TMQA BLOG # 1: CLINICAL TRIAL AMENDMENTS

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There is more to implementing an amendment than obtaining the relevant approvals. The distribution of the amendment, provision of any necessary training and obtaining subject re-consent (if necessary) must also be taken into account before an amendment can be considered to be properly 'implemented'. This blog discusses some common issues related to the implementation of substantial amendments detected during audits and some of the issues are also transferable to the management of non-substantial amendments.

Amendments are regarded 'substantial' when they are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant[1]. Amendments can also impact the conduct or management of the trial or the quality of the Investigational Medicinal Product and may constitute changes to the Investigator's Brochure (IB), Investigational Medicinal Product Dossier, Patient Information Sheet/Informed Consent Form (PIS/ICF), etc. The sponsor (sometimes with the help of an established advisory committee) is responsible for determining whether an amendment is substantial or non-substantial and retaining documentation supporting the decision. There is immediate application of changes allowed when it is necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s))[2]. When the sponsor and/or the investigator has taken urgent safety measures to protect the subjects against any immediate hazard, the sponsor shall forthwith inform the Competent Authorities (CAs) of the underlying events and the measures taken and the Ethics Committee (EC) is required to be notified at the same time[1].

It is often noted during audits that it can take several months to implement an amendment (sometimes even up to a year), which cannot be considered a timely roll-out of the required changes. The following are some common issues:

- It takes a long time to submit a protocol amendment (sometimes months) as the related documents are not prepared (and translated, if applicable) in a timely manner.
- It takes long to review the amended documentation by the CA and/or the EC/Institutional Review Board (IRB), or to receive the required decision documentation from the authorities (there is often no documented follow-up by the sponsor and/or the investigator). The amendment review process can be protracted in some countries, but the sponsor/delegate should exercise due diligence and follow-up on the status of the submission (which should be documented). Also, it is not always obvious from the available documentation when the decision documentation was received by the sponsor/delegate. This is especially important if the CA/EC/IRB issue the documentation with a delay relative to the decision date.
- The amended documents and approvals are provided to sites with a delay. Also, the date of receipt of the documentation by site cannot always be determined from site records (e.g. for the receipt of hard copies of documents such as PIS/ICF).

- The necessary training to site staff is not provided in a timely manner (e.g. by the monitor), it is not provided at all or the training documentation is lacking.
- In-person training by the monitor is mandated prior to amendment implementation but this may not always be necessary. The Principal Investigator may be able to document that the amendment has been understood by him/her and the site staff trained accordingly.
- The roll-out of new procedures or sub-studies introduced via the amendment is delayed despite approval due to unavailability of the required equipment, materials, documentation (such as manuals), staff (such as qualified specialists), etc.
- New or amended procedures introduced via a protocol amendment are conducted prior to subject consent, for example the testing of additional laboratory parameters. The central lab is not informed that the relevant approvals are in place (e.g. per country) or that the subject has been consented with the updated PIS/ICF prior to testing.
- The amended protocol requires new data to be captured in the Case Report Form (CRF), however, the CRF is not modified in a timely manner to allow the collection of additional data by sites or it is not updated at all.
- Updated reference safety information (introduced via an IB update) is used for expectedness assessments of adverse reactions prior to the necessary approvals of the IB update.

These are some of the risk factors (you may be able to add others of your own). Identification and management of these risks will promote the safety of the subjects and the scientific validity of the study by ensuring speedy dissemination and implementation of protocol amendments.

References

[1]Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001
[2]ICH E6 (R2) 4.5.2