Medicines & Healthcare products Regulatory Agency

Central Advisory Committee (CAC)

Minutes of the meeting held on 13 October at 3:00pm via Microsoft Teams

Members attending	
Member	**Role**
Prof Jennifer Quint	Scientific member, and Chair
Dr Emily McFadden	Scientific member
Dr Ben Cairns	Scientific member
Dr Kate Fleming	Scientific member
Prof Susan Jick	Scientific member
Prof Umesh Kadam	Scientific member
Prof Li Wei	Scientific member
Prof Jo Knight	Scientific member

Apologies	
Member	**Role**
Ms Sherren Smith	Lay member
Prof Richard Martin	Scientific member (Resigned)
Prof Richard Stevens	Scientific member (Paused Membership)
Mr Edward Chapman	Lay member
Prof Deborah Saltman	Scientific member

In attendance	
Attendee	**Role/Post**
Dr Susan Hodgson	Head of Observational Research
Tarita Murray-Thomas	Research Data Quality and Governance Lead
Tarryn Gourley	Research Applications Officer
Kirstie Andrews	Research Applications Coordinator
Tao Haskins-Coulter	Researcher
Nadia Azimikorf	Research Data Governance Officer

1. Welcome and Apologies (Chair)

The Chair welcomed attendees to the Central Advisory Committee (CAC) and noted apologies. Members were reminded of the Terms of Reference for the Committee.

The Chair advised that this meeting would discuss moderation calibration through selected protocols and provide oversight of protocol triage via the Committee's agreed method.

2. Minutes of the 9 June 2023 Meeting (Chair)

The minutes of the CAC meeting held on 9 June 2023 were reviewed. No comments or corrections were made, and the minutes were confirmed as an accurate record.

3. CPRD Update (Susan Hodgson)

CPRD welcomed back Dr Kate Fleming and welcomed Dr Emily McFadden as a new ERC Chair. CPRD announced that Professor Richard Stevens temporarily paused his role for the academic year and that Dr Harry Ahmed, will become Acting Chair shortly.

CPRD provided an update on recent developments in CPRD.

- The CAC Lay Member recruitment is ongoing, with roles to be advertised.
- A CPRD user group meeting in September had good attendance (over 100 external attendees) and good engagement:
    - The Director of CPRD, Puja Myles, gave an update on CPRD database coverage, progress on the CPRD Trusted Research Environment (TRE), and CPRD Aurum. The CPRD Aurum September 2023 build was released in September, with quarterly updates planned for the remainder of the financial year.
    - The Head of Observational Research, Dr Susan Hodgson presented the CPRD plans for Strengthening Data Quality and the Data Quality strategy.
    - The Head of Health Data Science, Dr Darren Lunn, presented a TRE update informing of client testing due to take place later this year.
    - The Research Data Quality and Governance Lead, Tarita Murray-Thomas, presented proposed guidance on patient/ user involvement in CPRD research. The associated drop-in session was supported by Edward Chapman, CAC Lay Member.
- CPRD recently worked with IQVIA to flag the importance of applying the correct inclusion/exclusion criteria when using the CPRD Pregnancy Register, especially for uncertain pregnancy events, some of which are identified solely on specific advice codes. A letter highlighting this issue has been submitted for review.

There were no questions or comments following the CPRD Update.

4. Secretariat Update (Tarryn Gourley)

CPRD provided an update to the CAC on metrics relating to protocols received between 9 June and 21 September 2023.

88 new protocols were submitted within this period, of which 38 (43%) were triaged as routine for internal review, and 50 (57%) were triaged as non-routine for ERC review. Of routine studies that went for internal review, 5 (17%) were approved on first submission and 25 (83%) required resubmission. None were rejected. Of non-routine studies that were allocated to ERCs for review, 2 (6%) were approved on first submission, 28 (90%) required resubmission and 1 (3%) was rejected. CPRD will continue to monitor the difference in resubmissions between applications triaged as routine and non-routine.

