Medicines & Healthcare products Regulatory Agency

Central Advisory Committee (CAC)

Minutes of the meeting held on 09 June at 3:00pm via Microsoft Teams

Members attending	
Member	**Role**
Mr Edward Chapman	Lay member, and Chair
Dr Emily McFadden	Scientific member
Dr Ben Cairns	Scientific member
Prof Richard Martin	Scientific member
Prof Jo Knight	Scientific member
Prof Umesh Kadam	Scientific member
Prof Li Wei	Scientific member
Prof Jennifer Quint	Scientific member

Apologies	
Member	**Role**
Ms Sherren Smith	Lay member
Dr Kate Fleming	Scientific member
Prof Susan Jick	Scientific member
Prof Deborah Saltman	Scientific member

In attendance	
Attendee	**Role/Post**
Dr Susan Hodgson	Head of Observational Research
Tarita Murray-Thomas	Senior Researcher
Tarryn Gourley	Research Applications Officer
Kirstie Andrews	Research Applications Coordinator

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 current guidance on Clinical Practice Research Datalink (CPRD) triage criteria and the expedited review process.

2. Minutes of the 14 March 2023 Meeting (Chair)

The minutes of the CAC meeting held on 14th March 2023 were reviewed and attendees were given the opportunity to provide corrections or comments. No comments or corrections were made, and the minutes were confirmed as an accurate record.

3. CPRD Update (Susan Hodgson)

The Head of Observational Research (OR) – Susan Hodgson – welcomed both Professor Jo Knight (new chair of Expert Review committee (ERC) 4 replacing Professor Martin Gulliford) and Dr Emily McFadden who is currently serving as the Acting Chair for ERC 7 while Dr Kate Fleming is unavailable.

The Head of OR thanked all members for their contributions to the CAC and those who are continuing their positions after their initial two-year term. Following the meeting, updated terms of references would be circulated to all RDG members who renewed their tenure. In the updated terms, members' and chairs' responsibilities were elaborated to clearly distinguish between the two roles and the role of ad hoc reviewers was included in the terms of reference. The Head of OR requested feedback from members about the updated terms. The Head of OR provided an update on recent developments in CPRD.

- The recent RDG recruitment campaign resulted in the successful recruitment of five new members and a new chair to fill vacancies across various ERCs. New members had completed their orientation training and initial introductions would be facilitated by the RDG Secretariat.
- The new CPRD ethnicity records has been launched which provides categorised ethnicity data for the CPRD Aurum and GOLD databases. This allows a standard process for ethnicity to be categorised when using CPRD databases. More information is available on the CPRD website: https://cprd.com/cprd-algorithm-derived-data
- Medium fidelity synthetic datasets were available for both CPRD GOLD and Aurum. The synthetic data replicates the structure of real data and can be used as a training resource, for machine learning workflows, etc. More information is available on the CPRD website: https://cprd.com/synthetic-data
- Phase 2 development of CPRD's Trusted Research Environment (TRE) had been completed. This consisted of internal testing by CPRD researchers, access to CPRD Aurum and OMOP, and access to Python, R, and STATA. TRE testing is now moving to phase 3 which involves external user testing. Due to the transition plan for data access to be moved to TRE, CPRD are undertaking an assessment to evaluate the implications for the RDG process.

Members requested the link to training resources for synthetic data and it was confirmed the link to the webpage would be sent after the meeting.

4. Secretariat Update (Tarryn Gourley)

Tarryn Gourley provided an update to the CAC on the metrics of protocols received between 14th March and 1st June 2023.

54 new protocols were submitted within this period of which 24 (44%) were triaged as routine for internal review and 30 (56%) were triaged as non-routine for ERC review. Of routine studies that went for internal review, 3 (21%) were approved on first submission and 11 (79%) required resubmission. None were rejected. Of non-routine studies that were allocated to ERCs for review, 2 (12%) were approved on first submission, 14 (82%) required resubmission and 1 (6%) was rejected. CPRD will monitor the difference in resubmissions between applications triaged as routine and non-routine.

