Medicines & Healthcare products Regulatory Agency

MHRA

GCP Laboratories Stakeholder Engagement Meeting Minutes

Date: Tuesday 7th May 2019

Venue: MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU

Chair: Andrew Gray, MHRA

Attendees: Roisin Beehag, UCL
Samantha Carmichael, NHS Greater Glasgow & Clyde
Richard Cowie, Chief Scientist's Office - Scotland
Owen Driskell, NIHR CRN
Greg Elgar, Genomics England
Linzi Gillbanks, ACRO
Vanessa Grant, RQA
Steve Hoare, ABPI
Heather House, Association of UK University Hospitals
Okdeep Kaur, UK CRF Lab Managers Group
Simon Kerridge, UKCRC CTU
Peter Maple, IBMS
Elena Perez-del Notario, CR-UK
Stephen Roberts, HRA
Shona Ross, Scottish Life Sciences Association
Morag Ross, CQC

Stephen Vinter, MHRA
Jason Wakelin-Smith, MHRA (minutes)
Paula Walker, MHRA

Apologies: Ben Courtney, UKAS
Eldin Rammell, HSRAA
Christiane Abouzeid, BIA
The Russell Group of Universities

Introduction to the Stakeholder group – participants, purpose and terms of reference

Attendees were welcomed to the first meeting of the MHRA GCP Laboratories Stakeholder Engagement Meeting (StEM) and participant introductions given.

Stakeholder engagement with laboratories analysing or evaluating samples collected as part of a clinical trial has historically been via the main GCP StEM with mention of the inspection programme included at the Good Laboratory Practice StEM meeting also. Due to the technical and specific nature of the work undertaken by GCP Laboratories a separate StEM meeting for GCP Laboratories has been convened.

The StEM is intended to provide our stakeholders a forum for discussion on interpretation and implementation of Good Clinical Practice in laboratories analysing or evaluating samples collected as part of a clinical trial; issues of general concern or interest and to provide an opportunity for discussion on the operational aspects of the MHRA GCP Inspectorate related to the analysis of clinical trial samples. It is intended that this meeting is a two-way exchange and input into topics for discussion is welcomed.

Membership of the StEM will continue to expand as we identify additional organisations, professional bodies and interested parties and any suggestions can be sent to jason.wakelin-smith@mhra.gov.uk for consideration.

Inspectorate sources of information and communication channels

The MHRA laboratories group uses the following sites for providing and receiving communication:

- MHRA Inspectorate blog (https://mhrainspectorate.blog.gov.uk/)
- MHRA website (https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials)
- Laboratory team mailbox (gxplabs@mhra.gov.uk)
- Clinical trial helpline (ctdhelpline@mhra.gov.uk)
- MHRA Labs Symposium – attendees were invited to contribute hot topics for consideration for the next event.

MHRA action – to produce a blog covering this stakeholder meeting

The MHRA GCP Forum was also raised during the wider discussion as an area where laboratories could post questions for response by other users. A clinical laboratories section exists and can be found here: http://forums.mhra.gov.uk/forumdisplay.php?4-Clinical-laboratories.
(post meeting note – the GCP forum is moderated by the MHRA GCP Inspectors but we do not tend to respond to queries raised here. If you wish to have a response by the MHRA then this should be submitted to the laboratory team mailbox or clinical trial helpline).

Attendees were reminded of several guidance documents (not an exhaustive list):

- European Medicines Agency (EMA) Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-laboratories-perform-analysis-evaluation-clinical-trial-samples_en.pdf)
- MHRA Guidance on GxP data integrity (https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity)

Attendees were also encouraged to provide input into various documents currently being revised by the EMA/ICH including:

- ICH M10 on bioanalytical method validation (https://www.ema.europa.eu/en/ich-m10-bioanalytical-method-validation). We are involved in the revision of this document as an observer expert.

(post meeting note – ICH E8(R1) General Considerations for Clinical Studies is also currently under revision and contains high level mention of laboratory sample analysis)

The Laboratories Group actively participates in activities with the EMA Inspectors Working Group (GCP and bioequivalence sub-group), CMDh; US FDA and Health Canada alongside frequent interactions with European colleagues and other global regulators. We are also active in promoting our opinions and viewpoints at a variety of international conferences.

Introduction to the GCP laboratories inspection programme

A brief presentation was given setting the regulatory background for inspection and describing the development of the risk-based inspection programme. This included a few common high-level problems seen during set-up of the inspection primarily related to the provision of accurate information relating to the work undertaken by the lab as well as issues seen during inspection.

Clinical trial sample analysis and BS EN ISO 15189:2012

The MHRA recognises laboratories which are accredited against ISO 15189 in that the accreditation demonstrates that the laboratory participates in an external quality assurance programme and is likely to have the technical capabilities to conduct clinical trial sample analysis. However, inspection is still required to determine the compliance of the laboratory with the Medicines for Human Use (Clinical Trials) legislation and applicable guidance.
It is common that less time is spent on aspects such as the quality management system, technical training and equipment when inspecting ISO 15189 accredited laboratories with a focus on GCP aspects (such as serious breach reporting; protocol compliance; blinding; informed consent) and the verification of trial data generated by the laboratory.

Work was previously conducted with UKAS/CPA to look at common topics and audit/inspection approaches, but the clinical trial legislative requirements are complemented by but not replaced by ISO 15189 therefore both reviews remain necessary.