The CAC were then given an update on eRAP development. The main feature currently in development for eRAP is the ability for applicants to amend previously passed fields during resubmission. This was the main request from feedback given on eRAP and should make the review process more efficient. This is due to be delivered within this financial year. All eRAP users will be notified of these changes via the CPRD Bulletin.

The CAC was also reminded they could decline reviews at any point after they had been accepted, if necessary, and this process was demonstrated. The CAC were also reminded to notify the RDG secretariat, in advance of any periods of leave or unavailability.

5. Oversight of Routine/Non-Routine Triage (Chair & CPRD)

The CAC was reminded that an important function of the Committee is to provide oversight of protocol triage, which is conducted by CPRD. In the previous CAC meeting, it had been agreed to continue with triage exercises.

The CAC was asked prior to the meeting to complete a series of triage exercises; the CAC was split into three groups which each received five protocols (two in common across the groups) for the Committee to independently triage between 18 July 2023 and 18 September 2023. The CAC were asked whether they agreed or disagreed with the CPRD triage decision, and to provide further comments. The Chair of each Group then collated the assessments of each member and presented a summary of the group's feedback at this meeting.

Group one mostly agreed with CPRD's triage decisions. For one protocol, one member felt that this should have been triaged as non-standard as the protocol mentioned machine learning (and so could fall into non-routine triage category 2b Novel or non-standard methodological approaches). CPRD clarified that it has been re-evaluating how to triage protocols using Machine Learning/AI methods on a trial basis as applications proposing the use of such methods are becoming more common place. In the last quarter, where Machine Learning/AI methods proposed were used for risk prediction or prognosis, or hypothesis testing, CPRD has triaged such applications for ERC review. Where these methods were used for phenotyping, the triage team has been allocating these for CPRD internal review. CPRD will review the risk impact of this change in allocation with a view to updating the triage criteria at the next planned review. The Group agreed with all other protocol assessments and had no further comments.

Group two also mostly agreed with the triaging decisions, only questioning whether a COVID-19 related protocol should have been triaged for external review due to the current high interest in mental health (i.e., non-routine triage category 2a Major Public Health Interest or Public Health implications).

Group three also mostly agreed with the protocols triage decisions.

Overall, when classifying 'disagreement' as any difference in triage within the group, the total agreement across the Groups for the triage exercises was 8/11 (72.8%). All disagreements were in relation to protocols which had been triaged as routine by CPRD but as non-routine by the CAC. The CAC commented that disagreement with the CPRD triage decision was often made by only one individual within a group, as opposed to the whole group, meaning that the reported level of agreement is a conservative measure of agreement.

The triage exercise raised several discussion points:

1) The CAC asked if triage agreement was considered across meetings to see if there is any trend in levels of agreement. They also asked whether CPRD was aiming for a specific target level of agreement. CPRD indicated that a review of triage agreement across meetings was done in part for the 1-year review of the RDG process. CPRD agreed that a review of triage agreement across meetings beyond the 1-year review would be useful. CPRD also clarified that it was not aiming for complete agreement between CPRD and CAC triage decisions as there will be variation even when

reviewing with the same criteria. As long as there was an understanding of when and why there might be disagreement this was key in informing future triaging.

2) The CAC raised the issue of never knowing whether secondary or tertiary objectives in the protocol might be written up for publication as key findings. Where this is the case, triage might need to place equal weight on objectives, irrespective of whether these are primary, secondary, etc.
3) The CAC commented that there must be consideration for risk-benefit of doing public health interest studies i.e., is there a risk benefit balance that must be contemplated especially in terms confidentiality risks? CPRD reminded the Committee that a risk-benefit assessment is a necessary part of the scientific review process as stated in the scientific guidance for protocol review – Section '2c. Public health benefits and risks'.
4) The CAC questioned whether there were differences between reviews conducted by CPRD and ERCs. CPRD clarified that the same scientific review criteria are used by internal and ERC reviewers, however the range of professions undertaking the review, internally versus externally, likely differs (i.e., GPs and statisticians within ERCs), which might also explain some of the differences in review approaches.

6. ERC Review Moderation (Chair & CPRD)

The Chair reminded the CAC that one of the Committee's responsibilities is to facilitate calibration of reviews across the ERCs for consistency. This is important to ensure that there is consistent application of the reviewer guidelines and issuing of feedback to applicants.