Additionally, it was noted that there were a slightly higher number of studies still under review due to the May bank holidays.

Tarryn Gourley then provided an update on developments within eRAP. The most significant development request from feedback was the ability for applicants to amend fields that had already been 'passed', during resubmission. This was previously not possible due to the design of eRAP; however, it is the next focus of developers. This is a major development that involves changes to the architecture of the system but is intended to be delivered this financial year. Attendees were reminded that whilst these developments are underway, when failing a section they should fail all other related sections, to allow applicants to make required changes.

Additionally, the Ethnicity Record Linkage is now available for applicants to request via eRAP, and there have been various minor bug fixes to improve the functionality of eRAP. As well as amendment developments, CPRD are investigating the ability for CPRD to edit some review actions – this is also being explored as an interim solution to the amendment issues. Attendees were also reminded that they may decline reviews that they have previously accepted (for example, if there was a conflict of interest) and the process for doing this was demonstrated.

Members asked, if following the eRAP developments, whether reviewers would be signposted to new changes made by the applicant to sections that were already approved. It was confirmed that eRAP will flag any changes the applicant has made, and all edited sections would need to be approved again. The eRAP amendments / resubmission process was explained and it was clarified that applicants should not change the substance of the original application once it has been approved, only make amendments that are required for the study.

A member commented that synthetic datasets could potentially be beneficial for training for PhD / postdocs and questioned if it would be cost feasible for students. It was clarified that the multi-study license (MSL) incorporates the cost of synthetic data, but that for specific case uses (i.e., without an MSL) it is still affordable. Where synthetic data are used by students, one or more experienced researchers must be involved in the project. It was also clarified that users do not require an RDG application / approval to access synthetic data.

5. Guidance on Implementation of the CPRD Triage Criteria – Non - Routine Criteria Paper 1 (Tarita Murray-Thomas)

Tarita Murray-Thomas explained the purpose and scope of the CAC and the triage process. The review of CPRD's application of the remaining triage criteria for non-routine studies (major public health importance and novel methodologies, Paper 2) that was not discussed at the March 2023 CAC meeting were completed. The application of the triage criteria for routine studies was also discussed.

Non-Routine Studies (Major Public Health Importance)
Validation Studies:
There is currently no requirement to send validation studies for ERC review however these are often triaged as non-standard due to the public health risks inherent in such studies - poorly conducted validation studies may bring into question the findings from the original study and/or undermine the credibility of the CPRD database for research by generating doubt. Members recommended that validation studies should be included for ERC triage.

Clinical/treatment effectiveness studies:

These were predefined for internal review by CPRD. Due to the wide range of such research, CAC previously (Paper 22/02/07) recommended that such studies should also be eligible for ERC review.

Non-Routine Studies (Novel Methodologies)
Attending members were asked to comment on the criteria relating to novel methodologies and specifically whether any methodologies that could now be deemed to be routine e.g. should research using high-dimensional propensity scores (HDP) remain as non-routine given that they are becoming more routine now.

One member agreed that HDP scores should be removed as a non-routine triage criteria as most big data research routinely uses this method. This member added that HDP scores have been in mainstream use for a long time and considered it a standard methodology.

Another member would consider HDP scores within the context of each individual study, as in their opinion although it would likely be a reasonable approach, but it would need to be considered within the context of the aims and methods of the study. Another member agreed that context was important when triaging.

The Head of OR added that the HDP score can be used as a method of catching studies for ERC reviews that might otherwise have been missed.

A member added concern that a recently published paper, using CPRD data, conducted a study on HDP score found its use produced inconsistent results: if not used properly with correct sensitivity analysis etc, this approach can produce poor quality results, suggesting triage to ERCs is likely appropriate in many contexts.

