



Minutes of the meeting held on Tuesday 23 October 2018 from 11:00am at the MHRA office, 10 South Colonnade, Canary Wharf, London, E14 4PU.

Members attending	
Member	Role
Prof Deborah Saltman AM	Chair
Prof Richard Stevens	Deputy Chair and Scientific member
Prof Sinead Brophy	Scientific member
Dr Iain Carey	Scientific member
Ms Rosie Cornish	Scientific member
Dr Duncan Edwards	Scientific member
Prof David Fishwick	Scientific member
Dr Kate Fleming	Scientific member
Prof Evangelos Kontopantelis	Scientific member
Ms Sally Malin	Lay member
Dr Emily McFadden	Observer
Prof Andrew Morris	Scientific member
Prof Keith Neal	Scientific member
Dr Grace Okoli	Scientific member
Ms Marcia Saunders	Lay member
Prof Sara Thomas	Scientific member
Dr Paul Welsh	Scientific member
Prof Ian Wong	Scientific member

Apologies	
Member	Role
Prof Ann John	Scientific member
Dr Jennifer Quint	Scientific member
Prof Martin Tobin	Scientific member
Dr Hester Ward	Scientific member
Dr Stephen Weng	Scientific member

In attendance	
Attendee	Role/Post
Dr Janet Valentine	CPRD Director
Dr Puja Myles	CPRD Head of Observational Research
Ms Tarita Murray-Thomas	CPRD Senior Researcher
Mr Jonathan Lind	CPRD Research Applications Manager
Ms Eleanor Yelland	CPRD Researcher
Mr Sam Speer	CPRD Research Applications Coordinator

1. Welcome and apologies

The Chair opened the meeting and welcomed those members in attendance.

Dr Emily McFadden was welcomed back to the Committee and would be observing on this occasion.

Profs Ann John and Martin Tobin, and Drs Jennifer Quint, Hester Ward, and Stephen Weng had sent their apologies for the meeting.

The Chair acknowledged that Professor Sonia Saxena and Dr Wendy Knibb had resigned from the Committee and thanked them for their service in absentia.

The Chair noted that this was the third and final meeting of 2018 following the cancellation of the July meeting. The July meeting was cancelled as quorum could not be reached.

Sally Malin and Marcia Saunders would be tendering their resignations from the Committee following the meeting, and the Chair thanked them for their longstanding work on the Committee.

2. Minutes of the last meeting

The full and summary versions of the minutes from the April 2018 meeting were approved by the Committee as circulated in the meeting papers.

Action: The Secretariat to upload approved summary minutes for the April 2018 meeting to CPRD and MHRA websites.

3. Matters Arising

The Committee was asked to consider the quorum criteria for Committee meetings. The Committee reaffirmed that quorum could not be reached without a lay member in attendance.

Sara Thomas was invited to present a paper on weighting of reviewer comments when reviewing research protocols. The Committee agreed to the guidance contained within the paper.

4. Head of Observational Research's Report

Puja Myles informed the Committee of an ongoing pilot of revised guidance for internal reviewers that was initiated in discussion with the ISAC Chair. The Committee recommended that the revised guidance for internal reviewers should be aligned with the ongoing Committee discussions on weighting of reviewer comments.

The Committee was informed of a pilot for a new feasibility studies approval process. The Committee requested an update of the feasibility studies approval pilot at the next Committee meeting.

Action: Feasibility studies update to be presented by the Head of Observational Research at the next Committee meeting.

5. ISAC Secretariat Report

Jonathan Lind provided an update to the Committee on the number of ISAC protocols, resubmissions, and amendments received in Q1-2 of 2018/19 (paper 3). There were 147

protocols submitted for review and 174 protocols approved by ISAC during the first two quarters of the 2018/19 financial year; an increase of 1% and 4% respectively on the same period last year. 128 resubmission and 99 amendments were received in the reporting period; an increase of 22% and 39% respectively on the previous year.

The Committee were thanked for their timely reviews of protocols during this period.

6. CPRD Director's Report

The CPRD Director updated ISAC on the expansion of the CPRD primary care database to include data contributions from more than 1 in 10 GP practices in the UK, providing coverage of over 15% of the UK population. With the onboarding of EMIS GP practices into the new CPRD Aurum database, the total number of patients available had increased to 35 million. Data volumes were set to grow significantly in the future with the recent public commitment from TPP to flow data from TPP/SystemOne GP practices to CPRD from 2019/20.

Since the last ISAC meeting, four new datasets had been included as part of the quarterly routine data linkage, namely the Radiotherapy dataset from Public Health England and three new socio-economic/indices of deprivation datasets. Data from CPRD Aurum has been included as part of the standard data linkage for the first time.

In response to customer feedback and the need to develop a scalable data access model in line with the increasing volumes of data available, a new multi-study licence model and associated pricing structure had been developed. The new pricing model, which was finalised after extensive customer engagement, would be rolled-out over the next 12 months.

7. ISAC Audit Closure Report

Following the presentation of the ISAC audit findings by the ISAC Deputy Chair at the CPRD Mid-year User Group, Professor Richard Stevens and Dr Puja Myles presented a Closure Report on the project referred to as the Audit Project, which commenced in 2012 under the Chairmanship of Professor Patrick Waller, comparing publications using GPRD/CPRD to the corresponding ISAC protocols. Prof Stevens reminded members that the primary aim of the project was to inform CPRD and ISAC about current practice in the user community and hence inform our own procedures, while a secondary aim discussed at ISAC meetings was to potentially publish the project in a scientific journal.

