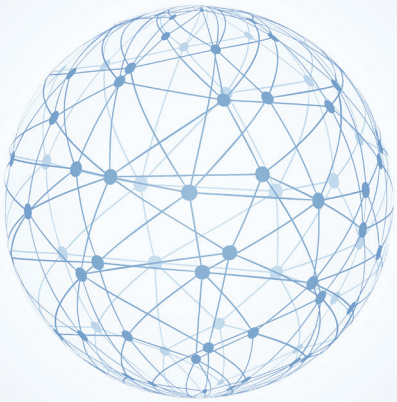

CONDUCTING GLOBAL CLINICAL RESEARCH TRIALS:

COMPARING AND CONTRASTING FDA MEDICAL DEVICE REGULATIONS FOR CLINICAL INVESTIGATORS WITH ISO 14155:2011

Introduction

Today's clinical research landscape for the medical device industry is global in nature. In an effort to avoid redundancy, reduce costs, provide patients with access to their device as soon as safely possible, and gain the edge on their competitors, medical device companies regularly explore options to conduct trials internationally. Doing so requires a global strategy, which involves complying with multiple layers of regulatory requirements. Whether conducting a U.S. study with additional international sites, or conducting the entire study outside the US, sponsors must be well-informed about the multiple requirements in order to run a well-controlled trial that will withstand the scrutiny of worldwide regulatory agencies. Conducting a trial under the umbrella of both 21 CFR and ISO 14155:2011 (ISO 14155) will position the sponsor well globally at trial end, but implementing this can create confusion and chaos during study conduct. With a focus specifically on clinical investigators, this white paper will examine common findings from FDA inspections done both in the US and internationally, and highlight some differences between 21 CFR and ISO 14155 related to those findings that would be beneficial for study teams to know.

Background

The regulations pertaining to the conduct of clinical trials in 21 CFR include Parts 11 (Electronic Records), 50 (Informed Consent), 54 (Financial Disclosure), 56 (IRB), and 812 (IDE). IDEs are required for some Class II and all Class III investigational devices intended for market in the U.S. 21 CFR 812.140 specifies that IDEs must be conducted according to the federal regulations, investigator agreements, investigational plan, and requirements of the IRB under which the investigation is being conducted. Should any of these four tenets specify that the investigation will also be conducted according ISO 14155 they must then also comply with these guidelines in order to maintain compliance.

ISO 14155 was 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. Currently, ISO 14155 is in its second edition, which supersedes the previous version, ISO 14155:2003. While ISO 14155 is not law in the United States, it serves as the seminal device guideline that parallels The International Conference on Harmonization Good Clinical Practices Guidelines (ICH/GCP) and was officially recognized as a standard by the FDA.

Summary of Findings

Each year, FDA's Bioresearch Monitoring Program (BIMO) conducts inspections of clinical investigators; sponsors, contract research organizations, and monitors; non-clinical laboratories; in-vivo bioequivalence; and institutional review boards (IRB). FDA publishes a summary of the results of these inspections to their website in the form of inspection metrics at www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm261409.htm. Currently, fiscal years 2007 through 2013 are available for review. The inspection metrics also break down the results of international inspections conducted by FDA in these areas. Between 2007 and 2013, the FDA has conducted an average of 183 (range of 155 – 218) inspections of clinical investigators involved in device studies. Of these inspections, approximately 1% each year were international in scope (range of .05% - 1%). For example, in 2013, the Center for Devices and Radiologic Health (CDRH) conducted 193 inspections of US clinical investigators conducting device studies and inspected 12 OUS investigators conducting device studies. In regards to the international inspection findings, the FDA describes them as "similar to domestic inspectional findings" among which the following are included:

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

Comparison – FDA vs. ISO

The tables that follow contain comparisons between the FDA regulations and ISO 14155 in the above-mentioned areas, as well as other important components of the clinical research process. Key differences are highlighted. A summary of the difference in each key area is then provided to help the reader assimilate the information.

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 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.	ISO 14155 6.1: The clinical investigation shall not commence until written approval/favourable opinion from the ethics committee and, if required, the relevant regulatory authorities of the countries where the clinical investigation is taking place has been received.

Here, FDA and ISO are in agreement in that the investigation may not be conducted until both IRB/ethics committee (EC) approval and FDA/relevant regulatory authority approval have been granted. However, ISO speaks only to 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. So in this case, FDA regulations are more stringent. Simply following ISO and not taking into consideration these additional requirements of the FDA regulations could be cause for a finding during an FDA inspection.