One member felt that HDP scores are still relatively novel as there are still papers being produced that are investigating potential uses. Another member agreed and added that although HDP scores are routinely used in research these studies are not necessarily low risk or routine in CPRD terms, and they are not well reported or consistently applied.

Following this discussion, members recommended that HDP scores should be retained as a non-standard triage criterion due to it being a developing area.

Routine Studies (Descriptive and/or Hypothesis Testing Studies with Standard (Non-novel) Methodology)
CPRD indicated that the criteria for routine studies was relatively straightforward to apply. The triage team proposed some minor changes to some criteria to improve application of the criteria e.g., the reference to drug treatment would be replaced with intervention as exposures could be medicines or devices; although interrupted time series was included as standard design it was not included as a standard methodology and CPRD would update this in the next review of the criteria. One or more criteria were also combined.

Members were asked for advice on whether descriptive studies with an emphasis on clinical pathways that did not include hypothesis testing were likely to represent high public health risk, otherwise these could be reviewed via the routine route (CPRD team). These were regularly triaged as non-routine on the premise that they may benefit from clinical input.

One clinician on the CAC indicated that he was not always familiar with the guidance on a particular area and would need to look this up if a clinical view was required. A second clinician indicated that they would support the decision that descriptive studies with an

emphasis on clinical pathways (that did not include hypothesis testing) could reviewed by CPRD.

CPRD would take the advice and recommendations of the CAC into consideration in its next review of the triage criteria.

6. Guidance on Implementation of the CPRD Triage Criteria – Routine Criteria Paper 2 (Tarita Murray-Thomas)

Tarita Murray-Thomas then explained the triage criteria that are used to assign studies for routine review. The routine criteria concerns studies that are low impact and have low / no reputational risk for CPRD, such as descriptive studies. Attendees were asked for feedback on proposed changes to the triage criteria, which were mainly clarifying the text.

When considering hypothesis testing studies, it is always considered what they are aiming to achieve and what study design is proposed, as well as the methods proposed to achieve that. If these methods overlap with those that ERC should be allocated this might tip a protocol towards ERC review.

The Head of OR reminded attendees that these types of studies are sent for internal review by CPRD researchers and moderation by a CPRD Senior Researcher, so still undergo a thorough review.

Currently clinical effectiveness studies are considered standard; however, it was proposed that only if the study does not include a comparison of equivalence, superiority, signal detection, or protective effect should it be triaged for internal review.

Currently no clinical pathways studies are triaged for internal review as there are no clinician researchers within CPRD and so usually RDG will allocate to ERC with clinician. A member asked if clinical pathways studies are necessary to be allocated for external review, especially if they are descriptive and form a background to bigger studies. It was added that clinical pathway studies are more data driven and if hypothesis testing is in relation to the pathway this would be considered more likely to need ERC review.

In summary it was agreed that clinical pathway studies, if data driven and descriptive, should be triaged for internal review. Clinical effectiveness studies if crossing a certain threshold will be sent to an ERC for review. CPRD would take the advice and recommendations of the CAC into consideration in its next review of the triage criteria.

7. RDG Expedited Review Process (Tarita Murray-Thomas)

Tarita Murray-Thomas explained the RDG expedited review process for the benefit of new members. An expedited review (ER) process was implemented during the COVID-19 pandemic. CPRD would like to retain this process and expand its use beyond COVID-19 applications. As such applications have a faster turnaround than the standard review process. This will be supported and led by the ERC Chairs. Attending members were asked for comments on the expedited review criteria.

It was clarified that poorly planned studies should not be an excuse for expedited review. Applicants would continue to be asked to provide an impact statement to justify the need for an ER prior to their application submission. CPRD would decide whether expedited or routine processing was indicated.

A member asked if the cost was the same for ER requests as standard applications and it was confirmed that there are no costs associated with the RDG review process.

