



**Minutes of the Stakeholder Engagement Meeting (StEM)
14 May 2018**

MHRA, 501-503, 5th Floor, 151 Buckingham Palace Rd, London, SW1W 9SZ

External Attendees:

Claire Snowdon, UK Clinical Research Network (UK CRN)
Emma Armstrong, UK Clinical Research Network (UK CRN)
Jenny Lamport, The Organisation for Professionals in Regulatory Affairs (TOPRA)
Jonathan Sheffield, NIHR CRN
Professor Rupert Pearse, Royal College of Anaesthetists
Sarah Qureshi, UK CRC
Emma Lowe, DHSC
Heather House, Association of UK University Hospitals
Helena Rosado, Royal Pharmaceutical Society
John Hladkiwskyl, CCRA
Michelle Berkeley, Royal College of Nursing
Sue Waller, Cancer Research UK (CRUK)
Ulrike Lorch, AHPPI
Anthea Mould, NIHR CRN
Jacqueline Mathews, NIHR CRN
Michael D Hammond, AHPPI and British Pharmacological Society
Barney Horne, RQA
Dr Kevan Cassidy, MfE
Russell Joyce, DIA TMF Group
Sarah Rappaport, Wellcome Trust
Liberty Dixon, AMS
Christine d Balincourt, EORTC
Juliet Tizzard, HRA
Kevin Freeman Ferguson, Healthcare Improvement Scotland
Matt Jones, EFGCP
Neil Konopka, eClinical Forum
Derek Johnston, ACRO
Amy Thomas, Human Tissue Authority (HTA)
Alison Messom, ICR
Caroline Watson, NTS CGTC
Clive Collett, HRA
Laura Farrelly, MRC

MHRA Attendees:

Gail Francis (GF), Expert GCP Inspector
Paula Walker (PW), GCP Operations Manager and GCP Inspector
Hayley Dixey (HD), GCP Inspector
Kirsty Wydenbach (KW), Deputy Unit Manager, CTU
Andy Fisher (AF), Lead Senior GCP Inspector
Mandy Budwal-Jagait (MBJ), GCP Inspector
Jason Wakelin-Smith (JWS), Lead Senior GCP and GLP Inspector
Michael McGuinness (MM), GLP and GCP Inspector



1. Introduction and MHRA Update (MHRA, PW)

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

- MHRA is undergoing a period of change and internal operational transformation
- MHRA GCP Inspectorate work and collaboration with FDA
- MHRA GCP symposium announced for 05-06 September 2018, in Leeds. The MHRA blog will announce the symposium and will provide full details. It is therefore recommended to sign-up to blog updates.
- MHRA GCP blog is becoming increasingly used by GCP and the Inspectorate in general and is being widely read globally.
- The MHRA move to Canary Wharf is underway and the York office has also now moved from the FERA site to the city centre (see website for new address).

2. ICH Meeting AMS/ Wellcome Trust Update & Discussion (Wellcome/AMS)

Feedback was provided by AMS and Wellcome Trust from the recent meeting on ICH guidelines. The following was discussed:

- The meeting had discussed how ICH was a potential barrier to health trials being conducted and it was felt that this was a good time to review the scope of ICH as the renovation of ICH E8 and E6 is underway. There was some opportunity to feed in to the formal process but AMS/Wellcome needed to look into how this would be done.
- The meeting was held in March 2018 with over 100 researchers attended
- Key messages coming out of the meeting included: GCP principles were largely positive but issues were in how it was translated, particularly for academic trials that are not for new product development. There was a sense that ICH GCP was being inappropriately applied with a perception that there was no guidance on non-IMP trials therefore overapplication of the principles. What should be used to fill the gap in guidance? High level principles i.e. based on existing GCP principles but would these give sufficient guidance, or would this just lead to having the same outcome of overapplication. A two-tier system was discussed i.e. having an academic guideline. But then would that rightly or wrongly give perception of different standards? How would they work together?
- Meeting was very passionate, lots of engagement, with many really wanting to see changes in this area.
- Wellcome have been looking into short and long-term solutions to this.
- MHRA also attended this meeting and feedback from MHRA representative was similar.