Conclusion > Following FDA will ensure compliance with ISO

Table 2 - Protocol deviations.

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 4.5.4 (b): 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.

Here again, a great deal of congruency between FDA and ISO are noted. Both speak to documenting deviations from the protocol, including doing so for emergency use situations. Further, both state that emergency use should be reported to the sponsor and IRB/EC as soon as possible. However, FDA regulations go a step further by stating that emergency use situations must be reported in no event later than 5 working days. Again, simply following ISO in this case could leave an investigator vulnerable to an inspectional finding based on timeframes provided for reporting emergency use situations.

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 relating to the investigator's participation in an investigation: 1) Correspondence 2) Device disposition 3) Subject case history, including informed consent, relevant observations such as adverse device effects, and exposure to the investigational device 4) Protocol, including dates and reasons for deviations 5) Any other records FDA requires	The following shall be documented: 1) ISO 14155 4.7.1: Informed consent 2) ISO 14155 6.4: Adverse events and device deficiencies 3) ISO 14155 6.9: Investigational device accountability 4) ISO 14155 6.10: Accounting for subjects 5) ISO 14155 4.5: Communication with the ethics committee 6) ISO 14155 9.6 (g): Deviations from the investigational plan
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
Not specifically required	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 log with details

In regards to record keeping, FDA and ISO have different requirements regarding the content of what records are required to be maintained. ISO provides more stringent criteria than FDA by requiring the principal investigator or designee to sign and date printed as well as electronic CRFs. Additionally, ISO specifies that printed electronic source documents shall be signed and dated with a statement indicating they are a true reproduction of the original while FDA does not. Further, ISO requires the use of a delegation log and FDA does not. Conversely, FDA is more inclusive to note a timeframe of 2 years to retain records and 10 working days to notify them regarding records transfer. ISO states to follow the applicable regulatory requirement regarding the records retention period, but does not comment on notification regarding records transfer.

Conclusion > Care must be taken to follow FDA and ISO to ensure compliance

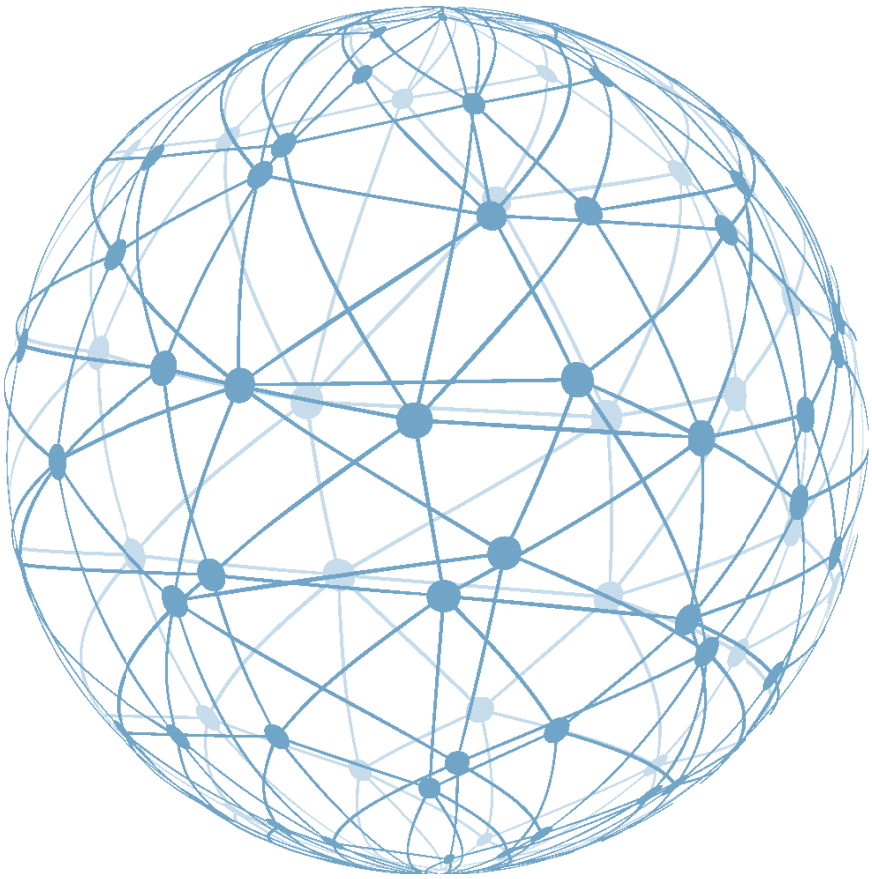

Table 4 – Inadequate accountability for the investigational product.

