Medicines & Healthcare products Regulatory Agency

Central Advisory Committee (CAC)

Minutes of the meeting held on 14 March 2023 at 3:00pm via Microsoft Teams

Members attending	
Member	**Role**
Dr Kate Fleming	Chair
Mr Edward Chapman	Lay member
Prof Richard Stevens	Scientific member
Prof Susan Jick	Scientific member
Prof Martin Gulliford	Scientific member
Prof Richard Martin	Scientific member
Prof Deborah Saltman AM	Scientific member
Dr Ben Cairns	Scientific member (leaving early)
Prof Li Wei	Scientific member
Prof Jennifer Quint	Scientific member

Apologies	
Member	**Role**
Ms Sherren Smith	Lay member
Prof Deborah Saltman AM	Chair

In attendance	
Attendee	**Role/Post**
Dr Puja Myles	Director of CPRD
Dr Susan Hodgson	Head of Observational Research
Tarita Murray-Thomas	Senior Researcher
Zara Cuccu	Researcher
Preveina Mahadevan	Researcher
Tarryn Gourley	Research Applications Advisor
Kirstie Andrews	Research Applications Coordinator
John Latham-Mollart	Research Data Governance Team Leader (attendance for agenda item 8 only)

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. Sherren Smith was welcomed (in absentia) as Lay member and Sonia Patton was thanked after stepping down as Lay member. The Chair informed the meeting that Ben Cairns would be attending later.

The Chair thanked Martin Gulliford for his contribution as Chair, as he will be stepping down once his term of office comes to an end in May 2023. Richard Martin was welcomed as a new ERC chair.

The Chair also congratulated Susan Hodgson for becoming the new Head of Observational Research and John Latham-Mollart as the new Research Data Governance (RDG) Team Leader.

The Chair advised attendees that there would be an opportunity for any other business at the end of the agenda.

2. Minutes of the 28 January 2022 Meeting (Chair)

The minutes of the CAC meeting held on 17th October 2022 were reviewed and attendees were given the opportunity to provide corrections or comments. Tarita Murray-Thomas noted that an issue of lower death rate in CPRD Aurum data raised as an AOB at the previous meeting had been subsequently confirmed by CPRD. CPRD is currently considering guidance for applicants/ users.

No other comments or corrections were made, and the minutes were confirmed as an accurate record.

3. Director Update (Puja Myles)

The Director provided an update to the CAC on recent developments in Clinical Practice Research Datalink (CPRD).

The Director announced that Susan Hodgson was the new Head of OR, and John Latham-Mollart was appointed as the new RDG team lead for Information Governance. The Director advised that John would join the meeting later for the item on PPIE.

The new CPRD ethnicity record was discussed. This will not be a traditional linked dataset however will need to be requested separately on eRAP (as with the Pregnancy Register). Quarterly updates are planned for this record. A paper describing the algorithm, which generates a patient's ethnicity from primary care data and several linked datasets, is being produced. The paper highlights that CPRD-HES provides the ethnicity of 81.7% of registered patients and is broadly representative of major ethnic categories with some overrepresentation of minority ethnic groups.

The production and benefits of synthetic data were discussed. Medium-fidelity synthetic data can be used as sample CPRD Aurum and GOLD datasets to better understand data structure, and for running codes and scripts outside of studies. These two synthetic datasets have undergone privacy risk assessments and the medium-fidelity CPRD Aurum synthetic dataset is already available with the CPRD GOLD synthetic dataset launch scheduled for May 2023. Synthetic sample datasets could potentially be used for teaching, machine learning workflows, or analytical tool development. More information is available on our webpage: https://cprd.com/synthetic-data.

There has been a publication in the British Medical Journal on how CPRD supports digitally enabled decentralised research. The publication in Evidence Based Medicine was co-authored with Birmingham University researchers and outlines how a digitally decentralised approach offers opportunity to open up participation in consented clinical research to a more representative population. This can be achieved by using a data source like CPRD to select patients who meet specific eligibility criteria and invite them to participate in studies via their GPs. For consenting patients long-term clinical and health outcomes can be followed up passively using their electronic healthcare record providing the patient has not left their original GP practice.

