



Comparing ICH E6 and ISO 14155 for Drug and Device Clinical Trials

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1000 W Buena Vista Drive Lake Buena Vista, FL 32830

Dr. Joy Frestedt, PhD, CPI, RAC, FRAPS

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Presenter: Dr. Frestedt



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Joy L. Frestedt, PhD, CPI, RAC, FRAPS is President and CEO of **Frestedt Incorporated** (www.frestedt.com) and **Alimentix, the Minnesota Diet Research Center** (www.alimentix.com).

Dr. Frestedt holds a PhD in Pathobiology from the University of Minnesota Medical School and a BA in genetics from Knox College. She is a member of SOCRA, RAPS, ASCO, AAPS and other organizations. Dr. Frestedt is among the “**100 Most Inspiring People in the Life Sciences Industry**” (PharmaVOICE, 2011) and the **top 25 “Industry Leaders”** (Minneapolis/St. Paul Business Journal, 2011). She recently authored the book “**Warning Letters: 2016 Reference Guide**” with Barnett International.

Dr. Frestedt has spent more than 35 years managing clinical trials, negotiating regulatory submissions and updating quality systems in health care, pharmaceutical, medical device and food industries including the University of Minnesota, Orphan Medical, Johnson and Johnson, Astra Zeneca, CNS Therapeutics, Mayo Clinical Trial Services, Medtronic, etc.

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Disclosure

I have no financial conflicts of interest related to this presentation.

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Course Overview

This talk will review TWO international standards:

ICH-E6 (R2) Addendum - International Good Clinical Practice (GCP)
standard for pharmaceutical clinical trials

AND

ISO 14155:2011 - International GCP standard for medical device clinical trials

Audience participation will be solicited to see how these
standards are working in the field right now.

Learning Objectives

- After attending this session, the learner should be able to:
 - Describe contents of ICH E6 (R2)(2016) and ISO 14155:2011
 - Identify similarities and differences between these guidelines for drug and device trials
 - Apply concepts from these two international guidelines to ensure clinical trial GCP.

Learning Objectives



Agenda

- Introduction, Terms, Ethics
- Investigator Role & Responsibility
- Sponsor Role & Responsibility
- Clinical Trial Conduct
- Conclusion



POLL: Audience Member Experience?

Show of hands

- 1) How many work with:
 - a) Drugs?
 - b) Devices?
 - c) Other (food, etc.)?
- 2) How many years in clinical research?
 - a) 0-3?
 - b) 3-10?
 - c) More than 10?
- 3) How many work in:
 - a) Industry?
 - b) Academic?
 - c) FDA?
 - d) Other (CRO, etc.)?

INTRODUCTION: ICH-E6 (R2) & ISO14155:2011

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

**INTEGRATED ADDENDUM TO ICH E6(R1):
GUIDELINE FOR GOOD CLINICAL PRACTICE**

E6(R2)

Current *Step 4* version
dated 9 November 2016

INTERNATIONAL
STANDARD

**ISO
14155**

Second edition
2011-02-01

**Clinical investigation of medical devices
for human subjects — Good clinical
practice**

*Investigation clinique des dispositifs médicaux pour sujets humains —
Bonnes pratiques cliniques*

Overview of ICH-E6 (R2) Amendment

ICH is a combined standard for the EU, Japan, US, Canada, Switzerland bringing regulatory authorities and the pharmaceutical industry together to develop mutually acceptable clinical trial data for regulatory purposes

R2 amends the GCP guideline for designing, conducting, recording and reporting human drug clinical trials

The amendment is meant to:

- Update investigator and sponsor responsibilities, esp. supervision and quality management using risk based approaches
- Improve risk based monitoring approaches, record keeping, root cause analysis and CAPA
- Ensure essential documents are stored for retrieval using certified copies as appropriate

Overview of ISO 14155:2011

International Organization for Standardization (ISO) is a federation of national standard bodies

Updated GCP guideline for clinical trial investigation of medical devices in humans for regulatory purposes

This revision is meant to:

- Protect rights, safety and well-being of human subjects
- Ensure scientific conduct of clinical investigation and credibility of clinical investigation results
- Define responsibilities of sponsor and principal investigator and add a list of essential documents for device trials similar to drug trials
- Assist sponsor, investigators, ethics committees, regulatory authorities and other bodies involved in conformity assessment of medical devices.