The Chair facilitated the discussion of a research application that was nominated for discussion due to concerns about feasibility in CPRD and potential information governance risks. The protocol was allocated for review by an ERC team with a GP reviewer. Lay review and Information Governance (IG) review was also requested. The outcome following review was that the application should be rejected.

CPRD's Research Data Governance Officer joined the discussion to provide further context on the decision to reject the application - there was a significant likelihood of patients being spontaneously or indirectly reidentified due to the relatively small number of patients in the study alongside the prevalence of information in the public domain concerning the topic of interest. This reidentification risk was not sufficiently mitigated in the application.

The CAC concluded that the study had prompted an important discussion and considered whether there could be an additional review process to evaluate protocols where there is a high IG risk but also high potential for public health benefit. For example, suggestions could be made to try and mitigate the risk to an extent that the research could take place. CPRD indicated that advice was provided to the applicants about potential/ appropriate risk mitigation approaches could be undertaken to enable the research. Protocols with high potential for public health benefit but where the risk of reidentification cannot be sufficiently mitigated can be referred to the Confidentiality Advisory Group (CAG).

The CAC was reminded that CPRD data licences include terms and conditions to ensure that researchers mitigate risk of reidentification and ensure data remains effectively anonymised.

The CAC was asked to note that the recommendation of the IG team takes precedence over the final recommendation of an ERC where the outcome following IG review is 'Reject'.

7. Standing item: CAC members discussion (Susan Jick)

One CAC member nominated ‘evaluating writing quality within a protocol review’ as the standing item. The Committee was asked to consider whether a poorly written protocol indicates that the applicants are incapable of conducting a high-quality research project.

One Member stated that if more than two sections require comments on the writing quality, they will request that the protocol section be rewritten or clarified.

Some Members felt they would not be justified in failing the protocol due to the applicants’ writing quality and conveyed that they found poor writing quality was generally indicative of an inexperienced and unsupported Research Team, or that the protocol was rushed. Some protocols may also be written by students.

CPRD members stated that the Chief Investigator on a protocol is responsible for the study and have a role in assuring the quality of the application before the student submits it for review. It was also clarified that the RDG team does not review writing quality during the triage process.

A Member commented that usually when protocols are badly written, they also usually require other amendments, and although language barriers could be an issue, short sentences can be used efficiently. Several Members agreed that if the content of each section in a protocol could be understood, they would accept poor writing quality and may leave a discretionary comment about the issue.

Some Members felt that if the writing quality is poor enough that the protocol is difficult to review, or the intellectual content cannot be understood, it should be failed or sent back to the applicant with amendments required. Members also felt that standard responses would be helpful for these situations. CPRD advised responses relevant to each section may be more helpful to the applicants, as a standard response across all failed sections may not be easily actionable.

It was also suggested that a poorly written protocol could be brought to a CAC meeting for discussion.

8. AOB (CPRD)

The CAC raised the proposal of the CAC having a session in the future on CPRD Aurum versus CPRD GOLD as many protocols being reviewed currently request either or both. Reviewers may not be aware of how similarities/differences in these datasets would affect the analysis. CPRD agreed that this would be useful, thus it will be considered as a future agenda item.

Regarding protocol resubmissions, the CAC was reminded to leave a comment in the Protocol comment box at the end of the application indicating whether they would like CPRD to handle the ERC resubmission.

9. Summary and Close (Chair)

The Chair thanked the Committee for their contributions to the CAC and the meeting and confirmed that the agreed minutes of the CAC meeting held on the 9th of June 2023 would be published on the CPRD website.

The Minutes from this meeting would be included in the document pack for the next meeting. The next CAC Meeting has already been confirmed to take place on Friday 2nd February 2024 at 3.00 PM.

The meeting was then closed.

Agenda item	Action	Date to be completed by
7	Select poorly written example protocol and circulate to Members to prompt discussion	Future CAC meeting
8	Agenda item on CPRD Aurum versus CPRD GOLD	Future CAC meeting