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: 2) Records of receipt, use, or disposition of a device that relate to: i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark. ii) The names of all persons who received, used, or disposed of each device. iii) 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 a) the date of receipt, b) identification of each investigational device (batch number/serial number or unique code), c) the expiry date, if applicable, d) the date or dates of use, e) subject identification, f) date on which the investigational device was returned/explanted from subject, if applicable, and g) the date of return of unused, expired or malfunctioning investigational devices, if applicable.

For device accountability, FDA and ISO do have some subtle but important differences in what is required. FDA states that the names of all persons who received, used, or disposed of each device, as well as the time each device was used, are required. ISO 14155 does not. ISO 14155 states that the investigator shall keep records documenting expiry date, whereas FDA does not. In this case, the investigator would be wise to ensure both of these nuances are documented. Once again, following ISO alone would subject the investigator to inspectional observations. Vice versa, following FDA regulations alone would result in potentially not recording expiry dates that are required per ISO 14155.

Conclusion > Care must be taken to follow FDA and ISO 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

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: (ii) 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: 1) 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 a) record every adverse event and observed device deficiency, together with an assessment, b) 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, c) 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, d) 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 e) supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

Regarding informed consent, ISO again demonstrates more stringent criteria than FDA. Specifically, ISO requires the signed and dated copy of the informed consent be provided to the subject whereas FDA requires only a copy. Also, while both indicate that subjects must be informed of new information learned during the course of participation, ISO is more detailed to note how it must be provided in written form confirmed in writing.

When examining the difference in safety reporting requirements, two themes emerge. While both require the investigator to record any observations that are adverse, ISO is more conservative than FDA when it comes to reporting. Specifically, ISO requires 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 only requires unanticipated adverse device effects to be reported in a timely fashion. Conversely to this, FDA again specifies a timeframe for reporting UADEs as soon as possible and no later than 10 days after becoming aware while ISO only specifies “without unjustified delay” without providing a hard and fast timeframe. One could view this to suggest that ISO requires more reporting in a looser timeframe while FDA requires less reporting in a tighter timeframe.

Conclusion > Care must be taken to follow FDA and ISO to ensure compliance

Summary

With industry conducting more and more device trials globally, now more than ever it is important to understand the differences between the FDA regulations and ISO 14155. The review provided herein indicates that the two exhibit a great deal more overlap than discrepancy. Conducting an investigation according to both tenets should result in the highest integrity device trial that affords the most stringent level of protection for human research subjects. While this may be challenging, it can be accomplished with hard work and proper preparation. Ensuring trials comply with both allows companies that conduct international trials to feel confident that the resulting data is acceptable not only in the U.S., but also to worldwide regulatory agencies.

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Shawn's introduction to working in clinical research was as a Clinical Research Coordinator at Case Western Reserve University. For seven years, he coordinated trials for the adolescent psychiatry department for over ten different studies – both industry- and NIH- sponsored. Shawn joined IMARC as a clinical research associate in March of 2012.

While at IMARC, Shawn has worked in various therapeutic areas, with much of his experience including various treatments for aortic aneurysms. He is also a part of IMARC's physician-sponsored IDE team, monitoring for studies where the physician holds the responsibilities of both the sponsor and the site. Shawn's background as a research coordinator has been extremely helpful as he truly understands what it takes to do the job. He immediately forms strong relationships with sites and consistently receives praise from sites and sponsors alike for his helpful approach and attitude. In January of 2014, Shawn became a Lead Clinical Research Trainer at IMARC. He has created and conducted multiple training activities ranging from full day workshops to web-based presentations for clients. He also coordinates IMARC's new employee orientation program. Shawn holds a BA in Psychology from Kent State University and a Masters in Clinical Psychology from The University of Tulsa. He is also a member of the Society of Clinical Research Associates where he holds his certification (CCRP).

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For more information on how you can help prepare your sites for a better outcome, starting from Day One, please contact John Lehmann at 440.801.1540 or via e-mail at jlehmann@imarcresearch.com.

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