ISO 14155:2020 Clinical Investigation Planning (July 2020)

Slides released 04NOV2020

DISCLAIMER

These slides are not meant to replace the purchase of the ISO 14155:2020 standard from ISO available at https://www.iso.org/standard/71690.html

These YouTube discussions exist, too:

https://www.youtube.com/watch?v=WK7X3nrJVyo

https://www.youtube.com/watch?v=TG8GTPTDrYk

ISO 14155 Version History and Resources

- ISO 14155 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS — GOOD CLINICAL PRACTICE [CURRENT]

- ISO 14155:2011 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS — GOOD CLINICAL PRACTICE [WITHDRAWN]
  - ISO 14155:2011/COR 1:2011 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS — GOOD CLINICAL PRACTICE — TECHNICAL CORRIGENDUM 1 [WITHDRAWN]

- ISO 14155-1:2003 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS — PART 1: GENERAL REQUIREMENTS [WITHDRAWN]
  - ISO 14155-2:2003 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS — PART 2: CLINICAL INVESTIGATION PLANS [WITHDRAWN]

- ISO 14155:1996 CLINICAL INVESTIGATION OF MEDICAL DEVICES [WITHDRAWN]

Major Changes

ISO 14155:2020 includes new guidance for:

- Clinical quality management
- Risk based monitoring and related monitoring plans
- Addressing increased statistical requirements by notified bodies
- Ethics committees
- Clinical investigation audits
- In-vitro diagnostic medical devices (IVDs)

Major Changes

- Increased emphasis on risk management (ISO 14971)
- Clinical investigation planning requires inclusion of personnel with relevant medical expertise
- Alignment with definitions with current updated GCP guidelines
- Emphasis of clinical evidence in European Regulations

ISO 14155:2020 implementation should not result in major changes in clinical research operations if already in compliance with ISO 14155:2011

ISO 14971:2019

- Application of risk management to medical devices
- Major components include:
  - Risk management system
  - Risk analysis
  - Risk evaluation
  - Risk control
  - Evaluation of residual risk
  - Risk Management review
  - Production and post-production activities

Risk Management in Practice

- Implementation ISO 14971 involves a system for risk management
- Risk Management Plan identifies, evaluates, ranks and controls risks
  - RMPs can be inclusive of risk from entire product life cycle
  - Risks can be product related or patient related
  - Can be applied to project specific risks (clinical trials)
- Formal risk management processes is focus of ISO 14155:2020

Clinical Quality Management

- Quality Management processes include SOPs, computerized quality systems and personnel training
- Sponsor is responsible for clinical study quality even if study management is outsourced to third-party
- Document control process for study files such as protocol, IB, etc.
- Complete records maintenance
- Preparation for audits
- Identify, justify and document exceptions to requirements

European Regulations

- European Medical Device Regulation (EU MDR 2017/745) implementation is currently ongoing
- Aim is to increase patient benefit risk ratio by increasing clinical data requirements
- ISO 14155:2020 Annex ZC details how “General Safety and Performance Requirements of Regulation (EU) 2017/745” is addressed / implemented in document

Scope (1)

Addresses good clinical practices (design, conduct, recording, reporting) for clinical investigations in human subjects (clinical performance or effectiveness and safety) of medical devices.

- Protection of subjects
- Ensure scientific conduct
- Defines responsibilities of principal investigator (PI), sponsor, other parties

Normative References (2)

Normative documents are referred to in the text so their content is required for this document.

- ISO 14971, Medical devices – Application of risk management to medical devices

Terms and Definitions (3)

ISO and IEC maintain terminological databases for standardization

- ISO : http://www.iso.org/obp
- IEC: http://electropedia.org/

Commonly used terms:

- Adverse Event (AE)
- Case Report Form (CRF)
- Medical Device (software, reagent for *in vitro* use, etc.)

* Some jurisdictions have different criteria for medical devices (*in vitro* devices, devices with animal/human tissue)

Summary of Good Clinical Practice (GCP) Principles (4)

- Ethical principles
- Risk-benefit ratio
- Rights, safety, well-being of subjects
- Scientifically sound
- Ethics Committee (EC) approval
- Expert advice and care
- Education/experience
- Privacy, confidentiality
- Systems for quality control

Ethical Considerations (5)

Principles in Clause 4 must be understood, observed and applied in every step in the clinical investigation.

https://www.coursebuffet.com/course_images/coursera/vacctrials.png

- Coercion
- Compensation
- Registration and public access
- Responsibilities (all parties)
- Communication with EC (use this document and record)
- Information from EC (approval documents)
- Informed consent

Frestedt incorporated

EC Responsibility (Annex G)

Provides guidance on best practices for operation of EC reviewing clinical investigations of medical devices.