Major Similarities and Differences

ICH-E6 (R2)

- Created for pharmaceutical companies
- How to generate clinical trial data being submitted to regulatory authorities.

ISO 14155:2011

- Created for medical device companies
- How to perform a clinical trial to assess investigational medical devices
- Not applicable to *in vitro* diagnostics

Both international GCP guidelines focus on designing, conducting, recording and reporting results from clinical trials designed to assess the safety and efficacy/performance of drugs/devices.

POLL: Who uses these standards?

Show of hands

How many use ICH-E6? Every day?

How many use ISO-14155? Every day?

Anyone willing to speak up:

Any difficulties with NEW versions (R2 for ICH-E6 and 2011 for ISO1455)?

Any plans for the new ISO 14155? (final draft is circulating at ISO)

Let's Compare TERMS



Next 8 slides are for reference, we will not cover these terms in detail, but please note the language artistry...

Key Terms to Compare

ICH-E6 (R2)

- **Adverse Event (AE)**
- Adverse Drug Reaction (ADR)
- **Serious Adverse Event (SAE)**
 - ✓ Serious Adverse Drug Reaction (SADR)
- Clinical Trial/Study
- International Research Board (IRB)/Independent Ethics Committee (IEC)
- Protocol
- Investigational Product (IP)

ISO 14155:2011

- **Adverse Event (AE)**
- Adverse Device Effect (ADE)
- **Serious Adverse Event (SAE)**
 - ✓ Serious Adverse Device Effect (SADE)
- Clinical Investigation
- Ethics Committee (EC)

- Clinical Investigation Plan (CIP)
- Investigational Medical Device

Adverse Event (AE)

ICH-E6

- Any untoward medical occurrence in a patient or clinical investigation subject **administered a pharmaceutical product** and that does not necessarily have a causal relationship with this treatment.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally **associated with the use of a medicinal (investigational) product**, whether or not related to the medicinal (investigational) product

ISO14155:2011

- Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, **whether or not related to the investigational medical device.**
- Includes events related to the investigational medical device or the comparator and events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational medical devices.

**Can an AE exist without exposure to the test product?
Does Risk Based thinking apply here?**

Adverse Drug Reaction, Device Effect

ICH-E6

Adverse drug reaction (ADR):

- “All noxious and unintended responses to a **medicinal product** related to any dose should be considered ADRs.”
- “A causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.”

ISO14155:2011

Adverse device effect (ADE):

- “Adverse event related to the use of an **investigational medical device**.”
- “Includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.”
- Includes events resulting from user error or intentional misuse of investigational medical device

Both ADR and ADE require a possible link between the test product and any unintended/adverse responses/effects

Serious Adverse Event

ICH-E6

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

- An adverse event at **any dose level** resulting in death, life-threatening condition, inpatient or prolonged hospitalization, persistent/significant disability/incapacity or congenital anomaly/birth defect

ISO14155:2011

Serious Adverse Event (SAE) Serious Adverse Device Event (SADE)

- An adverse (device) event leading to death, serious health deterioration resulting in life-threatening illness/injury, permanent impairment, inpatient or prolonged hospitalization, **OR medical or surgical intervention to prevent the above**, OR led to fetal distress/death or congenital anomaly/birth defect
- “NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, **without serious deterioration in health**, is not considered a serious adverse event”

ICH-E6 does not explicitly include medical intervention to prevent SAE and does not explicitly exclude planned hospitalizations from SAE definition

Clinical Trial, Study, Investigation

ICH-E6

Clinical Trial/Study:

- Investigation in humans subjects intended to discover or verify the effects of an **investigational product**.
- The terms clinical trial and clinical study are synonymous.

