Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Minutes of the Stakeholder Engagement Meeting (StEM)
18 March 2016
MHRA, 501-503, 5th Floor, 151 Buckingham Palace Rd, London, SW1W 9SZ

External Attendees:
GCP
Claire Snowdon, UK CRN
Emma Lowe, UK CRNDerek Johnston, ACRO
Elizabeth Hooper, SAG
Gary Roper, Brunswick Group
Barney Horne, RQA
Will Bowen, HRA
Paul Strickland, EFGCP
Richard Redhead, ABPI
Laura Farrelly, CRUK
Jenny Lamport, TOPRA (via TC)

MHRA Attendees:
Gail Francis (GF), Expert Inspector
Paula Walker (PW), GCP Operations Manager and Senior GCP Inspector
Steven Vinter (SV), GLP Operations Manager and GLP/GCP Inspector
Mandeep Rai (MR), GPvP Operations Manager and Senior GCP Inspector
Balall Naeem (BN), GCP Inspector
Andy Fisher (AF), Senior GCP Inspector
Hayley Dixey (HD), GCP Inspector

1. Welcome

1.1. GF opened the meeting by welcoming everyone to the Stakeholder Engagement Meeting (StEM). All attendees introduced themselves.

2. MHRA Update (PW)

01_StEM_MHRA Update_March2016.p

PW presented a brief regulatory update including timelines for the new CT regulation implementation, HRA approval process, and GCP inspection programme updates. PW explained that compliance reports were no longer being requested and the reasoning behind this, and the current scoping projects being undertaken. It was reiterated that the way the MHRA conduct GCP inspections remains the same. The following questions and answers were raised:

Q. Is the frequency of inspections still the same i.e. low risk organisations approximately every 36 months?
A. The MHRA currently inspect low risk organisations approximately every 4-5years, medium approximately every 3-4 years, and high risk approximately every 1-2 years.

Q. In relation to the scoping exercise, will organisations be required to report this information to the MHRA on a regular/routine basis? I.e. every 2-3 years?

A. This is yet to be determined, however it is possible that it will become an ongoing request to notify the MHRA GCP Inspectorate of any significant organisational changes such as mergers and acquisitions.

Q. What will be the timelines for requesting CROs to complete the scoping exercise?
A. This is likely to be within the next 6 months.

Q. What will be the timelines for requesting non-commercial organisations to complete the scoping exercise? Will this follow on from the CROs?
A. This is likely to also be within the next 6 months, not necessarily after the CROs, this may be requested around the same time.

Q. In relation to the GCP symposiums for 2016, are there any plans to have a separate one focused on GCP in non-commercial environments?
A. No, there are no plans for this. The symposium will be conducted later in the year; there will be two GCP days, which will be a repeat of the same content each day due to the popularity of the symposiums, followed directly by a GLP day. The content of the GCP days will be equally applicable to both commercial and non-commercial organisations.

Q. In relation to the GCP online forum, if a query or area of particular interest was to be discussed are there mechanisms/ways of ensuring the information is more widely distributed?
A. Yes, the intention of the Inspectorate blog is to do this for 'hot topics' relevant to regulatory compliance. The blog is now used to provide further information, guidance and explain the Inspectorate's view point on identified hot topics, for example the recent blog on Reference Safety Information (RSI).

The current MHRA Innovation Office 'one-stop-shop' for regulatory advice on regenerative medicines (including ATIMPs) was discussed as an example of an established cross-regulatory office. The office acts as a single point of contact between the MHRA, HRA, HFEA and HTA. A request was made to circulate the link for this. This was distributed via email in follow-up to the meeting, and can also be found here:
https://www.gov.uk/government/groups/mhra-innovation-office#regulatory-queries-on-regenerative-medicines

3. Trial Master Files (AF)

02_StEM_TMF Presentation_March 2

AF presented on Trial Master Files (TMFs) covering common GCP findings, EU Legislation and Guidance News/Updates relating to TMF, Essential Documents, Data and CRO/Sponsor Interaction and Sponsor Oversight. The following questions were raised and discussed:

Q. What would be the expectation for filing documentation on the trial 'fringe' e.g. system validation documents? It was stated that it is often difficult to provide these at an inspection.

