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ICH E6 (R1) has stood as the Gold Standard for International Good Clinical Practice, since 1996 and now a new draft (draft Revision 2 [R2]) has been released for comments (step 2b of the ICH process). **This is the biggest revision to International GCP for two decades.** GCP Inspectors have been able to update ICH GCP guidance, to include items that have been "Hot Topics" in their GCP inspections in recent years and/or featured in various guidance documents issued by one or other Regulatory Authority. If you are familiar with the findings of GCP Inspections, then these hot topics will be no surprise. If you are not, then now is the time to learn about them. The effect of this R2 update is that it is more prescriptive than previous versions, giving more detail on areas of compliance. When this draft becomes final, sponsors who claim compliance with ICH GCP (E6) (R2), will have to follow these new guidance requirements. This means that the impact will be felt internationally and far more widespread than just the jurisdictions of the three main parties (Europe, USA & Japan).

Introduction

At the end of July 2015 the International Conference on Harmonisation (ICH) released its 11 June 2015 draft ICH E6 (R2) Step 2b, for comments by 31 Jan 2016 (in EU & USA) and 30 Sep 2015 (in Japan). This new draft lists 26 items of change consisting of:- 3 items in definitions; new sections on investigator responsibilities including oversight; inclusion of ALCOAC (now including an extra "C"); a substantial new sponsor section on Quality Management, including risk assessment; monitoring plans defined and implemented; introducing Risk Based Monitoring; new section on computer validation and electronic records; Serious Breaches are mentioned under non-compliance; warnings about sponsor exclusive control of investigator's CRFs and essential documents; and clarification regarding the fact that the TMF could contain more that the ICH section 8 list of essential documents.

The regulatory authorities of the European Union, Japan, the USA, Health Canada and Switzerland will conduct internal and external consultation, according to their national or regional procedures. Following the review of these comments, the ICH process will move forward to final guidance (Step 4). In Europe the new Clinical Trial Regulation 536/2014 (CTR) [See RQA webcast on CTR for details - www.therqa.com] is likely to "apply" to new clinical, at about the same time as ICH E6 (R2) becomes final. The CTR quotes ICH GCP in several places. CTR Article 47 states that:- "Without prejudice to any other provision of Union law or Commission guidelines, the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall also take appropriate account of the quality standards and the ICH guidelines on good clinical practice". The quality standards of ICH GCP should be used in Europe, unless the CTR (or other law or commission guideline) already includes an appropriate requirement. Although not making ICH GCP the law in the EU, it does give it prominence as a quality standard and a sponsor should have very good reasons for not complying with it.

What are these 'hot topics' that have become part of the new draft ICH GCP?

Investigator oversight of their site (4.2.5 & 4.2.6)

This is the subject of many inspection findings by various Regulatory Authorities. ICH E6 (R2) proposes that: - "The investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site" (4.2.5) and "If the investigator/institution retains the services of any party to perform study tasks they should ensure this party is qualified to perform those study tasks and should implement procedures to ensure the integrity of the study tasks performed and any data generated" (4.2.6).

It appears that ICH E6 (R2) is echoing what the regulators have been saying for some time. The FDA guidance on investigator responsibilities (2009) proposed a ten point oversight plan that the PI should implement and document. The FDA states that: - "The investigator is responsible for supervising the study tasks performed by this staff, even though they are not in his/her direct employ .... If the investigator retains the services of a facility to perform study assessments, the investigator should take steps to ensure that the facility is adequate... The investigator may also institute procedures to ensure the integrity of data and records obtained from the facility providing the information (e.g. a process to ensure that records identified as coming from the facility are authentic and accurate)".

The new EU Clinical Trial Regulation 536/2014 (CTR) (Article 73) reinforces that the PI has oversight responsibilities: - "A principal investigator shall *ensure* compliance of a clinical trial at a clinical trial site with the requirements of this Regulation... [and] ... shall assign tasks among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated..."

