Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Minutes of the Stakeholder Engagement Meeting (StEM)
07 May 2019
MHRA, 10 South Colonnade, Canary Wharf, E14 4PU

External Attendees:

Organisation	Representative
AHPPI and British Pharmacological Society	Michael D Hammond
Royal Pharmaceutical Society	Helena Rosado
AHPPI	Ulrike Lorch
ACDM	Rob Nichols
RQA	Barney Horne
MRC	Laura Farrelly
NPCTAG - National Pharmacy Clinical Trials Advisory Group	Mandy Wan
Scottish Life Sciences Association	Andrew Waddell
Scottish Life Sciences Association	Shona Ross
Torbay & South Devon NHS Foundation Trust	Mark Santillo
Association of UK University Hospitals	Heather House
Balanced Clinical Research	John Hladkiwskyj
Care Quality Commission (CQC)	Morag Ross
DIA - TMF Group	Karen Roy
eClinical Forum	Neil Konopka
eClinical Forum	Jonathan Palmer
EFGCP	Louise Mawer
General Medical Council	Joanna Hayman
HRA	Nicola Burgess
HRA	Charlotte Allen
MRC	Dr Rachel Knowles
Royal College of Anaesthetists	Rupert Pearse
Royal College of Radiologists	Dr Nicola Strickland
Scientific Archivist Group/ HSRAA	Eldin Rammell
Scottish Government	Dr Samantha Carmichael
UKCRC	Ms Sarah Qureshi
NOCRI	Matthew Hallsworth
NOCRI	Theo Bond
Nuffield Council for Bioethics	Ranveig Svenning Berg
Royal College of Paediatrics and Child Health	Dr Sabita Uthaya
NHS Pharmacists	Anne Black
ACRO	Derek Johnson
ACRO	Fiona Maini
Dept of Health Isle of Man	Becky Rowley
UKCRC CTU	Patricia Henley
NIHR CRN	Jacqueline Mathews
ICR	Alison Messom

MHRA Attendees:
Paula Walker (PW), Unit Manager Inspectorate Operations
Gail Francis (GF), Expert Inspector GCP
Jenny Martin (JM), GCP Operations Manager and Lead Senior GCP Inspector
Andy Fisher (AF), Lead Senior GCP Inspector
Jason Wakelin-Smith (JWS), Lead Senior GCP & GLP Inspector
Mandy Budwal-Jagait (MBJ), GCP Inspector
Maria Beatrice Panico (BP), Clinical Trials Unit (CTU) Senior Clinical Assessor

1. Introduction and MHRA Update (MHRA, PW)

PW opened the meeting by welcoming everyone to the Stakeholder Engagement Meeting (StEM) at the new offices in Canary Wharf. An update was provided covering the following:

- MHRA is undergoing a period of internal operational transformation.
- MHRA GCP operational transformation has included changes in the inspections process to reflect the increasing use of multiple electronic systems on inspection. PW explained any changes to inspection process will be discussed during the planning stage by the Lead Inspector.
- MHRA GCP Inspectorate use of Office Based Inspection (OBI) experience to date.
- MHRA GCP Inspectorate work and international collaboration with US FDA, Health Canada and PMDA.
- MHRA GCP Non-Commercial symposium announced for 11 September 2019, in Manchester. A separate MHRA-FDA Commercial-focussed GCP symposium is planned for March 2020 in London. The MHRA Inspectorate blog will announce the symposium and will provide full details. It is therefore recommended to sign-up to blog updates.

2. Artificial Intelligence and Experience in Clinical Trials (Oracle Health Sciences, Jonathan Palmer (JP)) & Discussion

Jonathan discussed the emergence of Artificial Intelligence (AI) in clinical trials and some potential uses. See slides by Jonathan Palmer.

The following questions and answers were raised:

Q: Concerns were raised over the ability to test and inspect different versions of the software algorithm which would continuously be evolving. From a medical perspective it is important for the medical doctor to be able to verify the interpretation produced by AI rather than to just accept it. How will the MHRA test and regulate AI software (e.g. in trials using data derived from devices)?
A: JP responded that AI should be viewed as augmented intelligence rather than artificial and there are currently no answers for how this will be regulated. AI is used in various industries and there are individuals in these industries who understand the algorithms and how to use them.
A: MHRA GCP inspectorate added that the devices regulation is also changing which will include the validation of medical devices. It was explained that the MHRA inspectorate and Innovations Office is looking into understanding and learning more about AI and its regulation.