The Director gave an update on the development of CPRD's Trusted Research Environment (TRE), which is approaching the end of phase two in March 2023. The phase 2 development provides several analytical tools; R, Python, Stata Atlas suite of tools, and synthetic CPRD Aurum. It also includes access to full CPRD Aurum database along with an OMOP common data model (CDM) version of CPRD Aurum. Phase three will commence in April 2023 and will bring in external users to engage with the process. This version will include CPRD GOLD and CPRD code browser tools. Preceding phase 3, the TRE will undergo rigorous testing of airlocks, logins, and tests by CPRD researchers.

Questions from members:
Members requested access to slides for the Directors Updates and the Director confirmed these would be shared with attendees.

One member asked if there was a process for primarily patient consented studies to go to research ethics committees and how these studies would be reviewed. The Director confirmed that consented patient studies were subject to review by an NHS Health Research Authority (HRA) Research Ethics Committee (REC) and advised anyone interested in such studies to contact the CPRD Interventional Research team for more information. It was advised that there is a separate system for generating feasibility counts and curation of a tailored list of eligible patients as CPRD only has access to pseudonymised patient data. Alerts are sent to GPs who can invite patients to participate in the study.

One member noted the benefits of synthetic data developments and raised whether the quality of the synthetic dataset would be determined by what data goes into the synthetic models, noting that any work in this area would have to be complemented by improvements in data quality. They also asked whether sample datasets were also available for CPRD Aurum, as it used to be for CPRD GOLD.

The Director advised that the recent CPRD Aurum data quality issues occurred when the GP software supplier migrated to a cloud-based infrastructure, requiring establishment of new data flow pipelines. CPRD is aware of data quality issues and has paused releases while actively investigating the issue. Currently CPRD is working to have a dedicated post for monitoring and improving data quality. A new page will also be created on the CPRD website to provide information on data quality. All data quality tests performed are being reviewed. There will be further details available in the next CAC meeting. The CPRD Heads of Observational Research and Health Data Science will be co-leading a data quality strategy for CPRD.

4. Secretariat Update (Tarryn Gourley)

Attendees were reminded of the ongoing ERC Member and Chair recruitment campaign and advised that the deadline for applications had been extended to 24th March 2023.

Tarryn Gourley provided an update to the CAC on the metrics of protocols received between 17th October 2022 and 3rd March 2023. 106 new protocol were submitted within this period of which 46 (43%) were triaged as routine for internal review and 60 (57%) were triaged as non-routine for ERC review. Of routine studies that went for internal review, 11 (24%) were approved on first submission and 28 (61%) required resubmission. None were rejected. Of non-routine studies that were allocated to ERCs for review, 1 (2%) was approved on first submission, 47 (78%) required resubmission and 1 (2%) was rejected. CPRD will monitor the difference in required resubmissions between applications triaged as routine and non-routine. Overall review times are just under 8 working days for routinely triaged studies,

whilst external reviews average just over 11 working days. This is just outside previously agreed timeframe commitments for external protocol reviews.

It was noted that the Christmas period, during which eRAP was closed, may have affected the number of protocols submitted in the period immediately after reopening of the service. Attendees were reminded of some common issues experienced by reviewers and advised that CPRD is planning to address these by adding more automated features to eRAP in future.

Attendees were then asked about the moderation time given for ERCs which is currently 7 working days. Feedback was that 7 working days is currently tight for moderations and contributes to longer feedback response times to applicants. Attendees were then asked to advise what a more reasonable time for moderation would be. Members agreed on 10 working days and CPRD confirmed that a moderation time of 10 working days would be introduced in the new financial year.