A. The MHRA would expect study specific validation documents i.e. documentation showing validation of eCRF study specific builds to be provided as part of the TMF. General systems validation documentation should be available on request and should be retained/ archived.

An example was provided of an inspection where the TMF was made up of over 40 systems. AF explained the importance of considering where documents and data should reside and be retained; it may be more appropriate to consolidate documents in a document repository system. AF gave the example of generating Monitoring Visit Reports (MVRs) and retaining in a CTMS when the output could be retained in the TMF. It should always be evaluated as to what is best to be retained in the system vs TMF.

Q. In the example above, what about the metadata? The metadata/process audit trail would be in the CTMS, would that be acceptable?
A. Yes this would be acceptable if it was available on request.
Q. So access would still be required to the CTMS?
A. Yes, but guided access may be appropriate to look at specific areas.

Q. When hosting inspections it is often not clear what access and access levels are required for the TMF electronic systems.
A. The core TMF needs to be useable and accessible for Inspectors to navigate. Some eTMF systems have required experts to locate documents. Guided access would be acceptable for the secondary more technical systems i.e. SAS.

AF recommended the use of TMF plans when a Sponsor is working with a CRO and outsourcing TMF tasks to a CRO.

Q. Could a TMF index be used for this purpose i.e. to set out which documents will be retained in which files, CRO or Sponsor?
A. Yes, a TMF index could be used in this way.

Q. Do you think it could go the other way, too much duplication?
A. Yes, this is possible. This is why a TMF plan could ensure this is not the case.

Q. Do the Inspectors review financial documents for a trial?
A. No, not usually as they are not of interest for compliance.

Q. When inspecting at a Sponsor organisation and the trial is being conducted at a CRO, what is expected to be within the Sponsor files?
A. The Inspectors would be looking at Sponsor oversight systems for example meetings/communication with the CRO, Sponsor approval of trial documents, co-monitoring, and internal meetings/communication about the trial.

AF provided the example that during an inspection of a Sponsor the eTMF which should have contained their oversight evidence was virtually empty as they had expected the CRO to do all the filing.

Q. What would be considered acceptable as filing within a TMF in a ‘timely manner’?
A. It is not possible to be specific as it depends on how important it is for the document to be available within the TMF, and there are no regulatory timeframes defining this e.g. dose escalation documents communicating decisions are essential to be readily

available, other documents such as those that are collated from an investigator site may be less urgent and could be filed at a later date.

AF provided the example from inspecting at a Sponsor organisation, 20% of documents uploaded to the eTMF had been uploaded within a week of the inspection this therefore implies the TMF was not inspection ready or readily available.

Q. If improvement of quality of eTMFs is seen over time could the MHRA change the critical finding definition?
A. Significant compliance issues are still being seen (and are widespread); therefore we do not anticipate this will be changed in the near future.

GF reiterated that the TMF continues to be a hot topic in relation to compliance levels.

4. ePRO MHRA Case Study (PW)

03_StEM_ePRO MHRA Case Study_M

PW presented a case study on ePRO. The following questions were discussed;

Q. Have examples been seen of ePRO systems being used well/effectively?
A. GF responded that this was a new area for us to be looking at and as yet we have not looked at a large number of systems. Problems so far have been seen, particularly due to User Acceptance Testing (UAT) not being conducted by the right people i.e. those that will actually be using the ePRO.

AF also added that there are common problems with data retention, and loss of control of data by the Investigator (data and metadata).

With the move towards mobile applications and 'bring your own device', this will no doubt raise many more questions and concerns.

Q. Are you considering and inspecting where the data is being transmitted to?
A. Yes, this would be an area we would look at. Metadata would also need to be considered.

Q. Who can make the changes? If a Health Care Assistant is making entries on behalf of a patient would that be acceptable?
A. We would expect to see patient approval of any changes to their ePRO data in the same way you would expect amendments to be made to paper patient diary cards or questionnaires.

