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FDA Medical Device Regulations vs. ISO 14155

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Medical device clinical trials must comply with 21 CFR Parts 11 (Electronic Records), 50 (Informed Consent), 54 (Financial Disclosure), 56 (IRBs), and 812 (IDEs). IDEs are required for some Class II and all Class III investigational devices intended for marketing in the U.S. 21 CFR 812.100 requires the sponsor of an IDE study to ensure the investigation is conducted according to the federal regulations, as well as the investigator agreement, the investigational plan, and written requirements of the IRB under which the investigation is being conducted. If any of these three documents specify that the study will be conducted according to ISO 14155,[3] the investigator must also comply with these guidelines. Even if ISO 14155 is not required, it is still good practice to conduct medical device trials to this higher standard because doing so affords greater participant protection and data integrity. In addition, some national regulations require compliance with ISO 14155, so the responsible regulatory body should be consulted.

The ISO 14155 standards were created to clarify the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. ISO 14155 is in its second edition: ISO 14155:2011. While ISO 14155 is not law in the United States, it plays a role similar to ICH Good Clinical Practices Guidelines (E6) and has been officially recognized as a standard by the FDA since 16 March 2012.[2]

FDA regulations and ISO 14155 standards include many requirements unique to each. However, they also overlap in some areas. To comply with both, it is important to understand these differences. The following tables and discussions compare FDA regulations and ISO 14155 in the five areas where FDA investigators most often find noncompliance with FDA regulations.[1] Differences are marked in red. Other similarities and differences between the FDA regulations and ISO 14155 that do not pertain to these five areas are not included in this review.

- Failure to follow the investigational plan and/or regulations
- Deviations from the protocol
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate subject protection – failure to report AEs and informed consent issues

Table 1. Failure to Follow the Investigational Plan and/or Regulations

Requirements per 21 CFR	Requirements per ISO 14155
21 CFR 812.110 (b): An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.	ISO 14155 9.6 (b): The principal investigator shall conduct the clinical investigation in compliance with the clinical investigation plan.
21 CFR 812.110 (a): An investigator may determine whether potential subjects would be interested in participating in an	ISO 14155 6.1: The clinical investigation shall not commence until written approval/favourable opinion from the ethics

Requirements per 21 CFR	Requirements per ISO 14155
investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.	committee and, if required, the relevant regulatory authorities of the countries where the clinical investigation is taking place has been received.

ISO standards require conducting the investigation in accordance with the clinical investigation plan, whereas FDA regulations also require the investigation to be conducted according to the signed agreement, FDA regulations, and conditions of the IRB.

Conclusion: Following FDA will ensure compliance with ISO.

Table 2. Deviations from the Protocol

Requirements per 21 CFR	Requirements per ISO 14155
21 CFR 812.140 (a) (4): A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: The protocol, with documents showing the dates of and reasons for each deviation from the protocol.	ISO 14155 9.6 (g): The principal investigator shall document and explain any deviation from the approved clinical investigation plan that occurred during the course of the clinical investigation.
21 CFR 812.150 (a) (4): An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 21 CFR 812.35 (a) also is required.	ISO 14155 9.4 (e): Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the ethics committee. Such deviations shall be documented and reported to the sponsor and ethics committee as soon as possible.

FDA regulations require that deviations in emergency use situations must, in no event, be reported later than five working days.

Conclusion: Following FDA will ensure compliance with ISO.

Table 3. Inadequate Record Keeping

Requirements per 21 CFR	Requirements per ISO 14155
21 CFR 812.140 (a): A participating investigator shall maintain the following accurate, complete and current records	• ISO 14155 4.7.1: Informed consent • ISO 14155 6.4: Adverse events and device deficiencies

Requirements per 21 CFR	Requirements per ISO 14155
relating to the investigator's participation in an investigation: • Correspondence • Device disposition • Subject case history, including informed consent, relevant observations such as adverse device effects, and exposure to the investigational device • Protocol, including dates and reasons for deviations • Any other records FDA requires	• ISO 14155 6.9: Investigational device accountability • ISO 14155 6.10: Accounting for subjects • ISO 14155 4.5: Communication with the ethics committee
21 CFR 812.140 (d): An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. 21 CFR 812.140 (e): An investigator or sponsor may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them under this part. Notice of transfer shall be given to FDA not later than 10 working days after transfer occurs.	ISO 14155 7.4: The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.
21 CFR 11.1: Electronic records, electronic signatures, and handwritten signatures executed to electronic records are considered trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.	ISO 14155 6.8.1: Printed copies of electronic source documents shall be signed and dated with a statement that it is a true reproduction of the original.
[Not specifically required]	ISO 14155 6.8.3(h): When electronic clinical databases or remote electronic clinical data systems are used, written procedures shall be implemented to ensure that all completed CRFs are signed by the principal investigator or authorized designee.
21 CFR 812.140: Maintain accurate, complete, and current records pertaining to each subject's case histories and exposure to the device.	ISO 14155 6.8.2: Case report forms shall be signed and dated by the Principal Investigator or designee.
[Not specifically required]	ISO 14155 8.2.1(e): Ensure the members of the investigation site team and their designated authorization(s) are identified in a