Feedback was received during the meeting that lapse of UKAS accreditation at an NHS site had caused a sponsor to hesitate in opening a trial at that site despite there being no requirement within the clinical trial legislation for laboratories to be accredited only that they comply with the legislative requirements and associated guidance. This suggested a lack of sponsor awareness of the clinical trial requirements.

GCP training for laboratory staff

Attendees were directed to a Inspectorate blog post (https://mhrainspectorate.blog.gov.uk/2018/11/05/making-gcp-training-relevant-and-applicable-its-not-just-for-clinical-staff/) which describes the expectations for GCP training and staff awareness of clinical trials within laboratories. In summary training requirements depend on the role(s) and responsibilities undertaken. Training requirements may vary from simple awareness that the laboratory is involved in the analysis of clinical trial samples and who to contact in the event of a problem through to more developed GCP and clinical trial focused training.

Multi-track analysers

It was discussed that the analysis of clinical trial samples on analytical platforms as part of a multi-track where clinical trial samples are handled in exactly the same way as routine clinical samples are generally considered low risk by the inspectorate, especially where the laboratory is accredited to ISO 15189. Problems have been seen where trial samples have had additional parameters analysed as part of a standard panel where the protocol and informed consent did not state that these tests would be conducted. This can then give rise to an ethical dilemma - what to do if you analyse additional parameters that you don't have consent for, and it comes back with a significant result? Another significant problem can arise with the automatic publication of results which may impact on the blinding of a trial.

MHRA action – to publish a blog covering the use of multi-track analysers in the analysis of clinical trial samples.

Safety labs

It was discussed that the focus of the inspection programme is laboratories generating data to support primary and secondary objectives or where laboratory data is used for key decision making (e.g. dose escalation, eligibility) however legislation and guidance does not differentiate between these laboratories / tests and those performing routine safety bloods or those generating data not directly linked to the trial (same applies to exploratory endpoints). Therefore, all laboratories involved in the analysis of samples, regardless of whether it is a primary, secondary or exploratory endpoint,

originating from a clinical trial should implement appropriate measures to assure the quality and integrity of the data whilst ensuring subject rights are not compromised.

From a practical standpoint an inspection tends not to focus on the safety laboratory sample analysis but may review some aspects such as control of blinded data and the tests being requested/conducted as part of the trial.

Discussion and questions

The following points were raised for discussion:

Lack of awareness within NHS laboratories about the requirements for laboratories involved in clinical trial work, suggesting that there is a need to put more information out in the public domain. This included mention of laboratories involved in therapeutic drug monitoring which may impact on the blinded nature of a trial and reflex testing in response to out of range clinical results.

A suggestion was made to establish a community of practice to consider how this could be improved.

MHRA action – to progress the set-up of a group to look at how the profile of clinical trials in non-commercial laboratories could be raised.

It was mentioned that the establishment of a small group had already been considered by the MHRA to support activities like that established for pharmacy (National Pharmacy Clinical Trials Advisory Group) and it was agreed to progress this.

Similarly, it was requested that more information be made available about the conduct of a GCP laboratory inspection such as how is an inspection planned, conducted including how is information reviewed, the topics inspected and example findings. Awareness that inspection fees would also be due following an inspection was also raised. Mention was made again of the EMA reflection paper which clearly sets out the expectations for laboratories undertaking this type of work and of the MHRA laboratories symposium next March (2020). Inspection findings are often used at symposia to illustrate what common or issues of interest and examples will also be used during future StEM meetings to guide discussion where relevant and useful.

MHRA action – to consider publishing a blog describing the conduct of a clinical laboratory inspection.
(post meeting note – there is likely to be a topic at the GCP non-commercial symposium to be run later this year relating to sponsor/host organisation oversight and awareness of laboratory activities. We will ensure that mention is made of UKAS accreditation and clinical trial requirements and the sponsor interactions described below).

Of concern was the feedback given that some laboratories were declining trials as a mechanism to keep the MHRA away. It is likely that this is influenced by the local lack of knowledge about the inspection process and should certainly not be a barrier to participating in research.

Sponsor Interactions were discussed, in particular where the laboratory had little or no awareness of the trials being conducted; what was included in the contract between the site and the sponsor/CRO; implementation of amendments or even being provided with the protocol and subsequent amendments in the first place. This is likely to be best managed via the investigator site's capacity and capability assessment process.

The relationship between UK and US FDA was raised in the context of UK laboratories not being told where data was to be submitted so that appropriate regulatory standards could be applied. It was confirmed that there is no mutual acceptance of data arrangement for clinical trial data (unlike data generated for Good Laboratory Practice for preclinical and safety studies) therefore laboratories could undergo inspection by the FDA. The inspection approaches used differ between the FDA and MHRA

in that those conducted by the FDA tend to be based on a current application whereas MHRA operates a systems-based approach to inspection. The MHRA has a good open dialogue with the FDA and if discussion points arise from inspection by US FDA (or other foreign regulators for that matter) then please let the inspectorate know via gxplabs@mhra.gov.uk.

(post meeting note – the current revision of ICH M10 may assist with this in the future. Details can be found here (https://www.ema.europa.eu/en/ich-m10-bioanalytical-method-validation).

Post-Meeting Comments

The MHRA would like to thank the attendees for coming and for providing valuable input into this first stakeholder engagement meeting. We hope you found it useful and we look forward to working with you as this meeting develops.

The next meeting will be held in 2020 with details to be communicated in due course and will include information relating to the MHRA inspection process and sponsor vs laboratory responsibilities as requested during this meeting.