Tarryn Gourley then gave an update on eRAP developments. Attendees asked if reviewers will be able to see all updated areas of a resubmitted protocol even if they were not originally failed and it was confirmed that all changes will be visible to reviewers in the updated system. This will be tested before launch.

5. Feedback on ERC Pairings (Tarryn Gourley)

Attendees were asked to provide feedback on the ERC pairings which were initially created in the May 2022 CAC meeting. Attendees were asked if pairs had met since the last CAC meeting. Some pairs had not met and some ERCs are yet to meet with their own team members.

Attendees were reminded of the rationale behind the ERC pairings – to facilitate consistency across the ERC groups. Some members expressed that their understanding was that CPRD would facilitate the paired meetings. Tarita clarified that the RDG secretariat is not responsible for organising ERC pair meetings. A reminder email will be sent to CPRD ERC members who will assist in organising these meetings. The Director reminded attendees that due to international members face to face meetings are not possible. There was general agreement that ERC members should be more responsive to CPRD organisation and provide feedback.

6. Guidance on implementation of the CPRD triage criteria - Paper 1 (Tarita Murray-Thomas)

MHRA Patient Safety and Engagement Committee recommended the CAC provide oversight of triage procedure for CPRD, following the implementation of the Research Data Governance (RDG) Process. The RDG process replaced the ISAC from 1 June 2021. Tarita laid out the current triage procedure; if an application is low risk the protocol is reviewed by CPRD internally, however with an opportunity to escalate to an external review if necessary. An Information Governance review and/ or lay review may be requested for a protocol at any point in the application process from submission to review.

Paper 1 focused on the application of the triage criteria for non-routine submissions by the CPRD RDG Scientific team. The triage criteria for ERC review are classified into four categories; studies of major public health interest/ implications, studies using novel or non-

standard methodological approaches, other studies (e.g. requesting access to sensitive concepts, or submitted by CPRD staff), and studies of uncertain triage rating.

The first area of discussion was research assessing the impact of or challenge to an NHS policy or NICE clinical guidance. Where protocols are assessing this area, the data governance concerns are around whether feasibility concerns or lack of robust methods may lead to spurious findings. Such spurious findings may undermine the guidance/ policy implementation and undermine public health. The triage team considers two perspectives when assessing whether studies included research on NHS/ NICE policy when this is the main study aim: policy effectiveness or novel methods.

One member asked whether we should be basing triage decisions on whether a factor determining the need for non-routine review is listed in the protocol as being a primary or secondary objective, as a secondary objective may not be any lower a risk than a primary objective. Tarita explained the process looks at whether the proposed work is largely descriptive. An example would be a descriptive study that aims to describe trends and is nested in a wider piece of work which is also descriptive; this would be triaged internally for CPRD review, but if hypothesis testing was involved this would be sent to an ERC. It was pointed out that researchers may decide to do hypothesis testing after the protocol is approved, or for descriptive studies to involve comparisons or statistical hypothesis testing and thus, it may be safer to treat all study objectives with the same level of scrutiny irrespective of whether they are listed as primary or secondary objectives.

Tarita requested advice from members concerning if UK primary care experience should be mandatory for all protocol research teams, or if not, that the protocol should automatically be sent to an ERC with a clinical reviewer. One member felt that having a primary care experienced team member should be recommended, as using the data could be challenging otherwise. Another member pointed out that research teams who had been analysing UK primary care data for years should already know the data and felt that only if applicants were a new group without primary care experience could this be an issue. The current guidance of communicating with the ERC group's CPRD reviewer for advice on any concerns was considered sufficient, and usually within the body of the protocol it is apparent if the research team has experience with UK primary care data. Tarita clarified that in the current triage system, if a protocol does not have any investigators with UK primary care experience, then the triage team will consider sending it to an ERC with a clinical reviewer.