- Purpose of EC

Composed of members who collectively have experience/qualification to review/evaluate scientific medical, methodological, statistical and ethical aspects of proposed clinical investigation

- Members
- Procedures/records

Clinical Development Stages (Annex I)

Provides possible types of clinical investigations in different clinical development stages and from a regulatory status applies to both pre- and post-market clinical investigations.

- Pre-market clinical investigation
- Post-market clinical investigation
- Clinical development stages (pilot, pivotal and post-market stage)
- Types of clinical investigation design (Exploratory, confirmatory and observational)

Clinical Development Stages (Annex I)

- Description of clinical investigations
  - First in human clinical investigation
  - Early feasibility clinical investigation
  - Traditional feasibility clinical investigations
  - Pivotal clinical investigation
  - Registry

Clinical Development Stages (Annex I)

APPLICABILITY OF THIS DOCUMENT'S PRINCIPLES

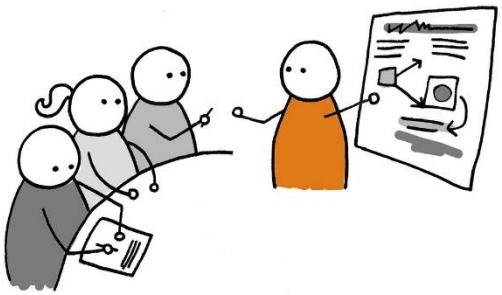
The principles of this document are expected to protect human subject's rights, safety and well-being, scientific outcome and credibility of clinical data and overall risk management of clinical investigation of medical devices.

http://www.bodyprojex.com/understanding-how-the-depuy-knee-replacement-recall-may-affect-you/

Frestedt incorporated

Clinical Investigation Planning (6)
General (6.1)

- All involved with trial design and conduct must be qualified by education, training or experience.
  - Qualifications must be documented
- The sponsor must have access to medical expertise relevant to the trial



https://www.flickr.com/photos/flat61/3883611573

https://www.flickr.com/photos/cwkarl/13317874924

Risk Management (6.2)

Balance risks associated with device and related clinical procedure (including follow-up) against anticipated benefits to subjects

The sponsor should predefine risk acceptability thresholds

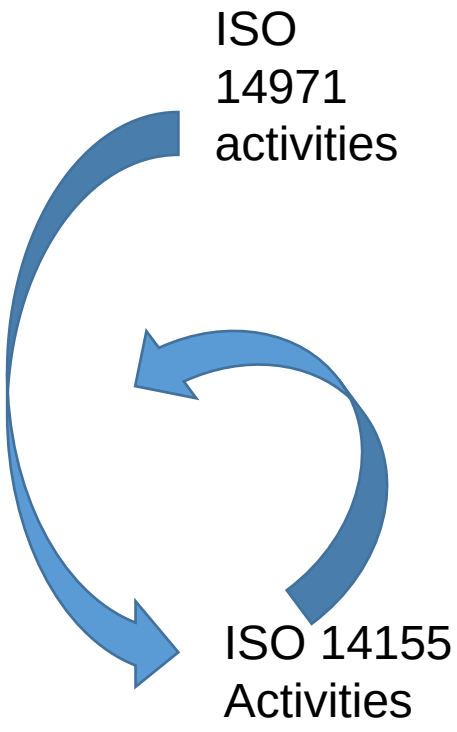
- If threshold is reached or exceeded, risk assessment to determine whether/what actions are needed

Application of ISO 14971 (6.2, Annex H)

ISO14971 about risk management for medical devices

Risk control effectiveness evaluated through device lifecycle, including during trials

Trials provide data to support/refute acceptability of benefit-risk ratio



Design of Clinical Investigation (6.3)

Design trial to evaluate if device suitable for intended purpose and population.

