Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Minutes of the MHRA GCP Stakeholder Engagement Meeting (StEM)
15 March 2021, 13.30 – 15.30 GMT
Virtual Video Conference

External Attendees:

Organisation	Representative
Alkaloid AD Skopje	Rozeta Mileva Peceva
Anapharm Bioanalytics	Natalia Caparrós
Association for Clinical Data Management (ACDM)	Rob Nichols
Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI)	Ulrike Lorch
Association of Clinical Research Organisations (ACRO)	Derek Johnston
Association of Clinical Research Organisations (ACRO)	Fiona Maini
Association of the British Pharmaceutical Industry (ABPI)	Belen Granell Villen
Association of the British Pharmaceutical Industry (ABPI)	Jennifer Harris
Balanced Clinical Research	John Hladkiwskyj
Biogen	Sarah Deeley
BioPharma Services	Jo Ann Di Sensi
British Pharmacological Society	Michael Hammond
Cancer Research UK	Amber Holmes
Cancer Research UK & University College London Cancer Trials Centre (UCL CTC)	Roisin Beehag
Care Quality Commission (CQC)	Morag Ross
Chugai	Sobia Chaudhry
Clinical Trials & Research Governance, University of Oxford	Clare Riddle
Drug Information Association (DIA) TMF Group	Karen Roy
eClinical Forum	Neil Konopka
EORTC	Christine de Balincourt
European CRO Federation (EUCROF)	Mika Lindroos
European Forum for Good Clinical Practice (EFGCP)	Mary Kearns
European Forum for Good Clinical Practice (EFGCP)	Louise Mawer
Food and Drug Administration (FDA)	Cara Alfaro
Food and Drug Administration (FDA)	Cynthia Kleppinger
Health Sciences Records and Archives Association (HSRAA)	Dora Endreffy
Medical Research Council	Sarah Dickson
Newcastle upon Tyne Hospitals NHS Foundation Trust	Maria Allen
NHS Pharmacists	Anne Black
NHS Pharmacists - MCRN Local Research Network	Penny Bradley
NHS R&D Forum	Kate Greenwood
Research Quality Association (RQA)	Cathy Dove
Research Quality Association (RQA)	Monjit Summy
Sandoz	Dietmar Heigl
Sandoz	Stephanie Limones
Scottish Government	Samantha Carmichael
Scottish Government	Caroline Watson
Scottish Lifesciences Association	Andrew Waddell
Synthon	Diet Gröneveld
The Health Sciences Records and Archives Association	Russell Joyce

UCB	Kasia Nowok
UK BioIndustry Association (UK BIA)	Chritiane Abouzeid
UK Clinical Research Network (UK CRN)	Claire Snowdon
University College London	Jessica Britto Carrilho
University College London Comprehensive Clinical Trials Unit	Tom Lazenby
Vertex Pharmaceuticals	Antonella Cambareri
Vertex Pharmaceuticals	Kath Cresswell

MHRA Attendees:

Andrew Fisher (AF), Lead Senior GCP Inspector
Emma Whale, Senior GCP and GLP Inspector
Funmi Agbesanwa, GCP Inspector
Gail Francis (GF), Expert GCP Inspector
Hayley Dixey, Senior GCP Inspector
Jennifer Martin (JM), GCP Operations Manager and Lead Senior GCP Inspector
Martin O'Kane (MOK), Head of Clinical Trials Unit
Michael McGuinness, Senior GLP Inspector
Michelle Gabriel, GCP Inspector
Paula Walker (PW), Inspectorate Deputy Group Manager and GCP/GPvP/GLP Unit Manager
Rachel Mead, GCP Inspector
Sean Kaiser (SK), Quality, Improvement and Engagement (QIE) Manager

1. Agency Update, including Remote Inspections (MHRA, PW)

PW opened the meeting by welcoming everyone to the Stakeholder Engagement Meeting (StEM). An update was provided covering the following:

- MHRA transformation of inspection model to remote and the challenges faced during the pandemic.
- Development of COVID-19 guidance for managing clinical trials.
- Introduction of the MHRA's new Innovative Licensing and Access Pathway (ILAP).

See slides by PW.

2. Forward Look (MHRA, GF)

GF discussed:

- Passing of the Medicines and Medical Devices (MMD) Act 2021 which gives powers to amend or supplement the law relating to human medicines (and devices). Any updates to legislation and guidance will include the wider network (e.g. HRA and devolved nations) and stakeholder consultation. Some areas may take longer to explore, therefore changes will be conducted in a phased approach.
- ICH E6 currently undergoing extensive review (R3) (GF and AF are part of the Expert Working Group, representing the Pharmaceutical Inspection Co-operation Scheme (PIC/S)). Estimated to be ready for endorsement/public consultation by December 2021 and full adoption November 2022. Will include major revisions to data governance, monitoring and more on proportionality, emphasis on reliability of trial results, rather than the accuracy of every single data point, involvement of subjects in trial design and electronic systems.
- Following on from NIHR Restart, the Clinical Research Recovery, Resilience and Growth (RRG) Strategy was born and is led by the Department of Health and Lord Bethell. It is overseen and coordinated by the Programme Board which includes