Requirements per 21 CFR	Requirements per ISO 14155
	log with details.

ISO requires the principal investigator or designee to sign and date printed as well as electronic CRFs. Additionally, ISO specifies that printed electronic source documents must be signed and dated with a statement indicating they are a true reproduction of the original. ISO requires the use of a delegation log.

FDA requires record retention for two years and 10 working days to notify FDA of any records transfer.

Conclusion: Follow the more stringent FDA or ISO rules to ensure compliance.

Table 4. Inadequate Accountability for the Investigational Product

Requirements per 21 CFR	Requirements per ISO 14155
21 CFR 812.110 (c): An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it. 21 CFR 812.140 (a) (2): A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: Records of receipt, use or disposition of a device that relate to: • The type and quantity of the device, the dates of its receipt, and the batch number or code mark. • The names of all persons who received, used, or disposed of each device. • Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of. 21 CFR 812.140 (a) (3) (iii): A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.	ISO 14155 6.9: Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the clinical investigation plan. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include: • the date of receipt, • identification of each investigational device (batch number/serial number or unique code), • the expiry date, if applicable, • the date or dates of use, • subject identification, • the date on which the investigational device was returned/explanted from subject, if applicable, and • the date of return of unused, expired or malfunctioning investigational devices, if applicable.

FDA regulations require recording the names of all persons who received, used or disposed of each device, as well as the when each device was used.

ISO standards require the investigator to keep records documenting expiry date.

Conclusion: Follow the more stringent FDA or ISO rules to ensure compliance.

Table 5. Human Subject Protection

Requirements per 21 CFR	Requirements per ISO 14155
21 CFR 50.27: Informed consent must be signed and dated by the subject.	ISO 14155 4.7.2 (g): Informed consent must include personally dated signature of subject.
21 CFR 50.27: A copy of the informed consent shall be provided to the subject.	ISO 14155 4.7.2 (h): Provide subject with a signed and dated copy of informed consent.
21 CFR 50.25 (b): Statement that significant new findings during the course of the trial which relate to willingness to continue participation will be provided.	ISO 14155 4.7.6: New information shall be provided in written form and confirmed in writing.

ISO standards require providing a signed and dated copy of the informed consent to the subject. In addition, ISO standards require that new information be provided in written form and confirmed in writing by the subject.

Conclusion: Following ISO will ensure compliance with FDA.

Table 6. Safety Reporting.

Requirements per 21 CFR	Requirements per ISO 14155
21 CFR 812.140 (a)(3): A participating investigator shall maintain the following accurate, complete and current records relating to the investigator's participation in an investigation: • All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of al diagnostic tests. 21 CFR 812.150 (a): An investigator shall prepare and submit the following complete, accurate, and timely reports: • Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.	ISO 14155 9.8: The principal investigator shall: • record every adverse event and observed device deficiency, together with an assessment, • report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the CIP, • report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or CIP or by the EC, • report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and • supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

ISO standards require serious adverse events that could have led to a serious adverse device effect to be reported to the sponsor, ethics committee, and regulatory authorities, while FDA regulations require only that unanticipated adverse device effects (UADEs) be reported to the Sponsor and reviewing IRB in a timely fashion. Specifically, FDA regulations require investigators to report UADEs as soon as possible and no later than 10 working

days, while ISO requires reporting "without unjustified delay," but does not specify a certain number of days.

Conclusion: Follow the more stringent FDA or ISO rules to ensure compliance.

References

1. U.S. Food and Drug Administration (2014). Annual BIMO Inspection Metrics. Retrieved from http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm261409.htm on July 31, 2014.
2. U.S. Food and Drug Administration (2012). Federal Register, Volume 77*(52)*, p. 15775.
3. International Standard ISO 14155, second edition (2011). Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice.

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