One member stated that they had understood that the policy was if the applicants did not have understanding of the data, either through previous studies with CPRD data or experience in primary care, then the applicants were advised to get a collaborator who does have experience. Tarita pointed out that it can be difficult to determine if it is an investigator's first study and would require investigation. Another member pointed out that international applicants often do not have experience with the NHS and it could be useful to know what research an applicant has undertaken before their submitted protocol.

Tarita and Tarryn Gourley clarified that eRAP already requests information from investigators in a summary format – such as experience. It was suggested that CPRD should provide clear information to guide ERC chairs on whether to recommend collaborators with experience to join a study. Tarita explained that during triage one thing that is considered is the multi-disciplinary diversity of the team – whether it has a good spread of experience. CPRD may make recommendations to investigators to add collaborators within the protocol's research area.

The next area of discussion within the triage process was research evaluating health programmes and initiatives. If a study proposes the use of less common methods, it is suggested for ERC review. However, attendees were reminded there is no single reason protocols are triaged for ERC review and other reasons may include the subject area, media impact potential, and whether an MHRA researcher is named on an application. If a lay review is required a protocol is usually sent for ERC review, though lay review can be sought for routine protocols as well.

An example would be a health programme about effectiveness where non-clinical outcomes are considered is triaged for CPRD review vs. when clinical outcomes are considered this would be triaged for ERC review. It was noted that more applications would need to go to ERC for review if drug safety studies are considered non routine. However, this may be a burden on the external review process and the ERC may be lacking in numbers to complete these reviews on time.

It was generally acknowledged that there is a degree of subjectivity with triaging. It is not feasible to have a protocol reviewed by the number of experts required to achieve a homogenous conclusion.

The next area of discussion was studies with a focus on equity in health care (for e.g., access and uptake of health care by vulnerable or disadvantaged populations). All studies where the main objective is access and uptake of health care, regardless of whether it is hypothesis testing, or descriptive studies, are recommended to be triaged for ERC review. Protocols are triaged based on whether the outcome of the study is likely to affect a vulnerable population in which case it is sent for ERC review. Usually, a GP reviewer is suggested for these applications, and the RDG secretariat tries to facilitate this; however, there are no specialist ERCs for this purpose and it is not always possible.

Tarita requested advice from attendees as to whether descriptive studies about rare conditions should come for ERC review and if patients with rare conditions should automatically be considered as vulnerable populations. There was a general agreement that these studies should not be de facto allocated to ERCs, especially if they involve descriptive analysis. One member added that if a protocol deals with a rare condition the possibility of disclosure should be considered, and an IG review should be requested. The applicants should also be asked how they would mitigate these circumstances. It was suggested that an IG review was more appropriate than an ERC review in such cases.

The next criterion was research with a focus on clinical or treatment pathways (optimal care process, sequencing, and timing of interventions by healthcare professionals, effectiveness, variation in care) or that may benefit from clinical review e.g., GP questionnaire studies. A protocol evaluating how a particular population is using primary care, including a GP validation questionnaire or developing a tool for when to treat patients and improve clinical practice, is triaged for ERC review, whereas a purely descriptive analysis e.g., how particular patient populations use health services, is triaged for CPRD review.

The Director clarified that all applications undergo review, even those that are triaged as ‘routine’, and are also moderated by CPRD members who are part of the ERCs. It was noted that internal CPRD reviewers had significant experience in CPRD primary care data, epidemiology, and in moderating reviews, so are still robustly reviewed via this ‘routine’ route.

One member added that protocols on clinical tool development/ clinical prediction rules, provided they’re going to be validated, could be considered routine in the absence of any

other reason for triage to an ERC. Tarita clarified that protocol on clinical tool development/ clinical prediction rules go to ERCs as CPRD reviewers are not clinicians, and these protocols would be recommended for GP review for a clinical perspective. The triage team look at all information written in a protocol e.g., objectives made initially compared to whether the methods can achieve those, and it is weighed up.