The MHRA GCP Guide (2012) says that "... it is essential that there is clear, documented evidence of the PI's oversight and involvement in the trial ..." (11.2.1). The MHRA then goes on to list "commonly used ... examples" of "suitable evidence" of oversight. Note that the MHRA use of the word "essential". The MHRA codified certain words in their GCP Guide (2012):- "must" is a requirement by legislation; "should" refers to guidance-related practices; and "recommended" is a suggestion for good practice [see RQA webcast on the MHRA GCP Guide (2012) for details- www.therqa.com]. The word "essential" does not appear to be a codified MHRA word. The appearance of PI oversight in the E6 (R2) guidance document, might mean that in future the MHRA refer to it as a "should" (i.e. guidance driven).

ALCOA or ALCOAC or ALCOACCEA for Source Documents? (4.9.0)

ICH E6 (R2) draft proposes: - "The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects ... Source data should be attributable, legible, contemporaneous, original, accurate, and complete ... Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g. via an audit trail)" (4.9.0). The well known acronym ALCOA, now has an added "C", but not an added "CCEA"?

The FDA (2007) has long proposed ALCOA (Attributable Legible, Contemporaneous, Original and Accurate). In 2010 the EMA proposed to add CCEA (Complete, Consistent, Enduring and Available when needed) to become ALCOACCEA. The original E6 (R1) always required "accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs" (4.9.1) and the monitor to ensure that "source documents and other trial records are accurate, complete, kept up-to-date and maintained" (5.18.4. k). This addition to E6 (R2) makes it more explicit regarding source documents, but does not include the requirement for "consistent, enduring and available" from the EMA guidance.

ICH E6 (R1) has long required that- "Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained)" (4.9.3), and that "the monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary)" (5.18.4. n). The new E6 (R2) (4.9.0 Addendum) now makes this an explicit investigator responsibility for source documents as well.

Sites should record location of documents (8.1)

The new R2 section 8.1 states that: - "The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents". This means that investigator/institutions should document where their essential documents and source documents are located. This is similar to the requirements of the EMA (2010) for a source document locator or a "study specific source data agreement" and the FDA (2013) "list of authorized data originators." The new R2 requirement is for all essential documents including source documents.

Sponsor oversight of vendors (5.2.1 & 5.2.2)

Sponsor oversight of their vendors (e.g. CROs) has been a GCP inspection hot topic for many regulatory inspectors.
The new E6 (R2) addendum states that: - "The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf (5.2.1) ... and ... The sponsor should document approval of any subcontracting of trial-related duties and functions by a CRO" (5.2.2).

MHRA GCP Guide (2012) states that: - "is *recommended* that the decision to select a particular vendor is documented and that the rationale for selection is clear". (1.3.2)... "Once the vendor has been selected, the sponsor will need to consider how it will maintain continuing oversight of the vendor's clinical trial-related (1.3.3)" ... "When contracting out monitoring, sponsors *must*[7] consider how they will maintain oversight of the monitoring team". ... It is therefore *useful* to ensure there are formalised handover procedures, for when monitoring of sites changes hands. Sponsors *may* also wish to review and approve contracted monitors for trials (for example by a review of CVs). It is *recommended* that these aspects should be considered when drawing up contracts with vendors" (7.4) [7 = Regulation 3(12) of SI 2004/1031]. The MHRA (above) uses words such as "recommended", "may also wish", "useful", "need to consider" which might all be suggestions for good practice. However with the new E6 (R2) this may change to a "should" meaning that it is contained in guidance.

The MHRA GCP Guide (2012) also states that: - "Contracts should clearly detail the delegated tasks .... and the process for further sub-contacting by the vendor (to ensure that sub-contacting does not occur without sponsor approval)" (1.3.2). It looks like the MHRA were ahead of E6 R2 in having guidance that sponsor "should" document approval of any subcontracting.

Quality Management (5.0)

By far the largest section of change to E6, is the new sponsor responsibility section 5.0 on Quality Management. It has pride of place, as the first item under sponsor responsibilities. E6 (R2) provides a great deal of detail on:- Implementing a system of quality management; Critical Process and Data Identification; Risk Identification; Risk Evaluation; Risk Control; Risk Communication; Risk Review; and Risk Reporting. It states that the:- " sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials... focus on trial activities essential to ensuring human subject protection and the reliability of trial results" (5.0). E6 (R2) usefully points out that: - "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" (5.0).

Risk assessment and risk mitigation/adaption are key hot topics with all regulatory authorities and many have published guidance on the topic. E6 (R2) follows this trend in stating that: - "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....." (5.0).

