ECMC GCP Training Day
20 November 2013

Q&A Panel

Q: How can you assess the effectiveness of an internal audit?
A: It's important to try and make the audit process seen as a benefit, for example by proposing process improvements or identifying redundant processes that will make things easier for the audited parties. Gaining feedback from those who were involved in the audit is also a valuable tool in improving the benefit and effectiveness of future audits.

Q: How long should you wait before asking for feedback?
A: Obtain feedback as soon as possible. Feedback is best gained this way as it is fresh in the mind.

Q: What are your views on the calibration of general laboratory equipments such as heated plate shakers, clocks etc? If calibration is recommended, how frequently should it be performed?
A: GCP guidance says that you have to demonstrate that equipment is fit-for-purpose, therefore it depends on what the equipment is used for.
Clocks: don't need to be calibrated but you should ensure that they say the correct time so check them every time the clocks go forward or back. You could look at getting synchronised clocks in different areas.
Plate shakers: depends on the criticality of the assays so go by the manual or manufacturers guidelines

Q: We have two platforms which we use for sequencing plasma and tumour tissue samples. Would this area need to be GCP validated as it is purely research?
A: The guidelines and regulations aren't clear therefore it would depend on the patient endpoint. The investigator should be an expert but it should be reviewed on a case by case basis. The MHRA recommends a risk-adapted approach.

Q: Do lab staff need to see evidence of consent before processing samples?
A: Labs need to show due diligence that consent has been asked for. This can be done in a variety of ways (eg. An email from Sponsor confirming consent has been given). Keeping copies of patient consent forms in the lab is not recommended, irrespective of whether this has been consented for (and has ethics approval as data protection legislation also applies. Requirements for notification of consent (and withdrawal of consent) from the Sponsor should be clear in the contract.

Q: Is an analytical laboratory expected to maintain paper file (TMF) of key trial documents such as contract, protocol, lab manual etc, or are electronic copies sufficient?
A: This depends on the specific procedures of the lab and whether they have paper or electronic document management processes. The TMF is the responsibility of the sponsor and these documents will be retained by the Sponsor. Laboratory records related to analysis however do fall under the scope of essential "source documents", and as such should be

retained for as long as is stipulated in the contract, or clinical protocol (in a paper or secured electronic format). Electronic copies (i.e. scanned copies of paper records are acceptable if these are authenticated copies of the paper originals so a clear process for ensuring all copied records have been authenticated would need to be in place. All parties should retain a copy of the contract. Retention of electronic records (e-data) depends on the system and if it is validated, or if these records are maintained in a secure location with secured, restricted access (i.e. restricted access folder on your network), this would be sufficient.

Q: Is it necessary to have a blind copy of the consent and the Patient Information Sheet in the lab so that staff know what patients have consented for?
A: It's good practice. It should be stated in the clinical trial protocol what patients are consenting to and the lab should have access to this. The sponsor and the lab should ensure that all of these elements are covered in their working agreement. The protocol will have had ethical approval so there is no need for copies of the consent.
EMA guidance states that there should be a communications mechanism for the withdrawal of consent as this is a more important issue.
[Comment – samples that are kept beyond the life-time of a trial go beyond the protocol and therefore it would be important to have the consent and the PIS for if there was any future analysis]

Q: What level of flexibility can be put into a protocol as technology is moving very rapidly and sometimes samples are banked for a couple of years before being analysed?
A: As long as you provide all the information that is required by the regulations it should be fine. You need to justify why you are being flexible in the protocol.

Q: If an analyst has developed an assay and no one has done it, who should be responsible for declaring them competent/trained in that assay?
A: It is management's responsibility as they are responsible for providing adequate facilities and appointing suitable trained and qualified personnel. You can be self-taught in the lab world; This should be recorded in training records to demonstrate competency/ expertise and management can authorise these records.

Q: If a clinical trial sample is being used for an exploratory study must it be analysed to GCP standard?
A: It would depend on the exploratory study; if there is a patient endpoint it would need to be done to GCP standard. This would need to be clearly documented in the contract.

Q: What happens if a laboratory and clinic have different procedures for chain-of-custody?
A: The chain of custody is the responsibility of all parties and full traceability of sample movements must be demonstrated (as a result of combined records from all parties. Deficiencies n the procedures/ documentation can (and should be mitigated by clarification, additional recording of information This issue should be discussed with the sponsor and agreed up front with clear documentation.