ISO14155:2011

Clinical Investigation:

- “Clinical investigation in one or more human subjects, undertaken to assess the safety or performance of a **medical device**.”
- “Clinical trial” or “clinical study” are synonymous with “clinical investigation

Clinical trial, clinical study and clinical investigation are synonymous and interchangeable

IRB, IEC, REC, EC

ICH-E6

International Research Board (IRB)/Independent Ethics Committee (IEC):

- Independent bodies consisting of medical/non-medical members responsible for the rights, safety and well-being of human subjects involved in a trial by reviewing, approving, and providing continuing review of trial protocol.
- The legal status of the IEC is different in each country, but should allow the IEC to act in agreement with the GCP in this guideline

ISO14155:2011

Ethics Committee (EC):

- Independent body responsible for reviewing clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation
- “For the purposes of this International Standard, ‘ethics committee’ is **synonymous** with ‘research ethics committee’ or ‘institutional review board.’”

IRB/IEC/REC/EC are synonymous bodies protecting human subjects but international ethics regulations may vary slightly

Protocol, Clinical Investigation Plan

ICH-E6

Protocol:

- States the “objectives, design, methodology, statistical considerations, and organization of a trial.”
- “Usually gives the background and rationale for the trial.”
- In ICH-E6, protocol refers to both, protocol and protocol amendments.

ISO14155:2011

Clinical Investigation Plan (CIP):

- States the “rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.”
- “Protocol” and “CIP” are interchangeable, but protocol can also refer to meanings not related to clinical investigations, and these vary from country to country. Therefore, ISO 14155 uses the term CIP.

Protocol and CIP are synonymous and interchangeable; however, protocol is used widely in many non-human settings

Investigational Product, Medical Device

ICH-E6

Investigational Product (IP)

- A **pharmaceutical form of an active ingredient or placebo** being tested or used as a reference in a clinical trial
- Includes products used for unapproved indication or to gain further information about approved use

ISO14155:2011

Investigational Medical Device

- “**Medical device** being assessed for safety or performance in a clinical investigation”
- Interchangeable with “investigational device”

IP can be used for drugs or devices

Let's Compare Ethics



Lots of similarities...
including oversight by
Ethics Committee (EC)

Ethic Committee (EC) Role and Responsibilities

- ECs are responsible for overseeing research and protecting rights, safety and well-being of trial subjects.
 - EC must establish and follow procedures
 - Determine frequency of review
 - Notify members of meetings
 - Make decisions with at least quorum
 - Specify no subject allowed in a trial before approval
- ICH-E6 specifies at least 5 members
 - at least 1 whose primary area of interest is nonscientific
 - at least 1 who is independent of the institution/trial site
- EC may invite nonmembers for special areas



EC Functions

Both guidelines state ECs must review and make a decision in a reasonable amount of time about the following documents:

- Trial protocol
- Written informed consent forms
- Available safety information
- Payment and compensation made available to subjects
- Subject recruitment procedures
- Investigator's Brochure (IB)
- Investigator's current curriculum vitae (CV),
- Other relevant documents needed to make a decision.
- The EC might also need to submit draft case report forms (CRF), payment related documents, compensation to PI or institution, conflicts of interest and CI insurance

Sponsor / Investigator / Staff must avoid improper influence and should only deviate from protocol/CIP in emergencies (deviations are reported to EC)

Let's Compare Investigator Responsibilities



Investigator: Qualifications and Resources

ICH-E6 (R2)

- Comply with GCP and regulatory requirements
- Allow sponsor to monitor and audit and regulatory authorities to inspect
- Maintain list of appropriately qualified persons with delegated trial duties

ISO 14155:2011

- Disclose conflicts of interest (including financial) with clinical investigation
- Know how to obtain informed consent

Both guidelines require the Investigator to:

- Be qualified by training, education and experience, must be trained on the protocol, use of IP and responsible to train others to follow the protocol.
- Manage day to day conduct and will demonstrate the site has the necessary number of eligible subjects within a time period
- Maintain qualified staff and facilities throughout the trial

Investigator: Investigational Products

ICH-E6 and ISO14155:2011



Investigator is responsible for investigational products/devices (IP)



Investigator may assign duties to others (e.g, for product accountability, etc.)