E6 (R2) proposes a three way risk evaluation methodology: - "The identified risks should be evaluated by considering: (a) The likelihood of errors occurring, given existing risk controls. (b) The impact of such errors on human subject protection and data integrity. (c) The extent to which such errors would be detectable" (5.0.3).

The concept of risk mitigation and risk acceptance is detailed in 5.0.4:- "The sponsor should identify those risks that should be reduced (through mitigating actions) and/or can be accepted. Risk mitigation activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures".

E6 (R2) is similar to the EMA (2013) proposal to set "quality tolerance limits":- "Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or data integrity. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed" (5.0.4).

Risk assessment is not a static event, but should be reviewed:- "The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience" (5.0.6).

E6 (R2) goes further than the FDA risk based monitoring guidance (2013) and is more like the EMA and/or MHRA guidance on risk based quality management of clinical trials.

It should be emphasised that the E6 (R2) risk assessment and mitigation plans are required, regardless of whether Risk Based Monitoring (RBM) is being utilised by the sponsor.

Risk Based Monitoring (RBM) 1.39, 5.18.3, 5.18.6(e), and 5.18.7

The proposed draft for R2 step2 has extensive entries about RBM and how to report it. E6 R2 says that the "sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials" (5.18.3).

Usefully there is a new definition (1.39 Addendum) which now includes reports from central monitoring in the section on monitoring reports: - "Outcomes of any centralized monitoring should also be reported". Also the monitoring plan should be "tailored to the specific human subject protection and data integrity risks of the trial" (5.18.7).

Section 5.18 now contains an extensive section on RBM and in many places provides definitions of terms. For instance, although not defined in the ICH glossary, centralised monitoring is defined as:- "a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner ... Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring" (5.18.3). This definition is similar to the FDA (2013) definition and although the wording is different to the EMA (2013) definition, the ideas are very similar.

The methodology of RBM is detailed in E6 (R2) 5.18.3 and it states that the following variables should be used to augment the frequency of on-site monitoring: - "(a) Routine review of submitted data. (b) Identification of missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems. (c) Using statistical analyses to identify data trends such as the range and consistency of data within and across sites. (d) Analyzing site characteristics and performance metrics. (e) Selection of sites and/or processes for targeted on-site monitoring" (5.18.3). The reporting of RBM is covered in definition 1.39 concerning central monitoring and a new entry at 5.18.6(e) details how monitoring reports should be timely and have sufficient detail. This is similar to the FDA (2013, section V) guidance proposal.

Controversial ideas put forward by the FDA (2013) and MHRA (2012), on remote monitoring of consent forms, are not mentioned in the new E6 (R2). The FDA (2013) proposed that: - "For example, the study site electronically sends (e.g., fax, e-mail) the signed page(s) of consent forms to the monitor, or the monitor performs remote comparison of dates of study procedures and documentation of informed consent on CRFs". The MHRA (2012) suggested that: - "...when collecting signed consent forms, laboratory results with subject identifiers or contact details for follow-up telephone calls/questionnaires, a formal system should be in place that complies with the Data Protection Act1998 to ensure access to the confidential information is restricted and that the subjects of the clinical trial are aware that a sponsor or third party may have access to their data" (7.5.3.2).

Serious Beaches of the trial protocol or GCP is mentioned (5.20)

ICH E6 (R1) has long had a section on non-compliance and when a sponsor has to terminate an investigator's participation for non-compliance, the sponsor should notify the regulatory authorities promptly (5.20.2). R2 goes further and says: - "When significant noncompliance is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions" and "If required by applicable law or regulation the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of the trial protocol or GCP". The UK has long had a law requiring the reporting of Serious Breaches. The new EU CTR (Article 52) will apply to the whole European Economic Area and requires sponsors to report Serious Beaches within 7 days of being aware. It appears that the new ICH GCP will also bring this to the attention of a much wider audience.

Sponsor control of investigator data & essential documents (8.1)

For some time now one of the GCP inspector's hot topics has been the control of investigator data by the sponsor or the sponsor's agent. This is still the topic of a great deal of debate. E6 (R2) 8.1 makes it clear that:- "The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor...The sponsor should not have exclusive control of those data".