Q: What are the consequences of a serious breach or fraud?
A: There are lots of consequences and they depend on the nature of the breach. Fraud has the highest penalty. The Sponsor will notify and liaise with the MHRA who will assess any breaches and internally set up an Inspection Action Group which will follow up with the Sponsor on the outcome of the Sponsors investigation, or take consequential action, if necessary. This group can also call for reinspection, enforcement activity, halt the whole trial or halt the trial just at that one site. The Sponsor would be actively involved in these actions (and may perform these actions as part of their procedure. They will also undoubtedly commission an audit to establish the root cause of the Serious Breach.

Q: For the data that is archived electronically, do you recommend to perform data retrieval exercises? If so, how often should these be done?
A: Of course. You need to demonstrate that the data is readable for the period that it needs to be retained for, and the frequency of retrieval is a business decision, which should be defined in the relevant SOP. The data needs to be in a human-readable format for the duration of the retention period, therefore consideration must be given to retain/maintain the hardware/ software that was used to access your legacy data. For example if the data is on floppy disks then you still need to be able to read these, if these are held within the archive retention period.

Q: If a sponsor has signed the contract for analytical work and this contains a plan of work, do they also need to sign off on the analytical study plan?
A: Technically they don't need to if it is covered in the contract. However practically many staff do not have access to the contract but do need to see the analytical plan. There is no need for two documents if the contract is accessible, updated, followed and consistent with the protocol.

Q: What happens in terms of validation with equipment-related software?
A: You need to validate some aspects especially with data capture: where it is captured; where it goes; can it be changed, can it be deleted. This is acceptance testing really.

Q: Are laboratories that are carrying out exploratory studies only (e.g. investigating whether there is a relationship between a biomarker and outcome) required to comply with the MHRA GCP for Laboratories guidance? (see earlier question for answer)
Following on from the above question, if a laboratory is accreditated by another scheme (e.g. CPA), must they still agree to comply with GCP for Laboratories?
A: If you are analysing samples from a clinical trial there will be some GCP that you must follow. What is missing from CPA is dealing with human samples where consent etc still apply.

Q: What are the 5 key things you look for in an analytical site when you audit?

A: 1) Awareness of GCP-specific aspects
2) Awareness of individual roles and responsibilities
3) Robust and clear procedures
4) Clear documentation
5) Robust sample handling management and assays

Q: What happens when a receiving laboratory and a clinic have different procedures for chain of custody? Worst case scenario: clinic sends samples without chain of custody forms despite receiving facility requesting sample details such as how many to expect and list of sample identifiers before sample shipment. Clinic was under the impression that chain of custody was not their responsibility. So whose is it? [Is it ever acceptable to have an obscure chain of custody?]

A: A chain has more than one link therefore is the responsibility of all parties. The chain of custody needs to be clearly documented and in the absence of information from one party, every step must be taken to record this information by the other party. Please see earlier question (and response)

<u>Questions submitted in advance but not answered at the meeting</u>

Q: Electronic files – can we PDF paper records (e.g. Certificate of Analysis) and destroy the paper version?

A: Yes, some paper records can be pdf'd provided that there is a process whereby each pdf is authenticated as a copy of the true original (accurate and complete). The process should itself be documented – i.e. a signature and date from the person confirming the authentication. However, you need to be careful that the pdfs are still readable and remain readable and secure for the period of retention.

Q: If a new version of software is introduced to a validated computerised system, what level of re-validation would be required?

A: I would suggest reviewing the release notes to establish what functionality is changing in the software. Then we would compare these changes against our user requirements. Any change that affects a user requirement must have the corresponding UATs updated. Consideration may also need to be given to requirement unaffected by the new realise, but that have direct functional links to the affected requirements.
Also, if the change is significant you should do some regressive testing on top of testing specific requirements to ensure general functionality was not affected.

Q: Are hard copy or electronic lab books preferable for GCP analytical work?

A: Either option is considered acceptable provided that any system being used to manage documents has been validated to show that it is fit for purpose with adequate security, e-sig and audit trail functionality. Either form of records (electronic or paper) should accord with the criteria described in the EMA reflection paper on electronic source documents: Accurate, Legible, Contemporaneous, Original, Attributable, Complete, Consistent, Enduring and Available when needed.