The following points were noted:

- A small-scale pilot identified that although investigators were asked to seek approval for major changes to an approved protocol, as of 2012 no definition of "major changes" existed. A definition of major and minor changes was therefore agreed by ISAC in 2012 and published for subsequent use by researchers.
- A pragmatic decision was taken to use this newly developed definition of major vs. minor change for the purposes of the 'audit' project, in the absence of any pre-existing definition.
- Following the pilot, all 133 papers published in 2013 were matched by the ISAC Secretariat against the definitions of major and minor deviations. The pilot findings were discussed in July 2014 by ISAC and the definitions revised.
- At the October 2015 ISAC meeting, concerns were expressed by ISAC that the audit criteria were being applied by administrative staff and it was agreed that ISAC members would need to validate the previous findings before the audit could be finalised.
- An interim report was tabled at the January 2016 ISAC meeting, identifying 18 differences between paper and protocol that might potentially be classified as major changes according to the definitions published in 2012. Following discussion, 15 of these

cases were classified as minor amendments that would not have needed an amendment submission to ISAC, and three protocols were upheld as potentially major deviations.

- The three protocols out of the original 133 were flagged by the administrative team as potential major deviations because of changes to
 - Title (publication title was more specific)
 - Objective (protocol referred to different drug names that are used interchangeably by clinicians)
 - Study duration (study start or end date different)
 - Matching variables (matching on fewer proposed variables)
 - Actual sample size included in analysis much smaller than estimated sample size
 - Analysis strategy (different statistical method or variant of initially proposed statistically method used; protocol stated that adjustment for confounders would be considered if relevant, but the publication only presented unadjusted results)
 - ISAC application only referred to CPRD data whereas publication presented CPRD results alongside results from two other international databases as part of a research collaboration for which separate approvals were in place
- In all three cases, there was no deviation from the stated purpose of the proposed work in the resulting publication. There were also no concerns raised about risks to patient confidentiality for any of these protocols and the resulting publications. The published work was deemed to be scientifically valid following scientific peer review.
- In January 2017, possible publication of the pilot audit was discussed. ISAC members agreed that, while the existing methods had been sufficient and appropriate for the primary aim, to inform ISAC processes, they were not sufficiently robust for the secondary aim of potential publication in a scientific journal. One of the major methodological concerns raised by ISAC was the retrospective evaluation of protocols against a standard that did not exist at the time the protocols were submitted to ISAC. The lack of parallel screening was also a methodological weakness for the secondary aim.
- Because the audit project had met the first aim of informing ISAC processes only, the Deputy Chair was asked to chair a sub-committee charged with presenting the pilot findings at a CPRD User Group.
- Professor Richard Stevens presented the pilot audit findings and lessons learned at the CPRD 2018 Mid-year User Group.

Members noted the positive outcomes of this exercise which included:

- ISAC guidance on major and minor amendments has been clarified;
- CPRD data licence terms place an obligation on researchers to specify the approved ISAC protocol number in the resulting publication to enable cross-referencing for future audits;
- CPRD publishes summaries of all approved ISAC protocols submitted to CPRD from 1st July 2015 on its website as part of its transparency policy (<https://www.cprd.com/protocol-list>);
- CPRD conducts a monthly online search of publications using CPRD data and maintains a bibliography of such publications on its website (<https://www.cprd.com/bibliography>);
- The CPRD Research team monitors publications based on CPRD data on a quarterly basis to ensure that any work conducted is within the scope of the data access terms and conditions.

8. Statistical methods for missing data

Sara Thomas led a discussion on what guidance may be made available to applicants regarding the 'Missing Data' section of ISAC protocols. The Committee agreed that applications simply listing "Not applicable" in the missing data section were unlikely to be approved.

Attention was drawn to the new guidance on completing the ISAC Application Form, which states that applicants must provide justification for any sections marked as “Not applicable”.

The Committee agreed to the wording of the guidance provided in the paper.

Action: The Secretariat to update the guidance on completing the ISAC Application Form with the agreed wording.

9. Propensity score matching

Evangelos Kontopantelis presented to the Committee on propensity score matching and the applicability of the technique to very large databases such as the CPRD.

The Committee reiterated that applicants were expected to acknowledge the limitations associated with propensity scoring for any proposed methods. The Committee agreed that it was outside their remit to recommend specific statistical methods. However, reviewers may provide discretionary advice to applicants on the techniques and methodologies detailed in protocol applications.

10. Prescriptions that are absent in CPRD primary care databases

Duncan Edwards and Grace Okoli presented a paper covering situations in which certain prescriptions may not appear in the database.

The Committee agreed that applicants should be aware of the limitations of the database, and should state this clearly in protocol applications in Section T.

11. Protocols discussed

Iain Carey, David Fishwick, and Eleanor Yelland led discussions on issues raised during the reviews of various ISAC protocols.

12. AOB

The Committee were reminded that the following dates had been secured for Committee meetings:

- 22 January 2019
- 23 April 2019
- 23 July 2019
- 22 October 2019