysis. While these may not necessarily impact on the results, the Group considered it introduced some uncertainty about the reliability of data abstraction. Professor Heneghan confirmed that the data had been abstracted by two people independently but that some of the studies were highly complex, the studies were conducted in an era before standards on study reporting were available, and so some errors may be present. Professor Heneghan could not respond on this specific point but offered to document how the numbers were derived and add this as supplementary information to the publication on the F1000 website.

[2] Torfs, C.P., L.Milkovich and B.J.Van den Berg (1981). "The relationship between hormonal pregnancy tests and congenital anomalies: A prospective study." American Journal of Epidemiology 113(5): 563-574.

6.4 The Group questioned whether it was possible that, irrespective of how carefully any data extraction was conducted, women who were at an increased risk of having a child with a congenital anomaly, would have been more likely to have a pregnancy test. Such confounding would bias associations between hormone pregnancy tests and congenital anomalies, compared with the causal effect. The possibility of uncontrolled confounding is particularly important for studies conducted in an era when modern methods to control confounding were not available, and most reported effect estimates were unadjusted. In addition, publication bias has historically been problematic. The Group cited the study by *Greenberg et al.* (1977)[3] which showed that a history of malformations was a risk factor for having a child with an anomaly and a secondary publication of the study by *Gal et al*. (1972)[4] which documented that in all but one of the index cases the pregnancy was unwanted.

6.5 Mrs Lyon stated that 57 members of the Association for Children Damaged by HPTs had received a negative genetic test and had no prior genetic issues. The Group noted that currently there is no genetic test that would rule out a genetic aetiology for an association between an exposure and an adverse outcome and that most genetic abnormalities occur where there is a lack of family history of abnormalities.

6.6 Professor Heneghan commented that while all studies generally had positive findings, if there had been publication bias, he would have expected more evidence to emerge over time with results nearer the null and some studies to have a positive effect, if only by chance. Furthermore, as the studies were conducted over a 15-year period it was implausible that every study had the same confounder. The Group noted that in studies that adjusted for confounding factors, such as a history of malformations, the risk was reduced, albeit not completely removed; in many other studies, information on potential confounding was either not collected or not presented making it difficult for it to be taken into account in subsequent studies. The Group considered that, given the limitations of reporting in these studies, it was not possible to determine whether residual confounding could plausibly explain the findings. As the meta-analysis of *Heneghan et al.*[1] relied on unadjusted results, the impact of this on the observed effect estimates would need to be taken into consideration.

[3] Greenberg G, Inman WHW, Weatherall, JAC et al. (1977). Maternal drug histories and congenital anomalies. BMJ; 2: 853-856

[4] Gal I. (1972). Hormonal imbalance in human reproduction. In: Advances in teratology. Volume five. Academic Press New York/London, Ed. D.H.M. Woollam

6.7 The Group discussed the Newcastle Ottawa Scale (NOS) for assessing individual study quality. The Group agreed that confounding is of fundamental importance in interpreting observational studies and the NOS reflects this by awarding up to two points for this aspect, one for controlling for the 'most important factor' and one for controlling for 'other factors'. The Group was therefore interested to know how the 'most important confounder' had been defined in the meta-analysis. Professor Heneghan stated that most important confounder was not known at the outset and was not therefore pre-specified in the protocol but was identified clinically upon review of the studies by the data extractors (table 3 of the publication). The most important confounder included age, parity and previous history of anomalies.

6.8 Given that the results used in the meta-analysis were unadjusted the Group questioned the rationale for giving one or two points for controlling for confounding to studies that presented unadjusted results or for studies for which control of confounding was through design alone. When questioned whether consideration had been given to the use of odds ratios derived from matched pairs, as in the study by *Greenberg et al*.[3], Professor Heneghan offered to re-analyse the results using matched pair data. The Group considered that while it was possible to do some things to provide a more reliable effect estimate, it would not be possible to produce adjusted results without access to the raw data. As a result, it would not be feasible to exclude the possibility of residual or unmeasured confounding.

6.9 The Group questioned the benefit of meta-analysing these particular studies because of their differing levels of uncontrolled confounding and other potential sources of bias. Because the limitations of many studies prevented a firm conclusion from being drawn, the Group considered it may have been better for the protocol to specify a priori inclusion of the more robust studies that provided convincing evidence, such as the study by *Greenberg et al*.[3] Professor Heneghan said that sensitivity analyses were conducted to understand the effect of study quality on the outcome. The Group emphasised that it was difficult to assess risk of bias or the extent to which any confounding plausibly explains the observed association because of the age of the studies and the limitations on reporting.

6.10 Regarding another of the NOS criteria, the Group noted that all studies received a point to denote that the outcome of congenital anomaly could not have occurred prior to exposure to HPTs. The validity of this was questioned because HPTs were given to women over a wide gestation period (from approximately 2 to 12 weeks). Professor Heneghan could not provide an immediate response to this point.