Q: Are there any plans for the MHRA GCP Inspectorate to look into AI further and what are the expectations regarding inspection of AI software.
A: A cross functional Agency group which includes the MHRA Inspectorate and Devices division is being set up to look into AI further. The MHRA Inspectorate blog will be used to communicate any developments from this group.

3. Challenges in Electronic Aspects of Clinical Trials (Barney Horne (BH), RQA)

Barney discussed challenges faced regarding electronic aspects of clinical trial management, particularly regarding the level of validation documentation required of

systems used in clinical trials and use of Electronic Patient Reported Outcome (EPRO) devices. See slides by Barney Horne.

4. Challenges in Developing Technologies (Louise Mawer (LW), EFGCP)

Louise Mawer discussed the challenges faced with the emergence of developing technologies in clinical trials such as mobile applications for Bring Your Own Devices (BYOD) and wearable devices. See slides by Louise Mawer.

5. Discussion and Questions

The following questions were raised following the two sessions on challenges faced with electronic aspects and technological advancements in clinical trials.

Questions raised to the questions raised in Barney's presentation were responded to by the inspectorate as follows:

Computer Systems Validation (CSV)

Q: What are acceptable levels of validation required for software provided by a vendor?
A: A risk-based approach to validation is acceptable and encouraged. The risk would depend on many factors including the criticality of the data being captured and use of the vendor. It should be possible to reconstruct software validation from documentation available. It is expected that the Sponsor/organisation's oversight of the risk based approach to validation can be demonstrated on inspection. There should also be an agreement with the vendor to permit access to and retention of software validation documents. Many eSystems vendors inspected are unaware that these validation documents are essential documents for the trial and therefore do not have procedures to maintain them.

Q: What are the MHRA expectations regarding level of validation required for systems/ registries which derive data directly from the patient electronic health record. What would be considered the source data if a trial is conducted using data from these registries and could it negate the need for a Case Report Form?
A: The electronic health record would remain as the source record as this is where the data was first recorded. The registry database is acting like a CRF and whilst use of such registries are not prohibited in CTIMPs, validation is required to demonstrate that the registry is deriving the data from the source record correctly. It was recommended to discuss use of national registries or databases with CPRD who have experience with use of similar technology.

Electronic Patient Reported Outcome (ePRO)

Q: BH presented scenarios and questions in regard to ePRO questionnaires/ devices. Questions were also raised regarding GDPR when the data is obtained from a patient's own device (e.g. BYOD).
A: ePRO data belongs to the investigator and not the Sponsor. It is the investigator's data and it is required by ICH E6 R2 that the sponsor does not have exclusive control of this data. Critical findings have been identified on inspection and published on the MHRA Inspectorate blog regarding sponsor control and editing of ePRO data. For clinical trials, the legal basis for processing data is not consent under GDPR and so this does not change who owns the data for clinical trials (e.g. if the data is collected for the purposes of a clinical trial then this is the Investigator's data). Further advice is available on the HRA

website. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/

Q:. What are the expectations regarding review of the ePRO data by the Investigator?
A: Investigators should always have access to their data and the metadata associated with it (not just at the end of the trial). Monitors should also be reviewing the data to verify who is entering data, when and confirming any data changes are recorded satisfactorily and explained. Evidence of review of ePRO data by the investigator is evidence of the investigators oversight of the trial and will depend on what is specified in the protocol and the functions of the device. Examples could include, the device has a review function or an audit trail of what the investigator has reviewed. Alternatively, the review could be documented in the source notes.

Q: Is it sufficient for site staff to review data in the audit trail?
A: Yes, if the audit trail clearly shows who did what when, what was reviewed and whether it was acceptable. It would also depend on what data is being reviewed as this would be different for eligibility for example, where the investigator would need to review the data in order to decide upon eligibility. Previous MHRA expectations on self-evident corrections also apply to ePRO data. It is often seen that contracts for ePRO are held between the vendor and sponsor and the investigator is cut out of the process regarding data changes and this is not acceptable, as only the subject and the investigator can agree changes to source data.

