



Medicines & Healthcare products
Regulatory Agency

Independent Scientific Advisory Committee

Minutes of the meeting held on Tuesday 25 April 2017 at 11:00am in R-T-503, 5th Floor, 151 Buckingham Palace Road, Victoria, SW1W 9SZ

Members attending

Member	Role
Prof Deborah Saltman AM	Chair
Dr Richard Stevens	Deputy Chair and Scientific member
Dr Angelyn Bethel	Scientific member
Dr Krishnan Bhaskaran	Scientific member
Prof Sinead Brophy	Scientific member
Dr Benjamin Cairns	Scientific member
Ms Rosie Cornish	Scientific member
Dr Christopher Edwards	Scientific member
Prof Peter Helms	Scientific member
Dr Evangelos Kontopantelis	Scientific member
Dr Wendy Knibb	Scientific member
Ms Sally Malin	Lay member
Prof Keith Neal	Scientific member
Dr Jennifer Quint	Scientific member
Ms Marcia Saunders	Lay member
Dr Sara Thomas	Scientific member
Prof Ian Wong	Scientific member

Apologies

Member	Role
Dr Duncan Edwards	Scientific member
Dr Caroline Jackson	Scientific member
Dr Hester Ward	Scientific member

On leave

Member	Role
Dr Emily McFadden	Scientific member

In attendance

Attendee	Role/Post
Mr Antony Haworth	CPRD Head of Information Governance & Assurance
Mr Daniel Brett	ISAC Secretariat
Ms Sonia Coton	CPRD Researcher
Mrs Tarita Murray-Thomas	CPRD Senior Researcher

1. Welcome and apologies

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

2. Minutes of the last meetings

The following minutes were approved by the Committee as circulated in the meeting papers with the exception of the minutes of the meeting of January 2017.

Minutes approved:

- July 2016 summary minutes.
- October 2016 full minutes.
- October 2016 summary minutes.
- January 2017 full minutes, with amendment.
- January 2017 summary minutes, with amendment.

2.1 January 2017 full and summary minutes

The minutes from the January 2017 ISAC meeting were approved pending one edit to the ISAC Audit item in both the full and summary versions. The agreed change would read:

“Members unanimously agreed to recommend that the findings of the audit should not be published as a scientific paper. Members agreed that the results of the audit would in its present form be unlikely to be acceptable for publication because of a number of deficiencies in its design and the changes made to the advice for applications to use CPRD data over the period of review. Members also did not favour publishing the findings in the Annual Report or comparing the preliminary data with outputs from more recent years.”

Actions: ISAC Secretariat to amend full and summary minutes from January 2017 and to publish the summary minutes to the CPRD website

3. Matters Arising

The actions list from the previous meeting was presented by the Chair.

3.1 Action from January 2017: *Secretariat to produce the following minutes: July 2016 summary, October 2016 full and summary, January 2017 full and summary.*

The minutes were approved subject to an amendment in the January 2017 meeting minutes.

3.2 Action from January 2017: *ISAC guidance on statements of ethical approval for observational studies approved by ISAC.*

The statement provided by Dr Richard Stevens was approved for inclusion in the ISAC guidance notes on the content of protocols.

Action: Secretariat to update ISAC guidance notes on the content of protocols and upload to website.

3.3 Action from January 2017: *Professor Peter Helms and Dr Duncan Edwards to provide a statement on behalf of ISAC to be included in the ISAC guidance for applicants on Primary Care expertise on study teams to be shared with the Committee at the next ISAC meeting.*

Professor Peter Helms proposed updated guidance on the primary care expertise required in research study teams. It was agreed to modify the guidance such that paragraphs 1 (Channelling by indication) and 2 (Reverse causation or association) would be moved to the bottom of the list of issues to be considered by the study team. It was also agreed that examples of the issues identified in paragraphs 3-7 would be helpful and that these would be added to the text.

Actions: Professor Peter Helms and Dr Duncan Edwards to update the guidance on primary care expertise in study teams, based on the above comments for approval at the July 2017 ISAC meeting.

3.4 Action from January 2017: *Secretariat to ensure that 'Approval with comments' would be considered for future meetings as an agenda item by the Chair.*

Covered under agenda item 8.

3.5 Action from January 2017: *The Deputy Chair to chair a sub-committee to present the ISAC Audit findings at a CPRD User Group meeting.*

The ISAC Audit sub-committee would present on the subject of the ISAC Audit at a CPRD User Group meeting. It was agreed that the sub-committee would present a draft presentation at the next ISAC meeting.

Action: Sub-committee to present a draft presentation of the ISAC Audit at a future ISAC meeting.

3.6 Action from January 2017: *Dr Sara Thomas, Dr Ben Cairns and Dr Evangelos Kontopantelis to prepare an update on data mining and machine learning for the next ISAC meeting.*

Covered under agenda item 7.

3.7 High and Low Priority Feedback to Applicants

The Chair confirmed the need for reviewers' comments to also include the relative importance of each comment so it is clear to the applicant how to best to address each comment if a resubmission of the protocol is requested.