The following questions and answers were raised:

Q. GF MHRA asked what are the next steps? How will you feed-in to the ICH guidance review, will this be done via EMA representative?

A. Yes, but this may not necessarily be the best way going forward.

Q. RQA – do you have representation on the ICH working groups for E6 and E8?

A. No, not directly. ICH have opened the process. Academics have been encouraged to comment when there is opportunity. Working groups however continue to be



restricted to existing group members and academics do not have specific representation.

Further comments. ICH scope is that it focuses on CTIMPs for product registration. Culture change is also needed for misapplication. There may be more time to feed into the ICH annexes. However, it is currently proving difficult to find a good pathway for feeding into the review.

Comments. Royal College of Anaesthetists and R&D Head at Bart's – principles of ICH are never massively going to change. There's always going to be a disconnect between academics and regulators i.e. some academics wanting no rules and regulators wanting rules applied to all clinical trials. Gap between research professionals and academics should be addressed by changing cultures. Wellcome, do you think researchers are found to be applying very strict rules? There are arguments and views that ICH GCP doesn't promote safety. Often it is the same few researchers that voice these opinions, not all are of the same mind. Culture should be the same for all the studies/research.

Comments MHRA, GF – risk proportionate approaches can and should be used. We are still not seeing this being widely applied and a culture change is needed to address this. The MHRA are still working on risk proportionate approaches and trying to engage more with stakeholders on this topic.

Comments. Scottish Life Science – a similar debate on GLP was had many years ago. Ultimately the principles are the principles and should be applied.

3. Digital CTIMPs – Industry perspective (EFGCP/ACRO & MHRA, GF)

See slides presented by EFGCP and ACRO.

MHRA feedback to the slides and discussion points was provided by MHRA, GF:

- Guidance on econsent is ongoing.
- EMA guidance on electronic systems and electronic data will cover a range of areas including medical records, ePRO, eCRFs, econsent, remote authentication, system security, validation, data lifecycle etc. Timelines for release of the guidance are yet to be confirmed as this guidance is currently in its early stage. AF, MHRA is part of this working group putting together the guidance. AF, MHRA commented that the guidance was in its early stages of working group allocation of responsibilities for writing the guidance. A stakeholder meeting was held to discuss what should be covered. Really aiming to try work with stakeholders on this guidance.

Q. Will this be followed by a MHRA Blog?

A. Guidance will be published on the EMA website.

- Medical devices and GCP to be aligned? Currently no formal plans with devices, however GCP are working more with devices and have closer communication.
- Challenges on inspections, challenging to host and discussion of provision of audit trails discussed. MHRA, GF stated MHRA haven't yet seen virtual trials. Inspections do differ, focus different when looking at electronic systems – access to what is needed, does need to be in a sensible readable format. If you are reviewing audit trails, what are you using i.e. during QA review/audit. Up front discussion with lead inspector is encouraged to discuss access requirements etc. User Requirement Specifications for electronic systems should consider



inspectors as they are also an essential user and therefore inspection of the system should be taken into account from the start of the validation process.

- MHRA, GF stated we have been focusing on system vendors, have been inspecting system vendors over past couple of years. Common findings; CSV common issues in the documentation especially with agile approaches i.e. documentation is not sufficient to demonstrate the process was done compliantly and/or documentation was not retained. Issues also seen with data integrity controls such as issues with a lack of investigator control of source/site data. Issues seen with overall project management including amendment management processes being deficient.