6.11 The Group discussed selection bias and the possibility that any studies restricted to live births could lead to a systematic underestimation of harm if HPTs increased the risk of miscarriage. The Group further discussed whether studying 'all anomalies' could potentially mask an effect on more specific outcomes and thereby introduce imprecision but agreed that in the absence of any mechanism for harm this was speculative. The Group commented that bladder extrophy and VACTERL were of greater interest because they are distinctive phenotypes with a low genetic contribution.

6.12 The Chair asked if there were any other points the Group wished to discuss. Mrs Lyon stated that it would have been useful if the experts had had sufficient time to send questions to Professor Heneghan and Professor Aronson in advance to facilitate a fully informed discussion.

6.13 The Group repeated their view that limitations in reporting, available methods at the time the studies were published, and the underlying data made it impossible to provide certainty over the observed association between HPTs and congenital anomalies. While it was possible that HPTs could increase the risk of congenital anomalies these limitations made the robustness of the evidence questionable. Mr Dobrik commented that this was consistent with the view of the original HPT EWG on the epidemiological data. Professor Heneghan stated that the law would not expect certainty, but an answer based on the balance of probability.

6.14 The Chair thanked Professor Heneghan and Professor Aronson for attending the meeting and responding to their questions.

7. Announcements

7.1 The Chair reminded those present that in line with the participation definitions stated in the invitation letters, the Invited Expert, Visiting Experts and Observers are not permitted to contribute to conclusions and recommendations. The following participants left the meeting at this point:

Invited Expert
Professor L Smeeth

Visiting Experts
Professor C Heneghan
Dr J Aronson

Observers
Mr N Dobrik
Mrs Marie Lyon
Ms L Pepper

Dr Macleod stayed for the discussion of conclusions and recommendations in carrying out her role as an observer from The Independent Medicines and Medical Devices Safety Review Team.

8. Conclusions and advice for the Commission on Human Medicines

Robustness of the meta-analysis by Heneghan et al

8.1 The Members considered that publication of a protocol is standard when conducting meta-analyses and would have been helpful in this case. The lack of a protocol or transparency over decisions made during data extraction and the selection of data and results for meta-analyses made it difficult to understand how or why certain choices were made or how some numbers had been derived.

8.2 The use of a scale such as the NOS for assessing study quality was considered outdated in light of the availability of newer tools such as ROBINS-I. However, Members recognised that ROBINS-I was not mandated by Cochrane, which referred to NOS as an alternative option. Nevertheless, Members had some concerns over the application of NOS in the meta-analysis by *Heneghan et al.*, particularly with respect to the scoring of confounding, which was considered to be particularly problematic, and the timing of exposure in relation to outcome. The Group considered that some of the principles of ROBINS-I with regard to evaluating the risk of bias should have been implemented.

8.3 The Members considered that the homogeneity of the studies was extreme and could be compatible either with a real effect or with biases common to all studies. However, it was not possible to investigate this further because of the limitations of the included studies. Publication bias was thought to be a major risk but had not been acknowledged sufficiently by the authors and, without access to the raw data, it was impossible to reach a conclusion on this.

8.4 Members stated that it is standard when conducting a meta-analysis to use adjusted data that takes account of confounding in the original studies. The use of unadjusted data in the meta-analysis by Heneghan et al., even when studies presented matched effect estimates, meant it was not possible to draw strong conclusions on the impact of bias on the observed association between HPTs and anomalies. The Group commented that ideally, the original studies should have systematically reviewed the phenotype of all cases to make an alternative diagnosis where possible and thus end up with a 'cleaner' subset of unexplained congenital anomalies.

8.5 Having considered the meta-analysis by Heneghan et al. at length the Members advised that the methods used were not in line with best practice, the application and choice of NOS was questionable, and the study could not be considered robust. The Members further advised that due to limitations in the design, reporting and analysis of the included studies there would be little value in re-analysing the data.

Clinical implications for currently authorised medicines

8.6 On the basis of the Group's findings, no implications for currently authorised medicines could be concluded.

8.7 ***Post meeting note:*** *A response from Professor Heneghan to some of the questions that were raised at the meeting of the Group was received on 28th March 2019. The response included further details of the selection of controls and reasons for exclusion of some control women from the analysis; selection of confounding variables across studies; an analysis of the data from studies that took account of a previous history of congenital malformations.*

Professor Heneghan also provided:

- *a protocol, date stamped 23rd October 2018, which was also published online on 25th March 2019*
- *a link to an article by the authors, dated 15th March 2019, on assessing bias in studies of harms*
- *a meta-analysis of the results presented in the report of the CHM Expert Working Group on HPTs, published in November 2017.*

All additional information provided by Professor Heneghan was sent to the Group on 5th April 2019. The Group was asked whether anything in the responses changed their overall conclusion on the suitability and robustness of the methodology, the selection and application of the data quality score and any clinical implications of the meta-analysis by Heneghan et al.

The Group advised that the additional information did not alter the conclusions that had been reached at its meeting on 18th March.

9. Any other Business

No additional issues were raised.

10. Meeting Close

10.1 The meeting closed at 16:12pm

P. Hannaford

Signed 3.5.19