4. Chair's Report

The ISAC Report for the period of 1 January 2015 – 31 March 2016 has been published on the CPRD and MHRA websites. The Chair thanked everyone who worked on the report.

The Chair thanked Committee members for their work in reviewing an increased number of protocols (over last year) since the last meeting in January. The topics of machine learning and data mining, and also Health Economics Outcomes Research were identified as important issues for discussion in up and coming ISAC meetings.

5. Secretariat Report

Mr Daniel Brett presented a report on ISAC protocols received over the 2016/17 financial year. There had been 305 submitted protocols and 272 approved protocols.

The Committee considered proposed changes to the ISAC application form and recommended the following alterations:

- If applicants select the 'Other' category for type of study, they would need to provide more details of what the study involves
- Replace the Knowledge Centre email address (kc@cprd.com) with the CPRD Enquiries email address (enquiries@cprd.com).
- Add the Pregnancy Register as a linkage.
- Update the colour of the section titles on the form.

An update was provided on the resourcing and recruitment to the ISAC Secretariat and to the Observational Research team. Dr Puja Myles (BDS MPH PhD FFPH) had joined CPRD as the Head of Observational Research. Ms Eleanor Yelland had joined as CPRD Researcher and will support the ISAC scientific reviews.

CPRD has initiated recruitment of new scientific Committee members to areas of scientific expertise required on the Committee.

6. CPRD Director's Report

Mr Antony Haworth presented the CPRD Director's Report on behalf of the CPRD Director Dr Janet Valentine. The report updated the Committee on the planned timetable for release of EMIS data, feedback from the CPRD User Group meeting held in March 2017 and the new CPRD Enquiry service that has replaced the CPRD Knowledge Centre help desk.

The Committee noted the importance of GP engagement and commented that it would be helpful to discuss incorporating ISAC as part of a future CPRD User Group meeting.

7. Machine Learning and Data Mining

Drs Sara Thomas, Ben Cairns and Evangelos Kontopantelis presented a paper on Machine Learning and Data Mining. Four issues were raised in the discussion of this topic:

- Supervised vs unsupervised machine learning
- Validation of the findings
- Matching methods to the dataset
- Importance of the proposed research

7.1 Supervised vs unsupervised machine learning

Supervised machine learning was defined as machine learning where the computer learns from paired input and output data provided by the researcher. Unsupervised machine learning was defined as machine learning where the algorithm was designed to identify relationships without giving the computer any signal of success or failure, sometimes called 'data mining'. It was recommended that supervised machine learning could be considered an acceptable use of the CPRD database.

7.2 Validation of the findings

It was noted that appropriate validation techniques were crucial where protocols propose machine learning, because of the high degree of freedom and range of choice of methods employed.

7.3 Clinical expertise on study teams proposing machine learning

Members agreed that it was very important for applicants proposing machine learning to demonstrate clinical expertise and input into the research protocol.

7.4 Recommendations

The working group recommended that when machine learning and data mining protocols were received, they should be noted by the Secretariat for consideration at a future ISAC meeting; and that all protocols that propose either approach should be reviewed by a Committee member.

8. Health Economics Outcomes Research

Dr Wendy Knibb presented a paper on ISAC protocols in the field of Health Economics Outcomes Research (HEOR). The purpose of the paper was to identify key indicators for an acceptable protocol application. The three points of discussion raised were when HEOR is provided as a 'bolt on' to a study, the level of HEOR expertise on study teams, and when HEOR analyses are provided as an appendix to the protocol application.

8.1 HEOR provided as a 'bolt on' to a study

Dr Wendy Knibb reported that one challenge faced in reviewing HEOR protocols is when little mention is given in the data analysis section of how the data will be used in a HEOR context.

8.2 HEOR expertise on study team

A second challenge faced by reviewers when reviewing protocols proposing HEOR techniques was to assess the level of expertise in HEOR demonstrated by members of the study team. The Chair noted that the Secretariat keeps a record of applicants' CVs and therefore when reviewers had a question about the expertise of the applicants, they should raise this with the Secretariat who could share the CVs as appropriate.

8.3 HEOR analysis provided as an appendix to the protocol application

It was reported that one issue faced by reviewers was when economic modelling was provided as an appendix to the protocol and not in the main body of the application. It was agreed that there was no problem with providing HEOR analyses as an appendix *per se*, and that they should be considered by reviewers.

Work proposing the use of patient level data should be included in the main body of a protocol application and not as an appendix.

Where HEOR analyses are included in a protocol or as an appendix they should be considered by the reviewer.

9 Protocols for discussion

The Committee discussed two protocols that had been highlighted as of interest over the last few months.

10. Evaluation of the year

Members were invited to reflect on the work of ISAC over the last year and suggest what they had perceived as being effective, what could be improved, and what more could be done.

The Chair thanked the Committee for their enthusiasm and energy at meetings. The aim of the discussions was to help improve the consistency of feedback from reviewers through continuing discussions at quarterly meetings.

The Chair thanked Members for their work in reviewing protocols and reminded the Committee of their target deadline of ten working days to complete reviews.

11. Next meeting

The next meeting will be held at 11am on 11 July 2017 at 151 Buckingham Palace Road, Victoria, SW1W 9SZ.