This is similar to the EMA (2010) guidance that: - "all data generated in a clinical trial relevant to patient care must be made available to the investigator at all times during and after the trial and all data held by the sponsor that has been generated in a clinical trial should be verifiable to a copy not held (or that has been held) by the sponsor".

E6 (R2) also clarifies that this applies to all essential documents: - "The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial". Similarly the MHRA GCP Guide (2012) states that:-"the investigator should retain control of documentation... in the investigator site file... should never be sent to the sponsor" (10.7.6). The sponsor can archive on behalf of the investigator, but according to certain strict conditions (10.7.6).

Trial Master File (TMF) may contain more that ICH E6 section 8 (8.1)

This is a hot topic of inspectors, particularly in Europe. There have been many inspection findings based upon the fact that the TMF only contained the bare minimum ICH E6 section 8 documents. The new E6 (R2) Section 8.1 contains more detail on the TMF: - "The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of the media used) should provide for document identification, search and retrieval. Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential document list. The sponsor and/or investigator/institution should include these as part of the trial master file". It would appear that the MHRA and EMA guidance (below) has largely been incorporated into ICH E6 (R2).
The MHRA GCP guide (2012):- “documentation listed in section 8 of ICH GCP and Chapter 3 [5?] of the TMF guidance document are useful guides for the minimum documents ... this list is not recommended to be used as a definitive checklist for TMF content....*Examples* of documents that are essential to reconstruct the trial but that are not contained in the above, QP certification, regulatory green light document to release and ship IMP and the database lock documentation" (MHRA GCP Guide 10.3.1).

EMA issued draft guidance (2013 & 2015) on the their expectations of the organisation and content of the TMF:- "The documentation listed in section 8 of ICH GCP and section 3 of the Volume 10 TMF guidance defines the minimum of documents that are considered essential ... however, this list is not recommended to be used as a definitive checklist for TMF content ... essential documents listed in regulatory guidance can be regarded as a subset of the potential documentation that could be regarded as essential for reconstruction of the conduct of the trial ... Any documentation which has been created during the trial and that helps reconstruct and evaluate the trial conduct must be filed in the TMF, irrespective of whether it is explicitly listed in these guidelines (Directive 201 2005/28/EC Articles 16 and 17)".

Monitoring plan (1.38.1, 5.18.7) and Monitoring Report (5.18.6(e))

It is interesting to speculate why Monitoring Plans were not in the original E6 (R1)? Was it just assumed that sponsors already had something that detailed the monitoring or was it that in the 1990s such detail was never used to describe this important clinical trial element? Of course many protocols included such information under 6.11 on quality control and so perhaps a separate monitoring plan was not thought necessary.

E6 (R2) draft proposes the following definition of monitoring plan and information on what should be in it: - “A description of the methods, responsibilities and requirements for monitoring the trial" (1.38.1). Also: - "The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use...the plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training...the monitoring plan should reference the applicable policies and procedures" (5.18.7).

Monitoring plans are obviously a hot topic for GCP inspectors. The MHRA GCP Guide (2012) states that: - "it is recommended that the monitoring strategy ... is formalised by the sponsor ... this usually takes the form of a monitoring plan" (7.3.4). Note that the MHRA only "recommend" this, they state that this is a suggestion for good practice, not a regulatory requirement or something in guidance. It is anticipated that if the E6 R2 draft is made final, then monitoring plans will become guidance.

FDA guidance (2013) states that: - "For each clinical trial, the sponsor should develop a monitoring plan that describes the monitoring methods, responsibilities, and requirements for the trial. The monitoring plan should include a brief description of the study, its objectives, and the critical data and study procedures, with particular attention to data and procedures that are unusual in relation to clinical routine and require training of study site staff" ... " It goes on to describe the "components of a monitoring plan which might include the following: 1. Description of Monitoring Approaches 2. Communication of Monitoring Results 3. Management of Noncompliance 4. Ensuring Quality Monitoring 5. Monitoring Plan Amendments" (section D).

Interestingly the FDA issued a notice in the Federal Register (July 2015) where the FDA understands that sponsors currently developing comprehensive monitoring plans, have not been including "all the elements described in the guidance". So a definite a hot topic with the FDA and it looks like they are examining monitoring plans.

