

The new ISO 14155: a practical approach to your quality assurance system

Caroline Ricklin and *Nicky Dodsworth* explain how companies can implement the new standard on clinical investigations of medical devices and the effects it may have on their existing quality management system.

Changes in the updated version of the international standard for clinical investigations of medical devices – ISO 14155 (2011) – will pose a number of challenges for manufacturers conducting trials in Europe that have not previously focused on clinical investigations.

The standard, which will essentially become a European “regulation” once the European Commission harmonises it by citing it in the *Official Journal* of the EU, will necessitate the reconfiguration of quality management systems and processes for companies to ensure they meet the new requirements. It is unlikely that there will be a transition period for the new standard. Although there is no fixed date for its publication in the *OJ*, standards can sometimes be published five to six months after their release; therefore, the new standard could be published in the third quarter of 2011. In the US, the Food and Drug Administration is still deciding whether to recognise ISO 14155 or whether to handle it in another way.

This article provides companies with practical advice on how they can implement the new standard and the effects it may have on an existing quality management system.

Areas of special attention

The new ISO 14155 – entitled Clinical investigation of medical devices for human subjects – good clinical practice – was released on 1 February 2011 and contains major changes compared with its 2003 predecessor^{1,2}. The new standard is much more detailed and the standards and terminology it uses follow the International Conference on Harmonisation’s E6 good clinical practice guideline³ more closely; an article on the essential modifications made to the standard was published in the May/June 2011 issue of *Regulatory Affairs Medtech*.

The new ISO 14155 requires organisations to implement a quality management system that comprises quality assurance and quality control. The new standard, in addition, provides recommendations on auditing and the need for risk assessment – in particular, the standard describes the requirement to comply with ISO 14971 on the application of risk management to medical devices.

Before starting to implement the new ISO requirements, companies should establish a clearly documented project plan.

They should begin by comparing the 2011 standard with the 2003 version and then conduct an in-depth analysis of the modifications in the new version.

After identifying the changes, companies should consider carefully the impact these will have on an existing quality system, the procedures already in place and the clinical investigations that are currently being conducted or are about to start.

Companies should then define how they will integrate the changes. They will be free to choose how they want to integrate ISO 14155 in their own system and how stringent they will be, but they should bear in mind that ISO 14155 is a recognised standard and should be embraced. Every company and every system is different and will require specific adaptations. In order to conduct a thorough review, a cross-functional approach that includes key members from various operational teams – eg quality assurance, regulatory affairs and safety reporting – will prove to be the most successful.

Once this exploratory phase is completed, the adaptations can start to be implemented into the quality system.

Companies should bear in mind the requirement to verify new terminology. For example, adverse event and adverse device effect have new definitions in the latest standard, while data monitoring committee, device deficiency, malfunction and vulnerable subject are all defined for the first time.

Quality assurance will be useful in ensuring gaps in the process are identified and will assist in bringing the organisation together to address them. Once the gaps have been addressed and processes written and made effective, the quality assurance team should conduct regular audits to monitor consistency and compliance. Always remember that new standard operating procedures or other documented processes need to be introduced in a timely manner (prior to a new standard being implemented) and sufficient time must be allowed between the release of the process and the date on which it comes into effect. A “pilot” scheme can be useful when introducing a new process, to make sure the process actually works.

As with any new processes or regulations, audits should be performed to ensure that staff are following them. In cases where new processes are not working, it is necessary to consider why they are not working and whether any changes can be made that cover the regulations but that do not make compliance too difficult.

In parallel to the steps outlined above, companies should ensure that everyone is kept well informed of the review process and

the stage of development of any new procedures. Communication with relevant staff must be maintained. Also, any necessary training should be scheduled and prepared well in advance. As there have been significant changes from the 2003 ISO 14155 version, it is recommended that extensive training is conducted.

In addition, companies are reminded that their subcontractors also need training with regards to the new standard and any new processes implemented. Subcontractors are an important part of the team and their time and ability to meet the new ISO standard must be considered. Re-assessment of vendors should be conducted to ensure they can comply with the ISO 14155 standard. To help meet the tight timeline concerning the implementation of the new standard, companies can conduct re-assessments via remote audits or checklists.

Dealing with ongoing clinical projects

Companies must identify which of their clinical investigations will be impacted by the new ISO and to what extent.

As a general rule, the new standard will apply to investigations that are ongoing at the time it is harmonised by the commission. It will not apply retrospectively to activities that have already been completed.