Office Based Inspections (OBI)

Q: BH raised issues regarding remote access to systems for OBI where systems are not set up to provide remote access.
A: Remote access is only requested for those systems with remote functionality built in (namely web-based systems such as the eTMF or eCRF). Issues are increasingly seen on inspection where SOPs and training records are held in an internal system to which the inspector is not provided direct access (on site), as the need for access to inspectors had not been considered as part of the user requirements for the system. OBI has been performed pre and post inspection to date. In addition, the MHRA acknowledge the increasing difficulty in providing trial documentation that is held in electronic format either in advance or during the inspection (e.g. document requests). Therefore, the MHRA is testing use of their own portal for the provision of electronic documents for inspection. However, where paper is used by inspected organisation, this is also acceptable and the provision of inspection documents should be discussed with the lead inspector.

6. HRA Update: Restructuring and Approvals (Charlotte Allen (CA))

CA presented changes within the HRA organisation and what this means for clinical trial applications for Research Ethics Committee (REC) and HRA approval. An overview of the Combined Ways of Working (CWoW) pilot for MHRA and HRA resulting in a single opinion for clinical trial applications was presented from the HRA perspective. See slides by Charlotte Allen.

Q: How does one get an invitation to the CWoW pilot?
A: Apply to the HRA (email cwow.admin@nhs.net)

Q: How are changes between the HRA and REC coordinated?
A: HRA ensures that RECs have everything they need for part I and part 2 of the assessment and ensuring that RECs are concise and clear for further requested

information. Essentially a single opinion will be provided incorporating MHRA, REC and HRA review for applications which go through CWoW.

Q: Is there opportunity to fix any issues raised during the HRA review prior to the REC Meeting?
A: Questions raised during the assessment of the study against research governance standards are not ethical questions and so will be different to questions raised during REC review. In order to streamline the process it is intended that all the questions will be provided at the same time rather than separately, unless it is required to validate the application.

7. CTU update (Maria Beatrice Panico)

MBP provided an overview of the CWoW pilot from a Clinical Trials Unit (CTU) perspective. See slides by Maria Beatrice Panico.

Q: Will shortened timelines be applicable to the CWoW?
A: Phase I trials in patients (who will derive no benefit) and healthy volunteer trials have been excluded from the CWoW pilot due to differences in approval timelines between MHRA and REC (e.g. MHRA don't stop the clock whereas RECs do). Aim in future for these types of trial to be included in CWoW, this is dependent on learnings from the pilot and IT infrastructure to ensure timelines for review can be met.

Q: Why are review timelines 90 days for ATIMPs rather than 60 days?
A: ATIMP timelines according to the regulations are 90 days. This is to allow the assessor to consult more people as well as obtain specialist input where required. The timelines are in line with current regulations.

In the UK, for high risk trials, expert advice can be obtained via the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG) and the Commission on Human Medicines (CHM).https://www.gov.uk/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk#applications-that-need-expert-advice

Q: Given the collaboration with the US FDA, is it possible in the future for the MHRA to align Clinical Trial Authorisation (CTA) approval timelines with the US FDA rather than EMA?
A: The remit of the working relationship with US FDA is regarding joint inspections and the use of resource and sharing intelligence, this does not impact on CTA approval timelines.

8. Summary/ Close (MHRA, PW)

PW closed the meeting by thanking everyone who had attended. The following closing remarks were made:

- MHRA GCP inspection strategy review is currently underway. Following external stakeholder feedback the Inspection Dossier is being revised.
- Keep up to date with latest news, developments and inspection issues via the MHRA Inspectorate blog.
- Any further questions following this meeting can be sent through the clinical trial helpline, where queries are directed to CTU and the GCP Inspectorate as appropriate: ctdhelpline@mhra.gov.uk.

- The GCP forum is ongoing and another source of information. The forum can be found here: http://forums.mhra.gov.uk/forumdisplay.php?1-Good-Clinical-Practice-(GCP)

9. Presentations:

I. Artificial Intelligence and Experience in Clinical Trials (Oracle Health Sciences, Jonathan Palmer)

II. Challenges in Electronic Aspects of Clinical Trials (Barney Horne , RQA)

III. Challenges in Developing Technologies (Louise Mawer, EFGCP)

IV. HRA Update: Restructuring and Approvals (Charlotte Allen)

V. CTU update (Beatrice Panico)