Q. This current trend towards to paperless systems, is this a challenge to the Inspectorate?
A. Yes, this is definitely an ongoing challenge. Direct access is needed to systems.

Q. Whose responsibility is it to arrange for inspectors access to the trial related electronic systems, the site?

A. Assessment needs to be made by Sponsors as to what should be provided.

GF stated that this is an issue for us including Health Records becoming electronic without considering trials/research. This prompted a discussion on the MHRA position statement being released on this. The link to this was distributed post meeting.

https://www.gov.uk/government/publications/clinical-trials-how-nhs-trusts-and-health-boards-can-maintain-compliant-electronic-health-record-systems

Q. In relation to electronic health records and CRA access, would an audit trail be sufficient to show a CRA/Monitor had used the access provided to them appropriately?
A. Yes if there was a contract/agreement in place between the monitor and the site stating that they would only access clinical trial patient data and the CRA had received relevant training on how to do this, and why they should not access any other data, this would be sufficient.

Q. What is the current thinking on CD-ROMs being used to archive data such as eCRFs?
A. Yes this could be acceptable, however the Sponsor would have to consider and ensure integrity of the data throughout the duration of the required archival period.

SV – Organisations need to consider futureproofing early.

AF – Sponsors need to ensure all data and metadata is archived. Examples have been seen of only the flat pdfs with no audit trails being retained therefore the trial cannot be fully reconstructed.

BN – Systems should have change control triggers i.e. changes to IT should trigger a change to ensure risk is mitigated over time.

Also archive areas need to be assessed by Sponsors including at Investigator sites if they are to be archiving source data.

5. Reference Safety Information (BN)

04_StEM_RSI_March 2016.pdf

BN presented on a current hot topic, Reference Safety Information (RSI) and current common inspection findings. The following questions were raised and discussed:

Q. Within non-commercial organisations there seems to be some confusion over what is meant by ‘approval’, i.e. approval of the Investigator Brochure (IB) or approval of IB for each trial it is used for. The guidance previously was not clear on this; will there be updates to the guidance?
A. The blog aims to do this, to provide some clear user-friendly guidance on this.

Q. IB updates are often sent straight to Investigators as updated safety information

A. Sponsors must wait for approval of a substantial change to the IB before issuing as the updated reference safety information (RSI).

It was discussed that systems in place at organisations do not seem to support CT-3 compliance, yet organisations are aware and understand this guidance when asked at interview. It was stated that examples have been seen where the RSI presented at inspection does not resemble the RSI listing in the IB.

BN discussed common problems seen at inspections of non-commercial organisations when expectedness assessments had been delegated by the Sponsor to the Investigators. Investigators are often not aware of the RSI and make their expectedness assessments against clinical knowledge e.g. events anticipated in the patient population (rather than events expected against the RSI). Training of Investigators in this area is key. This appears to be a fundamental difference between commercial and non-commercial pharmacovigilance. With commercially sponsored trials the expectedness assessment is very rarely delegated to Investigators. BN stated that there should be no reason for inconsistent assessments, the assessment should be made against the RSI listing with a Yes or No answer as the output i.e. is it listed or not. There is generally no need for complicated medical judgement.
All attendees were directed to the recently published blog on RSI. The link was distributed post meeting. GF requested that if it was found that further information was required then StEM committee members should inform the MHRA as this is a hot topic and it could therefore be useful to publish a second part to the blog.

https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/

6. Closing (GF)

In closing the meeting GF requested for feedback and discussion about future StEM meetings.

All agreed the format used at this meeting worked well, a round table discussion rather than classroom type presentations. Today's format encouraged helpful and useful interaction.

GF requested for other members to present to the MHRA, members stated they would be happy to this, yet felt insufficient time had been given to do so for today's meeting, and the agenda was set based on suggestions alone without further requests/discussion.

Members discussed the usefulness of the meetings and felt the meetings should be held at least annually. Members also stated that as members it could perhaps be made clearer what's expected of them, and they should ensure the information is disseminated within their organisations.

Members requested information on the other GxP StEM meetings; the contact details for enquiring further about these were distributed post meeting.