Clinical investigation plans and other essential documents may have to be updated for ongoing clinical investigations. Sponsors will need to decide on how many changes they will make to their clinical documentation in order for it to be aligned with the new standard. However, companies must remember that ISO 14155 will be implemented across the EU by all member states and conforming to it will be a requirement in getting medical devices CE marked and will help avoid unnecessary delays. It will also be taken into account during inspections by competent authorities and, as a consequence, it will be impossible to ignore.

Remember that the 2003 version does not take into account the amendments to Medical Devices Directive 93/42/EEC, as amended by Directive 2007/47/CE⁴. Thus, it is essential that the new ISO 14155 requirements are met.

Finally, it will be the sponsor’s notified bodies that will judge whether it must adopt the new ISO 14155 for ongoing clinical investigations.

Documenting impact

In any case, companies should document a summary rationale of the impact that ISO 14155 will have on ongoing clinical investigations

in order to identify any potential shortfalls that may arise, and show, in the rationale or by an addendum, how they would address them.

The objective of such addenda or rationale is to ensure continuity with post-marketing activities such as registry studies that involve reviewing studies conducted under the 2003 version of ISO 14155 and ensure there are no misunderstandings.

Set-up phase

For example, regarding the set-up phase of a clinical investigation (ie where the ethics committee(s) and competent authorities have approved the investigation, but no patients have been enrolled), both the clinical conduct of the investigation and the quality management system must comply with the new ISO requirements. This means that if a sponsor decides to update its clinical investigation plan or any other essential clinical documents, these amendments will have to be resubmitted to the commission and competent authority, as required.

Ongoing clinical investigations

Regarding ongoing clinical investigation (ie investigations in which patients are being enrolled), the new ISO 14155 requirements will apply to the remainder of the investigation from the time the new ISO comes into effect. This means that investigators and study staff must be trained in the new standard and understand their increased responsibilities. For example, device deficiency reporting forms should be created and implemented on site.

Moreover, principal investigators will have to ensure that communication with the ethics committee is continuous; appropriate information/approvals are obtained; clinical

investigation plan deviations are reported; maintenance and calibration of relevant equipment is ensured; and all subjects are provided with applicable information during the conduct of the clinical investigation.

However, the heaviest burden for the site will be the requirement for copies of source documents (or printouts of electronic source documents) to be signed and dated by a designated member of the site team after every site visit. Furthermore, a statement will have to be made to certify that these copies are true representations of the originals.

Completed clinical investigations

In the case of a completed clinical investigation (ie after the last subject has completed his/her follow-up and is out of the study), only the clinical investigation report should follow the format and content of the new ISO 14155. Annex D of the standard (previously C in version 2003) may be used as a template to document clinical investigation reports, but this is not mandatory. It provides extended instructions on how to complete each of the sections from the cover page to the annexes to be attached to the report. For example, an instructions for use, a device deficiencies table and an audit certificate (if applicable) are new annexes that are requested.

Conclusion

Most clinical investigations already follow GCP requirements. Moreover, the new revision of ISO 14155 has mainly served to expand, reinforce or add more detail to existing concepts; it has not reinvented the wheel. It explains in detail how to apply GCP to medical device clinical investigations, using an operational (mainly project management) approach. The inclusion of the phrase "good

clinical practice" in the title of the new ISO 14155 is enormously significant in that it reflects the increased alignment of medical device practices to ICH GCP, thereby improving patient care and safety in the clinical setting.

The new standard also goes some way to improving many of the previous deficiencies relating to clinical investigations. For example, the revised standard clearly states that the sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation; the sponsor will need to review all device deficiencies and determine and document in writing whether they can lead to a serious adverse device effect.

Adopting the new standard will be a challenge for those companies that have not previously focused on clinical investigations. They will need to ensure that their quality management systems and processes are reconfigured to meet the necessary compliance levels.

References

1. ISO 14155:2011, 01 Feb 2011, *Clinical investigation of medical devices for human subjects – Good clinical practice*, <http://bit.ly/nOCqYE>
2. Stark NJ, *Key revisions to medical device clinical investigations standard ISO 14155*, *Regulatory Affairs Medtech*, 11 May 2011
3. ICH *Guideline for Good Clinical Practice E6(R1) Step 4*, 10 Jun 1996, <http://bit.ly/rndBwm>
4. Directive 2007/47/EC, OJ, 21 September 2007, L247, 21-55, <http://bit.ly/pP22GI>

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