Investigator records must document receipt, use, return, disposal of IP

Product Use, Medical Care, Protocol Compliance

ICH-E6 (R2)

- Explain IP use to each subject and check that instructions are followed at appropriate intervals

ISO 14155:2011

- Provide subject with instructions on proper use, handling, storage and return of investigational device, and procedures for possible emergency situations related to the trial

Both guidelines require the Investigator to:

- Ensure adequate medical care is provided (e.g. physician, dentist for medical/dental decisions)
- Communicate with the EC and ensure compliance with EC/informed consent process and protocol directions
- Advise subject's physician when additional medical care is required (e.g., for AE or intercurrent illness)
- Make "reasonable effort" to ascertain reasons for withdrawal while respecting subject rights/privacy
- Protocol deviations must be explained, source documents maintained and CRFs must be accurate

Investigator: Safety Reporting

ICH-E6 (R2)

- Report all SAEs to sponsor, except for those where protocol identifies no need for immediate reporting
- Report unexpected SAEs to regulatory authorities and IRB/IEC, as required by regulations
- Report critical safety AEs to the sponsor
- Report deaths to the sponsor and IRB/IEC and provide any additional requested information (e.g., autopsy reports, etc)

ISO 14155:2011

- All AEs and device deficiency shall be recorded and assessed
- All SAEs and device deficiencies that could have led to SADE should be reported to sponsor, detailed in a report and reported to EC and regulatory authorities
- Supply sponsor with additional requested information related to safety reporting of an event.

Both guidelines require investigators to:

- Report safety information (e.g., SAEs, deaths) to the sponsor, IRB/IEC and regulatory authorities