One member asked if a protocol going through internal review can be referred for external review by reviewers during the review process. It was confirmed by Tarita that at any point a protocol can be escalated to external review or assigned an additional lay member review. Members suggested an internal review with an external moderator, in light of ERC workload concerns, if that would provide greater public assurance. The Director commented that the independent review of our process recommended the internal review route for routine applications as a more risk-proportionate view and added that this was the direction other review committees were going as well. It was noted that the depth of discussion on the topic highlighted that the triaging of protocols is not straight forward. It was concluded that further discussion is needed, the topic will be brought back in future meetings.

7. RDG Expedited review process - *Paper 2* (Tarita Murray-Thomas)

Item 7 will be addressed via email due to time constraints. Members should look at paper 2 and provide comments/questions/feedback on this item at next CAC meeting.

8. Standing item: CAC members discussion (Chair)

Kate Fleming introduced the standing item which focused on the patient and public involvement section of research protocols. It was noted that there is considerable variation in what is recorded in the patient public involvement (PPI) section and requested clarification from CPRD about PPI review. There were concerns that some applicants are just ‘box ticking’ rather than genuinely understanding the function of patient involvement. One member pointed out that not all PPI is equal – sometimes no public are involved and sometimes PPI is just a box ticked rather than deep involvement – and recommended that PPI should be central to studies to ensure the public benefits. Another questioned if we are pushing investigators further towards box ticking rather than deep involvement by pushing for PPI in the RDG protocol. The Director clarified that from the CPRDs perspective, if PPI hasn’t been involved in a study there needs to be clear justification for this in the protocol and that it is unacceptable to leave this section blank or write ‘not applicable’. It was noted that where applicants were able to reference PPI exercises conducted by others in the same topic area, it could be accepted to avoid duplication of effort.

A member pointed out that there may be cultural differences in non-UK research team attitudes towards PPI. It was also queried whether a key factor determining PPI was the kind of work being proposed for e.g., standard drug safety and data validation studies where there is no clear patient or public stakeholder group. It was emphasised that the assessment of this section requires consideration of the actual benefit and circumstances where PPI can be of benefit.

It was noted that different research funders have different requirements for PPI, if any, and the potential for PPI may vary – i.e., may not be required for a PhD thesis. It was further noted that there are different mechanisms to recompense people for PPI depending on the type of study.

The Director clarified that safety studies may be considered differently. For example, the PPI requirement is fulfilled later at the signal assessment stage, rather than prior to the study.

A member added that applicants may miss the opportunity for patient and public engagement if they do not consider it important. PPI should be encouraged as for many clinical studies it does improve the study. Another member commented that it depends on the research question and if there is a clinical outcome that the study should involve PPI. They noted that in some institutions PPI involvement is standard to improving methodology and forming an application. It was noted that it is possible to have PPI involvement in the writing of the lay summary. A member reflected that there was a lack of processes for PPI and often it has to be built from the ground up for each study, which makes it difficult. Some institutions already maintain a group of people to pick from, however, this is not always the case for other institutions and it shouldn't fall on each individual study to build from scratch. Another member commented that there is a growing body of resources for how to engage PPI available to researchers and they should be encouraged to access them.

Tarita added that guidance has been drafted about how to encourage/undertake PPI for investigators, including a wide range of PPI methods.

9. AOB (Chair)

There was no other business brought to this meeting.

10. Summary and Close

The meeting Chair thanked Members for contribution to the meeting discussions. Members were reminded to send further feedback on the triage criteria to RDG Secretariat and respond when contacted by ERC CPRD members about ERC meetings / ERC pairing meetings.

Agreed minutes from previous meeting will be published on the CPRD website and minutes for this meeting will be available for next meeting for comments/ corrections. Attendees were reminded that the next meeting will be held on the 9th of June 2023.

Agenda item	Action	Date to be completed by
5	ERC members to arrange meetings between pairs and approach CPRD members for support	Before next CAC meeting
7	Members to look at paper 2 and provide comments/ questions/ feedback	Next CAC meeting