Another member voiced concern about ER requests from government offices or courts potentially being fraudulent. It was clarified that ER requests from MPs or court orders etc are facilitated by contact directly with CPRD from MP offices or lawyers and these contacts are used as a measure of legitimacy.

A member commented that they would expect ER studies to be an even higher quality due to the impact of the study.

Another attendee voiced concern that a review by one chair would not be sufficient for ER, however, it was clarified that the ER process would consist of review by a team or several chairs and a CPRD reviewer, potentially with the addition of a lay reviewer.

One member asked how an ER would be evidenced and if it would go through eRAP with all the details required as per usual, it was confirmed the ER review process still takes place through eRAP.

It was further explained that the time advantage gained by an ER is marginal as the study still must undergo a thorough review, applicants are still required to have approved eRAP accounts etc. The turnaround time was 72 hours during the COVID-19 pandemic, however, this would be raised to 5 working days.

Members questioned the types of ER, who the researchers were, and whether they were from CPRD. CPRD attendees clarified that where CPRD staff are involved in a study, no named members of the team can serve as a CPRD reviewer. This is the same process applied to standard ERC reviews to ensure there is no conflict of interest. All studies for expedited review will be reviewed by a team of ERC Chairs. ERs would never be reviewed only internally.

A member questioned if there is currently a demand for ER now that we are post-pandemic. It was clarified that although the demand isn't expected to be high CPRD still wishes to have the ER process available. Members agreed that they are happy to support the ER process. Another member asked if the scientific review guidance for ER studies is still appropriate. CPRD clarified that the guidance is the same as for any other review with the only difference being the timeline.

One member agreed to be contacted following the meeting to discuss the expedited review criteria in greater detail.

8. Standing Item (Chair)

The standing item was proposed by the Chair and concerned how individual reviewers approach sections for review, with a focus on the 'Research Team'. The Chair commented that previously CPRD did not allow researchers to know who the applicants were to prevent potential bias and asked other members how they approach review of research team experience. Highlights of the discussion are provided below:

- Members concurred that research team experience is an important factor in the review of feasibility and delivery of the research.

- Where possible, one could look up the team members on professional websites or their institutional website. From this, one could judge the team members' professional experience, papers published, and previous funding.
- On some non-CPRD review committees, reviewers are blinded to the research team information. On NIHR Committees research team experience is critical to the feasibility of the research.
- There was a general feeling that CPRD should assure the experience of the research team before the application was sent out for review.
- CPRD confirmed the following:
    - CPRD undertakes a rigorous assessment of prospective applicant's funding/research organisations, to ensure that CPRD data are only accessed by bona fide researchers for public health research which is funded by trustworthy organisations.
    - All applicants must also have an approved eRAP account before they can apply, and so are again vetted by CPRD – this is the first review of the research team before the study is even submitted.
    - During the application validation and triage stage, CPRD also evaluates research team experience based on the number of applicants, range of experience and multidisciplinary input.
- One member asked if any issues have arisen due to the way that ERCs currently conduct the review of research team experience. At the time of the meeting the RDG team was not aware of any issues with ERC reviews relating to this matter.
- CPRD stressed that the research team does not need to be extensively investigated by ERC reviewers. The object of the standing item was to gain an understanding of how members were conducting reviews of this area to gauge consistency in the process.

9. AOB (Tarita Murray-Thomas)

Nothing was raised in AOB.

10. Summary and Close (Chair)

The Chair thanked members for their contributions to the CAC and the meeting and confirmed that the agreed minutes of the CAC meeting held on the 14th of March 2023 would be published on the CPRD website.

The Minutes from this meeting would be included in the document pack for the next meeting. Members will be contacted by the RDG secretariat to establish their availability for the next meeting.

The meeting was then closed.

Agenda item	Action	Date to be completed by
3	Updated terms of reference to be circulated to all ERC members	Next CAC meeting
7	TMT to contact a member to discuss the expedited review criteria in greater detail	Next CAC meeting