Department of Health and Social Care (DHSC), National Institute for Health Research (NIHR), Health Research Authority (HRA), MHRA (MOK sits on the board, GF deputises), AMRC, ABPI, NHSX/D, Office for Life Sciences (OLS) and the devolved administrations. The overarching goal of the strategy is to ensure the restoration of clinical research activity that was underway pre COVID-19 and then to maximise opportunities to 'build back better' and deliver on the commitment to make the UK the leading global hub for life sciences after the end of the EU transition period. More details can be found at www.gov.uk/government/news/uk-government-sets-out-bold-vision-for-the-future-of-clinical-research-delivery

3. The COVID Independent Review (MHRA, SK)

SK discussed the COVID Independent Review where the MHRA is planning a series of stakeholder workshops to gain feedback on its response to the COVID-19 pandemic from commercial and non-commercial sponsors. Further communication on this to be released over the next few weeks.

4. Use of eConsent in Clinical Trials (Chair: MHRA, JM)

- **Introduction, Security, Regulatory Compliance and Challenges (EUCROF, Mika Lindroos (ML))**

ML discussed issues surrounding the use of eConsent in clinical trials, defined eConsent and ways in which this could be achieved, regulations related to eConsent and the impact that COVID-19 has had on uptake. ML also introduced a tool which has been developed by EUCROF to guide those wishing to implement an eConsent solution. See slides by ML.

The following questions and answers were raised:

Q: Are eConsent system providers working with NHS Digital on development and integration of eConsent solutions which are already in place in routine care (for example consent for surgery).
A: For the time being the focus seems to be on development of these systems in the clinical trial setting, but this is something to think about for the future.

Q: Out of necessity, a workaround during the COVID-19 pandemic has been discussion over the telephone and paperwork sent, signed and returned through the post. How do you view this approach?
A: This would very much depend on the process and the GCP Inspectorate would need to review details to comment fully. It is important to consider how the identity of a potential participant would be verified and clear source records should be maintained to document the process (for example where the date of signature of participant would be different from the person taking consent).

Q: In the Subject Matter Expert (SME) group for brainstorming on eConsent, do you have patient group representatives?
A: There is currently no Patient and Public Involvement (PPI) representation but are keen to hear from anyone who was interested in joining.

Q: Is there planned guidance on longterm management of data on remote SDV platforms?
A: The GCP Inspectorate currently has limited experience with reviewing the use of an electronic source data verification (eSDV) solution. Any monitoring conducted should be clearly documented in the Trial Master File (TMF) and available for audit and inspection.

With regards to eConsent it important to ensure that monitors have access to the eConsent system when conducting their reviews, but there should be adequate controls in place to ensure that the sponsor cannot access personally identifiable data.

It also important to be careful to consider how systems are integrated, for example there should be controls in place to prevent personally identifiable data being integrated into an electronic data capture (eDC) system.

Q: What sort of back-up contingency is expected for eConsent processes?
A: MHRA/HRA joint guidance does state that there should be a back-up system for when electronic systems are unavailable.

EUCROF implementation guide also covers the need for a paper back-up system. Most systems would provide the facility to upload a paper consent form where this is used.

It is important to consider the use of eConsent in the trial risk assessment, it may be that eConsent may not be appropriate in some populations or situations (e.g. where internet connection is unstable).

Q: In NHS and non-commercial settings, there are a steady stream of requests for guidance on the use of eConsent but there still seems to be a lack of guidance on the practical considerations for implementation. What are the work-arounds that can be implemented when eConsent systems are unavailable?
A: As experience with the use of these systems is currently limited and few have been inspected it is difficult at this time to pre-empt 'what not to do'. We can provide guidance on what our expectations are but all trials are different and the way in which eConsent is used will differ.

5. Remote Monitoring and Source Data Verification (SDV) (Chair: MHRA, GF)

- **Experience of EFGCP (Mary Kearns (MK))**

MK discussed the Quality Working Party experience on remote monitoring and SDV. See slides by MK.

- **Experience of RQA (Cathy Dove (CD))**

CD discussed the feasibility of remote monitoring; it was noted that it can save time and allows the inclusion of additional SMEs. Conversely, it was discussed that the PI is less likely to engage with remote visits than in-person visits. Ad-hoc deployment of these remote monitoring techniques creates an element of risk. See slides by CD.

- **Experience of ACRO (Derek Johnston (DJ))**

DJ discussed current SDV/SDR definitions as well industry perspectives on re-monitoring of data subject to remote SDV. In addition, ACRO have also developed a 'Quality by Design' manual for decentralised trials. See slides by DJ.

- **Electronic Health Records (EHR) Guidance (MHRA, AF)**

AF provided an update to the current guidance on EHR:

- There are plans to develop guidance on the source data aspects within investigator sites e.g. source data agreements as well as data held in other electronic systems such as electronic Patient Reported Outcomes (ePRO).
- After further engagement in the project in late 2019, a new stakeholder group was created with a patient engagement group running alongside.

