

ICH E6 (R2) - Changes in a Nutshell

Expectedly in November, the International Council for Harmonisation (ICH), as is their new name as of October 2015, will release the final revision 2 of their E6 guideline, Good Clinical Practice.

Currently we have to go on the final draft for what the changes will be. The amazing thing about this second revision (the first constituted minor textual changes, no content changes) is that the outlined responsibilities in the original version have not changed! R2 only adds to the original text. It doesn't change anything from what we already know and do. It mainly specifies some responsibilities and adds today's world to a 20 year old guideline.



1. Quality Management

New: Yes, but then again...

Affects: All Clinical Research Professionals

The biggest impact of the update is the added Quality Management. ICH has taken the FDA and EMEA guidance on the Risk Based Approach to monitoring and combined those two to add Quality Management to GCP. Chapter 5.0 starts by stating that 'the sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials'.



'Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected.'

ICH continues to describe the risk based approach as:

1. Critical Process and Data Identification
2. Risk Identification
3. Risk Evaluation
4. Risk Control
5. Risk Communication
6. Risk Review
7. Risk Reporting

Is this something new? Well, describing the approach is certainly for GCP new. But taking a risk based approach was never not allowed! Many sponsors have opted for what they considered the safest approach. Fully quality controlling the data collected and micro-managing sites.

The more sensible approach is to put effort and energy into those activities that have the biggest impact on the level of quality of our trials. Risk Based Monitoring and Quality Management is basically the embodiment of that sentiment.

When discussing trial monitoring in 5.18.3, ICH specifically adds the use of a Risk Based Approach to monitoring. It is clarified that a strategy needs to be chosen (and documented) which can be a combination of on-site and centralised monitoring. It further clarifies what centralised monitoring entails.

Additionally, GCP now specifies that outcomes of centralised monitoring should also be reported in the monitoring report.

2. Investigator Oversight

New: No
Affects: Principal Investigators

Over the past years, lack of oversight has remained a common audit/inspection finding for sites that have a Principal Investigator (PI) who does not actually get involved in the trials that are being run on their site.

ICH is adding language to emphasise the need for PI oversight. Nothing new, that oversight was always a responsibility! However the number of findings that continue to occur warrant a stronger emphasis on this responsibility.

In 4.2, which deals with 'adequate resources', it will specifically add that 'the investigator is responsible for supervising' his team and any party that may be retained to perform any study task.

So, nothing new, just reiterated what was already the case. The PI is responsible for making sure that all parties involved on site, that includes the lab, the pharmacy, imaging and their entire trial team, are qualified and perform their tasks supervised. Procedures to ensure the integrity of the tasks performed and data generated need to be put in place.



3. Dealing with Noncompliance

New: Somewhat
Affects: Both site and sponsor staff

Noncompliance has never been a focus of GCP. The focus has always been on ensuring and achieving compliance. Noncompliance only had the brief section 5.20 and the word noncompliance was only used four times in the original ICH, including the title of 5.20.



The addition is just as brief, however not insignificant. So far it said that noncompliance 'should lead to prompt action by the sponsor to s e c u r e compliance'. But it never stated how!

Often, the motto was retraining! When noncompliance was identified, it was notified to both investigator and sponsor and the prompt action typically was limited to retraining those involved.

Now, with a few choice sentences, GCP states that the sponsor should perform a Root Cause Analysis (RCA) and implement Corrective And Preventive Actions (CAPA) as well as emphasises the need to inform regulatory authorities of serious breaches.

Quite a significant change in approach for many a sponsor representative!

4. Sponsor - CRO Oversight

New: Shouldn't be
Affects: Sponsors and CROs

The fact that Contract Research Organisations are being retained by sponsors is nothing new. The continued responsibility of the sponsor for the work done has also never been challenged.

Still, adding that the sponsor 'should maintain oversight' over retained services and should document approval if their service provider subcontracts part of their trial related duties and services is apparently necessary. Audits and inspections identified that this was not currently happening as diligently as it is needed.

5. Electronic record keeping

New: No
Affects: All Clinical Research Professionals

GCP now specifies that when it refers to the requirements of recording information, it applies to both paper and electronic records.

Electronic documentation wasn't the thing is it now, when ICH originally published GCP. But even then GCP in 5.5 when discussing data handling and record keeping outlined the responsibilities for the sponsor when using electronic systems in 5.5.3.



Haven't we already been working with electronic documentation for years? And don't we already know what the expectations are?

Well, when in doubt, ICH now ensures we know. It tells us we need validated systems and adds 'validation of computerised systems' to the glossary and tells us that that means 'ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system'.

It adds to 5.5.3, where it mentions the need for maintaining SOPs for the use of electronic systems what those SOPs should cover and underlines the need to ensure data integrity during software updates or data migration.



6. (Essential) Documents

New: not really

Affects: All Clinical Research Professionals

GCP always stated that data recorded and reported to the sponsor should be accurate, complete, legible and timely. Similar instructions have now been added to source data. Not really new, as that is data recorded, but there has been some discussion on exactly what the expectations for source data are.

The outcome is ALCOAC: Attributable, Legible, Contemporaneous, Original, Accurate and Complete. Also, it is emphasised that the needed audit trail also applies to source data and documents.

GCP R2 is adding a definition for 'certified copy' to the glossary. The term itself is not new, it was already in the definition of a source document. It just was not defined specifically.

Also, the monitoring plan got added to the glossary and to the added section 5.18.7, however not to the essential documents list. This is the place where, amongst other things, the rationale for the chosen monitoring strategy (on-site, centralised, or a combination) needs to be documented.

The need to document the location of essential documents, to be able to identify, search and retrieve them, is added. Along with the significant specification that the investigator should have control of all generated essential documents and records, before during and after the trial. And this includes the CRF data.

This adds an additional responsibility to the sponsor to ensure access to electronic CRF data even after the trial has ended. A CD-ROM with the data may not suffice anymore. Providing the CRF data is not the same as ensuring that the investigator has 'control of and continuous access' to said data. 'The sponsor should not have exclusive control'.

Already sponsors are starting to retain third parties to maintain the data and ensure access by all needed parties. It remains to be seen how this will generally play out. The intent is clear. The party generating the data is responsible for said data. And therefore has the right to have control over that data.



That's it! Those are the changes as we expect them to be finalised later this month. More extensive coverage of each of the topics will be published on the GCP-nerd blog: gcpnerd.com.