The EU CTR Article 48 is dedicated to "monitoring" but it does not explicitly define a "monitoring plan". It does state that the: - "extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment..." Annex 1.D.17 (ad) does require, in the protocol, "a description of arrangements for monitoring the conduct of the clinical trial." In Europe, Directive 2005/28/EC Article 4 already required that the protocol include a "definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy".

Monitoring reports have long been a central part of monitoring and are usually reviewed during GCP inspections. So it is interesting that after 20 years an addition to the requirements for reports is added. E6 (R2) proposes that:- (e) Monitoring results should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up as indicated. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan" (5.18.6(e)). This is very similar to the FDA (2013) guidance which states that: - "Documentation of monitoring should include sufficient detail to allow verification that the monitoring plan was followed. Monitoring documentation should be provided to appropriate management in a timely manner for review and follow-up, as indicated" (section v).

Electronic Systems and Data Handling (1.11.1, 1.60.1, 2.10, 5.0.2, 5.5.3(b) & (h))

The sections on electronic data handling have been enhanced by bringing in various detail from existing sources. Very usefully there is a definition of certified copy (1.11.1) that borrows from the FDA guidance (2007) but adds further detail. The new section 1.11.1 explicitly adds that the original can be electronic and that one method of producing certified copies is through a "validated process":- “A paper or electronic copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original." Also E6 (R2) section 8.1 adds that: - "When a copy is used to replace an original document, the copy should fulfill the requirements for certified copies".

The EMA reflection paper (2010) also had a similar definition of certified copy which included being able to verify the copy "by a validated electronic process" and the EMA also quote the CDISC Clinical Research Glossary Version 8.0, December 2009. It is a pity that the new E6 (R2) definition is not more specific about whether the process of being "verified... by a dated signature or ...” applies to each copied image, to complete documents or to groups of documents. A Principal Investigator, faced with verifying several hundred certified copies of documents, would prefer to be able to verify all of those documents at once. If the draft guidance had said "paper or electronic copy(ies)" then this would have explicitly allowed verification of a group of documents with a dated signature (or ...through a validated process).

The added definition of "Validation of computerized systems" (1.60.1) is very useful and is slightly different from that proposed by the EMA in 2010. The EMA (2010) definition: - "Process of establishing suitability to purpose for software and systems, establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes". The ICH E6 (R2) definition is: - "A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system"(1.60.1).

I'm not sure why the section on the principles of ICH GCP 2.10 has an addendum? It states that: - "This principle applies to all records (paper or electronic) referenced in this guideline." The original E6 (R1) principle 2.10 states that:- "All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification". I would have thought that the word "all" does the job of covering all types of information. However the new addendum now reinforces that this basic principle applies to electronic as well as paper based systems.

Computer systems are listed in the risk identification section (5.0.2), as being a critical trial process, at the system level: - "Risks to critical study processes and data should be identified.... Risks should be considered at both the system level (e.g., facilities, standard operating procedures, computerized systems, personnel, vendors) and clinical trial level (e.g., investigational product, trial design, data collection and recording)".

Section 5.5.3 on electronic trial data handling and/or remote electronic trial data systems, now includes clarification about what SOPs should include (addendum to (b)) and in addendum (h) on ensuring data integrity when making changes:- "SOPs should cover system setup, installation and use....describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and decommissioning....responsibilities of ... parties with respect to ... computerized systems should be clear, and the users should be provided with training"(5.5.3 b). With regard to ensuring "the integrity of the data including any data that describe the context, content and structure of the data.... particularly important when making changes to the computerized systems, such as software upgrades or migration of data"(5.5.3 h).

Concluding remarks

ICH GCP E6 (R1) has stood the test of time, in that it has been a successful International quality standard for conducting clinical trials. In fact, it is amazing how well it copes with the considerable changes since the 1990s and in some cases has been far seeing. This proposed update incorporates many of the GCP Inspection findings that have become hot topics in recent years. ICH proposes that the new guideline will reach step 4 and become a "final guideline" by November 2016. It will have an effect upon global GCP and hopefully will compliment the other big changes in GCP coming into effect at about the same time.

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