Let's Compare Sponsor Responsibilities



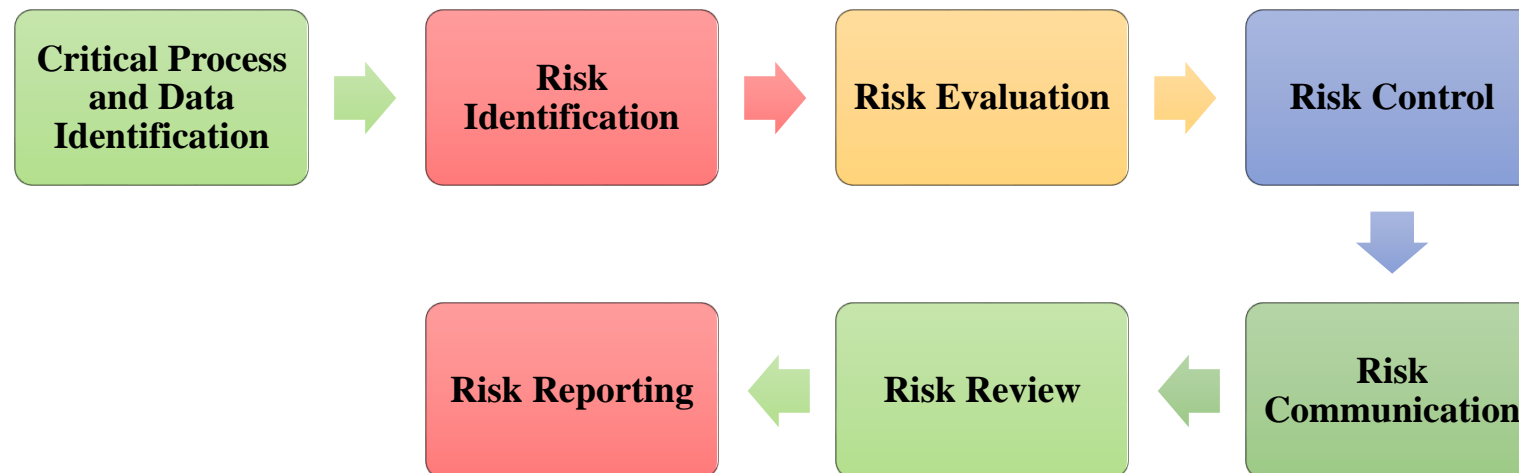
Sponsor: Quality Management

ICH-E6 (R2)

- More detailed quality management guidelines compared to ISO:14155
- Implement system to manage quality throughout all trial stages and focus on essential activities
- Use risk-based approach to quality management

ISO 14155:2011

- Refers to ISO 14971 for risk management process



Sponsor: Quality Assurance and Control

ICH-E6 (R2)

- Quality Control and Assurance should be included in the protocol and essential documents
- Secure “agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports.”
- Apply quality control (QC) to data handling to ensure reliable data (processed correctly)
- Clinical Trial Agreements should be in writing

ISO 14155:2011

- Keep record/document all parties involved in trial
- Use QC methods to meet auditing requirements
- Justify and document exceptions to requirements
- Refers to ISO 13485 for quality management

Both guidelines require sponsors to:

- Implement/maintain quality assurance and control system with written procedures (SOPs)
- Ensure trial/investigation is conducted and data are generated, documented, reported in compliance with protocol, GCP and regulatory requirements

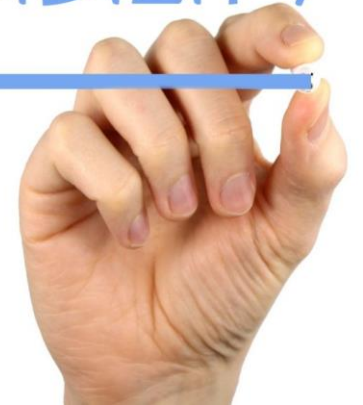


Sponsor: Contract Research Organization

ICH-E6 (R2) [and ISO14155:2011]

- Sponsor may transfer any or all duties and function to a CRO with signed agreement, “but the ultimate responsibility for the quality and integrity of the trial [clinical investigation] data always resides with the sponsor.”
- All requirements that apply to sponsor also apply to the CRO (if transferred to CRO)
- Transferred CRO duties and functions should be specified in writing

RESPONSIBILITY



Sponsor: Monitoring

Note: The extent and nature of “risk-based” monitoring was added to the newest ICH-E6

ICH-E6 (R2)

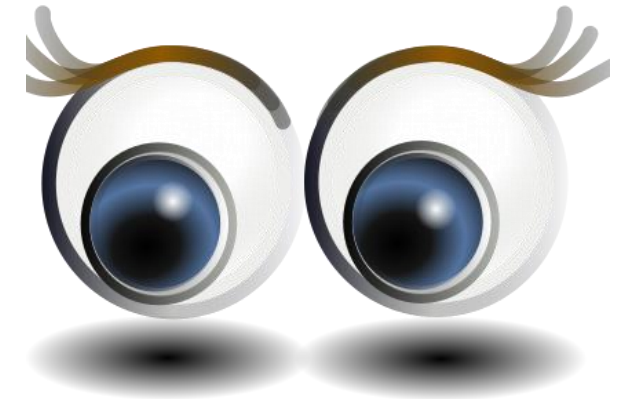
- Monitors must be appropriately trained and documented to have adequate scientific/clinical knowledge and to be thoroughly familiar with the IP, protocol, ICF, SOPs, GCP and regulatory requirements.
- Sponsor must ensure trials are “adequately monitored” using “risk-based” approach with sufficient oversight of monitoring procedures and reports following the monitoring plan.