- The MHRA published a position statement on the suitability of EHRs in clinical trials back in 2015. In 2020 an agreed position between MHRA, HRA and ICO was published to address direct onsite access of monitors to EHRs.
- A new statement is currently drafted that expands this to remote access to EHRs this is expected to be released in April 2021. This will specifically address the situation where a monitor or auditor has their own login to the system and not have to use a document sharing platform.
- AF extended an invite to other stakeholders that would also like to be involved.

The following questions and answers were raised:

Q: What are the MHRA's thoughts around onsite re-monitoring, will there be an expectation of further SDV?
A: It does depend, an assessment should be done. There may not be a need to repeat SDV unless there was less confidence in the data, if there was a good rationale SDV may not need to repeated. If it was critical data with no follow-up onsite SDV, then a mitigation would be required, which would rely on the robustness of the remote SDV process.

Q: What is your opinion on remote monitoring requiring the redaction of a large amount of identifiable information from NHS sites during the pandemic?
A: The expectation is that personal identifiers should not be leaving the site unless consented to by the trial participant. Through the current pandemic we do not want to see extra burden placed on investigator sites through lots of documents being scanned, redacted and uploaded. This is an unfair burden as the site is already busy and may also be involved in front line activities.

Q: Is there any planned guidance on the long-term management of data on remote SDV platforms?
A: The MHRA have not yet seen remote SDV platforms, therefore it is difficult to give recommendations. Activities should be documented, you need to be able to reconstruct what was done, including the documentation of the issues and how they were escalated.

Q: From a compliance perspective bearing in mind General Data Protection Regulation (GDPR)/data privacy, what is the standard requirement around keeping source data? How long do we expect data sets/scans being preserved, until end of trial or after that? 25 years?
A: The MHRA need to see evidence of the monitoring that was undertaken and that the long-term retention, according to legislation, of evidence is complied with regards to the monitoring plan and SOPs. We also want to avoid duplication of records at investigator sites.

Q: For remote SDV in international trials, the approach should probably be consistent across countries, which might be a challenge.
A: Yes, especially for global trials, as there is different guidance across countries and this can be problematic. Some countries are more stringent in guidance than others.

6. General Q&A (Chair: MHRA, JM)

Q: With regards to posting of investigation medicinal products (IMP) using Royal Mail, The MHRA GCP Guide mentions obtaining a signature. However, during the pandemic this is not possible. Is there any further guidance regarding this?
A: The GCP Inspectorate will consider adding some clarity on this point to the COVID-19 guidance. It is important to ensure that the risk of a package being undelivered or uncollected is considered in clinical trial risk mitigation plans.

Q: With the expected introduction of EU Regulation 536/2016 by the end of 2021, is the MHRA planning any guidance regarding the requirement to retain clinical trial information for 25 years from the date of completion of the trial. Whilst the simplification of the retention period is welcomed, maintaining the integrity of documents and data for this extended period is going to be challenging.
A: As part of updating the UK legislation we will be looking at what is in the Clinical Trial Regulation and consider what we may want to adopt into our legislation. Also TMF guidance will be reviewed.

Q: I would like to know more about the Advanced Therapies Centre Accreditation.
A: There was a stakeholder engagement meeting at the beginning of February 2021, it is still in discussion at the concept stage. Currently considering writing a blog post to put the initial information out.

Q: Can you expand on the examples of inspections that seemed impossible remotely but have consequently been managed?
A: This was in reference to bioequivalence (BE) inspections, often based in India or Canada, and consist of clinical tours, facility reviews and data reviews. It was first thought impossible remotely but are now embedded into current routine inspections.

There was an initial difficulty with investigator sites but the progress of electronic data now allows us to do this. There were also changes to the Phase I Accreditation Programme which is now digital and conducted remotely as well, not all aspects are covered, but the main accreditation can be inspected. The pharmacovigilance inspections in relation to Reference Safety Information (RSI) also lent itself well to remote inspections, while others are more difficult.

Q: Did the MHRA work with the FDA on remote inspection conduct?
A: There is currently an International Coalition of Medicines Regulatory Authorities (ICMRA) working group on inspections, chaired by the MHRA, which includes global regulators such as FDA, Health Canada and Swissmedic. There has been a collaborative approach in discussing the challenges with remote inspections and there is a plan to publish a reflection paper on current experiences.

Q: Are there any plans for blogs or similar regarding the changes and 'new normal' processes in the future i.e. service level agreements for implementing home-care providers?
A: The MHRA are always looking at guidance and the COVID-19 guidance has been updated many times. In respect to homecare providers, we are currently working with the HRA on providing a 'site types' document that outlines, for example, the hub and spoke approach. There have been a few iterations and we are currently awaiting the latest update from the HRA.

Q: The last update to COVID-19 guidance mentioned information on trial participants contacting the sponsor on a COVID-19 agreement, can this be clarified?
A: The wording has now been clarified and it is currently waiting to be published on the website.

7. Summary/Close (MHRA, JM)

JM closed the meeting by thanking everyone who had attended.