The Israeli Association for the Advancement of the Biomedical Research Community

January 31, 2016

Dear ICH Secretariat;

Thank you for sharing the upcoming proposed addendum to the E6(R2).

"C-Trials", the Israeli Association for Research and the Advancement of the Biomedical Community (a voluntary association), has conducted a discussion group inviting the local clinical trials community (e.g. the Ministry of Health, Ethic Committees, sponsors, CROs, investigators, site team personnel, etc.), hosting approximately 100 participants. The suggested changes were presented and an open discussion on the different topics was conducted, allowing the various parties to express their opinions.

Hereinafter is a summary of the discussion and the issues we would like you to consider for the upcoming addendum.

(Text marked in *Italic* is quotation from the current/amended guideline.)

1. **<u>Quality</u>:**

1.1. Principle #13 of the GCP refers to quality systems. CAPA and RCA are significant quality concepts/tools, which are required by other GXPs, are under the Regulator Authorities focus, and are widely implemented in practice. We suggest to comprehensively address these concepts throughout the guideline.

1.2. An additional quality/managerial concept widely used today in all aspects of the clinical trial, is Quality Risk Management.
Today this is referred to within the RBM concept, however we think this should be more explicitly detailed and required.
Specifically, we propose to amend the study management requirement to include Quality Risk Management.

2. **<u>Site; PI, Sub-Investigator and Site Team Members</u>:**

In general, we suggest to differentiate between the various functions within the site, and to clearly refer to site team members other than the investigators, in order to refer and stress some responsibilities which are generic but critical for the trial's success.

In addition, we suggest to add a function who is responsible for the management of the study in the site, i.e. responsible for the integration of all processes to ensure proper conduct and delivery. This task is in addition to the study oversight and the medical care of trial subjects, and may of course be carried out by the PI, however may also be delegated by the PI to another site member.

2.1. Add the term 'Principle Investigator (PI)' to the Glossary as a stand-alone term, in order to clearly differentiate between the PI and the Sub-investigators (when applicable).

2.2. Update chapter 4 to include all site team members.
For example, *"4.1.1 <u>The investigator(s)</u> should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial…"*
The current text refers only to investigators (PI and sub-investigators, as currently defined), however there are other site team members, who do not qualify as sub-investigators, but still require to be qualified by education, training and experience to assume the responsibility delegated to them by the PI.
The term " investigator's trial staff" is currently used several times throughout the guideline.

Another example, *"4.9.3… Sponsors should provide guidance to investigators and/or <u>the investigators' designated representatives</u> on making such corrections."*
This is the first and only appearance of this term. Suggest to unify the wording throughout the guideline.

2.3. PI Oversight:
Addendum 487-488, *"4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site."*
We think there should be more emphasis regarding the PI's responsibility on the study conduct at his/her site. We propose to include the term "PI oversight" which is nowadays commonly used, and a requirement known by the PIs.

2.4. Addendum 489-492, *"4.2.6 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."*
During the discussion group, Investigators have raised their concern regarding their capability to supervise satellite parties (e.g. imaging facilities outside of the institution). This reinforces our proposal for a managing function within the site, as detailed above.

3. <u>Investigational Product:</u>

3.1. *"4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol."*
Suggest to add a clear requirement, under the site's responsibility, to conduct real time assessment of subject treatment compliance.

4. <u>Monitoring:</u>

4.1. The term 'Monitor' is not recorded in the Glossary (while other critical functions such as Investigator is mentioned).

4.2. *"5.18.4 Monitor's Responsibilities…*
(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that… i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents."

As per 6.4.9 Source documents are not always required.
"6.4 Trial Design: …A description of the trial design, should include… 6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data."
We suggest adding the monitor's responsibility to confirm data in the CRF which does not have SD (as defined in the protocol).

4.3. We suggest updating section 5.18.4 Monitor's Responsibilities to include a requirement to verify/ensure PI Oversight.

4.4. Compliance to all study requirements:
"5.18 Monitoring, 5.18.1 Purpose… (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)."
"5.18.4 Monitor's Responsibilities… (d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any."
"5.19 Audit, 5.19.1 Purpose: …should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.
We suggest adding "additional study requirement" (in addition to the protocol), in all above sections, as there are additional study documents which should be adhered to by the site (e.g. IB, CRF Completion Guidelines, etc.)

4.5. *"5.18 Monitoring, 5.18.1 Purpose… (b) The reported trial data are accurate, complete, and verifiable from source documents."*
"5.18.4 Monitor's Responsibilities… (k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained."
For consistency, we suggest detailing the full requirements of ALCOAC.

5. Essential Documents:

5.1. *"4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region…"* (same in 5.5.11).
This timeframe cannot be clearly defined. We suggest to change to a requirement of 15 years after study end, conditioned to sponsor's approval (which is in correlation to local regulations in many countries).

6. Additional technical suggestions:

6.1. Combine lines 10-12 with Addendum 28-30.

6.2. Add the following terms to the Glossary:
Good Manufacturing Practice (GMP)
Root Cause Analysis (RCA)
Corrective and Preventive Actions (CAPA)

6.3. Add common and well known abbreviations, starting from the Glossary, and thereafter throughout the guideline:
- Informed Consent (IC)
- Informed Consent Form (ICF)
- Investigational Product (IP)
- Investigator's Brochure (IB)
- Legally Acceptable Representative (LAR)

6.4. Use abbreviation defined in the Glossary throughout the guideline.

6.5. The term "Non- therapeutic trial" appears 4 times in the current GCP. We suggest adding this term to the Glossary with a clear definition (as described in 4.8.13).
"4.8.13 …a non-therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject)…"

6.6. *"3.4 The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists."*
Update the wording to "The IRB/IEC should provide its written procedures and membership lists if requested by investigators, sponsors or regulatory authorities."

6.7. *"4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC."*
Delete the marked text and add it to the LAR definition in the Glossary.

6.8. *"4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following…"*
The current text does not include the subject's LAR.
Suggest updating as marked below:
"Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects or the subject's legally acceptable representative, should include explanations of the following…"

6.9. *"4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol…"*
In many emergency situations, the subject is the one (legally) required to provide consent and there is no LAR at all. So it is not that the "LAR is not available" but rather there is no LAR.
Suggest updating as marked below:
"In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if applicable, should be requested. When prior consent of the subject is not possible, and prior consent of the subject LAR is not available/applicable, enrolment of the subject..."

6.10. *"5.11.1 The sponsor should obtain from the investigator/institution…(c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested."*
The wording under requirement (c) is unclear.
Suggested updated text:
"The sponsor should obtain from the investigator/institution… (c) Documented IRB/IEC approval/favourable opinion of the study and of any additional documents requested by the sponsor and/or the IRB/IEC, such as a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects."

6.11. Multicentre Trials:

Sections 5.23.1, 5.23.2, 5.23.4 are relevant to all studies (and not just multicenter) and are covered throughout the guideline. We do not see the rational for this repetition with specific relation to multicentre trials.

We hope you find our comments and suggestions useful.
If there are any questions, or additional clarifications required, we would be more than happy to address them, available via e-mail and/or via phone:

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Warm Regards,

C-Trials
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