ISO 14155:2011

- Monitoring plan (which may be separate from CIP) is to be followed to monitor the conduct of the clinical investigation
- On-site vs. remote monitoring are discussed

Both guidelines require sponsors to:

- Appoint/oversee qualified monitors to verify subject “rights and well-being” are protected, data are “accurate, complete and verifiable from source documents” and trial conduct complies with protocol, GCP and regulatory requirements
- Follow a Monitoring Plan



Sponsor: Auditing Guidelines

ICH-E6 (R2)

- Purpose is to have an evaluation of trial conduct and protocol compliance independent from routing monitoring or quality controls
- Sponsor appoints individuals who are independent, qualified, and experienced
- Procedure
 - Document observations and findings
 - Shouldn't frequently request audits to preserve independence of the audit function.

ISO 14155:2011

- Clinical Trial audits “may be conducted by the sponsor or third parties designated by the sponsor to evaluate compliance with the CIP, written procedures, this international standard and the applicable regulatory requirements.”
- Audits are useful:
 - To assess monitoring effectiveness
 - To assess serious/repeated CIP deviations or suspicion of fraud
 - To prepare a site for regulatory inspection

Both guidelines require sponsors to:

- Ensure auditors are qualified by training and experience to conduct audits appropriately
- Ensure audits comply with sponsor written procedures (e.g., appropriate frequency, documented in audit report).

Sponsor: Reports

ICH-E6 (R2)

- Clinical trial reports needed for marketing applications should “meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports.”

ISO 14155:2011

- Ensure written reports includes: device identification, methodology, CIP deviations, “data analysis together with any statistics and a critical appraisal of the aims of the clinical investigation”
- If reviewer does not agree with the report, sponsor must record the comments and communicate this to other investigators
- Sponsor and PI keep documents as required

Both guidelines require sponsors to:

- Ensure “...clinical trial reports are prepared and provided to the regulatory agency(ies) as required” – regardless of trial completion or early termination
- Issue a signed and dated final study report, if required
- Give report to sponsor, site investigators (for review and comment), IRB/IEC, regulatory authorities, as required
- Ensure audits comply with sponsor written procedures (e.g., appropriate frequency, documented in audit report).



Let's Compare Clinical Trial Conduct

- **Informed Consent**
- **Investigator Brochure**
- **Protocol**



Informed Consent

ICH-E6 (R2)

- Process should follow GCP, IRB/IEC, and other applicable regulatory requirements
- In emergency situations, preapproved IRB/IEC protocols are implemented when obtaining consent is not possible
- Non-therapeutic trial should be done only subjects who personally give consent and date/sign.

ISO 14155:2011

- CIP contains process for obtaining consent
- Some emergency treatments require consent to be obtained as soon as possible, but is not required to follow a preapproved EC protocol
- Non-therapeutic trials and investigations are not discussed

Note: Consent is always obtained before beginning of the trial or any procedure. Process cannot allow subject to waive any legal rights or be coerced/influenced to continue. If subject is unable to read, a witness can explain the form to the individual and oral consent can be obtained.

Investigator's Brochure Contents

ICH-E6 (R2)

- Title page, Table of contents, Summary, Introduction
- Confidentiality statement
- **Physical, chemical, and pharmaceutical properties and formulation**
- Nonclinical studies
- **Effects in humans**
- Summary of data and guidance for the investigator

ISO 14155:2011

- General
- Investigational device information
- **Preclinical testing**
- Existing clinical data
- **Risk management**
- Regulatory and other references

Significant differences between the ICH-E6 and ISO 14155 IBs exist; however, both guidelines indicate the IB is meant to provide safety and efficacy/performance data from all nonclinical and clinical trials to assist investigators during the clinical trial.