4. Bring Your Own Device inspection experience (MHRA, HD)

HD presented a recent case study on a Bring Your Own Device (eduary) trial inspection. The following was discussed:

- A routine GCP inspection included review of a diary application at an Investigator Site inspection to be used/completed on parents/carers phones or tablets. Parents/carers had to complete data each day or ad-hoc, once data completed these would be submitted. Data could not be retrospectively entered or amended via the app.
- Lack of documentation in the TMF demonstrating CROs oversight of the app set-up and validation
- In advance of the inspection several documents/data requested; all relevant manuals, access to portal and demo app, eduary audit trail, helpdesk ticket log and issue resolution as well as standard documents such as monitoring plan, monitoring visit reports etc.
- In general, parents/carers were very keen to use the app at the trial start however this was before they started to use the app and have technical problems which then appeared to lead to disengagement in using the app.
- Parents/carers have had numerous problems in data transferring leading to loss of data and data having to be clarified at site visits. There was no paper back-up system in place.
- Unfortunately, the site hadn't kept clear documentation of escalating each issue found, so it was difficult/not possible to quantify the number of issues raised by the site with the helpdesk to determine the extent of data loss at the site due to technical issues rather than parent/carer non-compliance.

Q. What were the Investigators responsibilities?

A. Evidence of PI oversight/review was paper based in patient's medical records.

5. Reference Safety Information (RSI) Update & Discussion (MHRA, KW)

See slides presented by KW, MHRA Clinical Trials Unit.

KW confirmed that organisations can send in drafts to the CTU for review.

Q. A lot of trials in serious indications such as oncology have life threatening/fatal events which could be expected e.g. chest infection. Does it help to add these to IMP safety profile by classing them all as SUSARs?

A. Agreed and there has been a lot of discussion around this at the European level. Life threatening/fatal = always unexpected, If there is justification then a caveat could be applied if justified in covering letter, or AE section of the protocol. Example - life



threatening chest infection will not be reported as SUSARs due to which can then undergo MHRA CTU review.

Q. ABPI: if comparator is the company approved product can the RSI be the Company Core Data Sheet (CCDS)?

A. RSI should be contained in the IB but could be the CCDS as long as this is clearly specified and submitted for approval. RSI needs to be clearly identified.

Q. Is annual monitoring for RSI changes in SmPC adequate?

A. Yes, no more frequent than an IB would be expected.

Q. Guidance welcome by members for harmonisation. There have been problems particularly in First In Human (FIH) trials, initial RSI no expected serious events, small studies orphan implications, predictable SAEs from pre-clinical, if no meaningful way of quantifying numbers, what should be done?

A. Absolute numbers would be expected rather than percentages for early phase e.g. 0.1% would make no sense.

Q. If numbers increased, then would you be expected to submit an amendment for frequency change?

A. No - submit at annual update. Note, to see only one previous event must be justified to be in RSI as to why it is therefore expected.

6. RQA Inspection Feedback & Discussion (RQA & MHRA, AF)

See slides presented by RQA and MHRA.

No further questions/discussion followed the presentations.

7. e-Consent statement (HRA)

See slides presented by HRA.

MHRA Comment. Publication will also be available via MHRA blog from June onwards.

Q. ACRO, will the guidance include guidance on electronic signatures and acceptability?

A. The EMA guidance on electronic systems will include this.

Q. AHPPI. If a video is a short summary of a Patient Information Sheet (PIS) i.e. to replace info given by Dr/Nurse, would this need to be approved by REC?

A. Yes would be asked to submit, HRA looking into how this would actually be done i.e. the process for submission and review.

Q. If video, could it be the script that is submitted? As delays could be foreseen in having to film, production of videos could take time. and then submit etc.

A. It wouldn't be sufficient to state in the REC application 'we are using the PIS/ Informed Consent Form (ICF) as a basis' so you don't need to see it at REC.

Comment AHPPI. Risk of overcomplication, wouldn't approve the Dr information given. And wouldn't be possible to review individual Dr's.

A. HRA, if a video is available would need to see this, would need some sort of REC approval of video etc. It would not be acceptable for REC to have no oversight. HRA are pragmatically looking into ways of doing this.



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 with the aim to feedback at the GCP symposium on outcome and progress of this review.
- Upcoming blogs to watch out for: CSV, second blog on risk adaption, econsent and GCP symposium.
- 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-\(GCP\)](http://forums.mhra.gov.uk/forumdisplay.php?1-Good-Clinical-Practice-(GCP))