Clinical Trial Protocol and CIP Contents

ICH-E6 (R2)

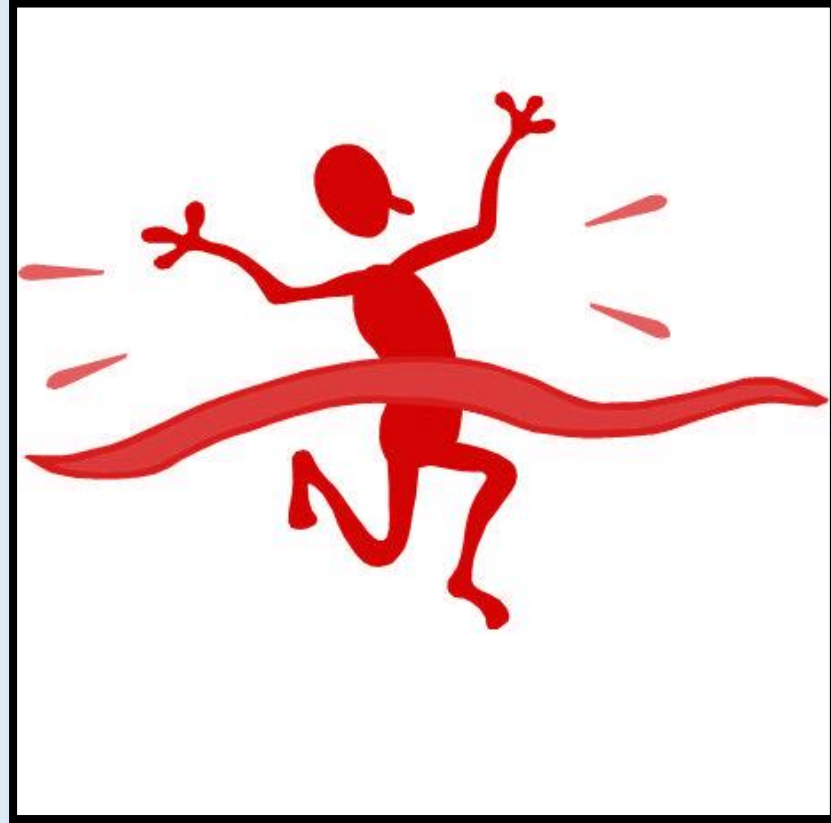
- General Info and Background
- Trial Objectives, Purpose and Design
- Selection and withdrawal of subjects
- **Treatment of subjects**
- **Assessment of efficacy and safety**
- Statistics
- Direct access to sources data/documents
- Quality control and assurance
- Ethics
- Data handling, financing and insurance
- Publication policy and supplements

ISO 14155:2011 – CIP Contents

- Introduction
- **Investigational Device Description**
- Justify design and discuss risks and benefits
- Objectives and hypotheses
- Clinical Investigation Design (I&E, procedures, monitoring plan)
- Statistical Design
- Data management
- Amendments to CIP and deviations from CIP
- **Device Accountability**, Statements of compliance and informed consent process
- AEs, ADEs, device deficiencies
- Vulnerable population, suspension or premature termination, publication policy

Significant differences between protocols exist; however, both guidelines require the protocol to include a trial design to minimize bias (e.g., randomization and blinding) and to include objectives, primary/secondary endpoints, etc.

Conclusion



Agenda

- Introduction, Terms, Ethics
- Investigator Role & Responsibility
- Sponsor Role & Responsibility
- Clinical Trial Conduct
- Conclusion



Learning Objectives

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 - Describe contents of ICH E6 (R2)(2016) and ISO 14155:2011
 - Identify similarities and differences between these guidelines for drug and device trials
 - Apply concepts from these two international guidelines to ensure clinical trial GCP.

Learning Objectives



Questions?



Thank You for listening!

Frestedt Incorporated

952-426-1747

info@frestedt.com

www.frestedt.com

Dr. Joy Frestedt
President and CEO

612-219-9982

jf@frestedt.com