Design based on pre-clinical data and clinical evaluation, aligned with risk assessment

- Clinical evaluation includes analysis of clinical performance, effectiveness and safety data of investigational device **or similar device**
- Use to justify endpoints, confounding factors, choice of control group(s), bias minimization, subject selection

Clinical Investigation Plan (CIP) (6.4, Annex A)

- Identification of CIP, Sponsor, principle investigator, coordinating investigator and investigation sites
- Objectives and hypothesis of clinical investigation
- Synopsis of investigation
- Identification and description of investigational device
- Design of clinical investigation including:
  - Investigation device(s) and comparator(s)
  - Subjects (e.g. inclusion/exclusion criteria)
  - Procedures
  - Monitoring Plan
- Justification of design
- Statistical design and analysis
- Data management (e.g. methods for data entry and collection, procedures for database cleaning)
- Benefits and risks of investigational device, clinical procedure and clinical investigation
- Description of procedures to amend CIP
- Deviations from CIP (e.g. Statement saying cannot deviate except as specified, procedures of recording and reporting deviations)
- Device accountability
- Statements of Compliance
- Informed Consent Process
- Adverse events, adverse device effects, device deficiencies
- Vulnerable Populations (if applicable)
- Suspension or premature termination of investigation
- Publication Policy
- Bibliography

Investigator's Brochure (IB) (6.5, Annex B)

Purpose: To provide principal investigator and investigation site team with sufficient safety and performance data to justify human exposure to investigational device

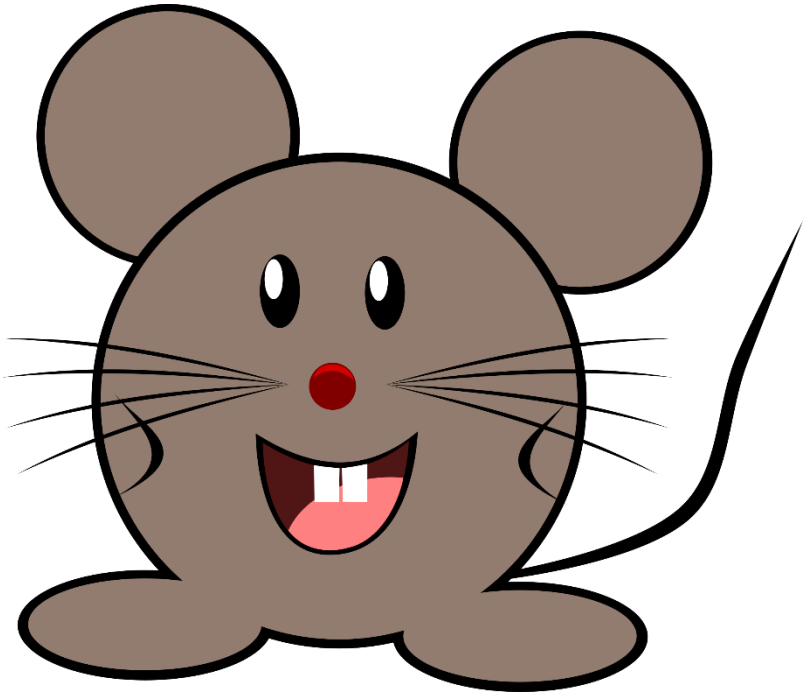
- Principal investigator(s) acknowledge receipt in writing and keep confidential

Update throughout investigation as new data becomes available

Update if investigational device design changes

IB Components (Annex B)

- Identification of IB
- Sponsor/Manufacturer
- Investigational device information
- Preclinical Testing
- Existing Clinical Data
- Risk Management of investigational device
- Regulatory and other references



Case Report Form (CRF) (6.6, Annex C)

Captures data for each enrolled subject

- Condition of each subject at beginning and throughout investigation
- Exposure to investigational device and other therapies

Format should minimize errors

- e.g. To avoid repeat entries, pre-print or pre-program elements such as name of clinical investigation, CRF version #, investigator identification number

CRF completion guidelines provide instructions for accurate completion, correction and signature of CRFs

If CIP amended, CRFs should be reviewed to determine if need revised

Risk Disclosure

Benefit-risk summary should be disclosed in relevant trial documents. For example:

- Residual risk in Investigator's Brochure (IB) and Instructions for Use (IFU)
- All anticipated AE device effects in Clinical Investigation Plan (CIP) and Informed Consent Form (ICF)
- Rationale for benefit-risk ratio in CIP

Monitoring Plan (6.7)

Determine appropriate monitoring based on risk assessment.

- Monitoring methods can differ between countries and should comply with national or regional regulations regarding personal data protection

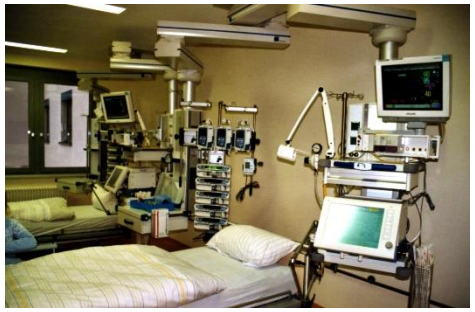
Monitoring Plan describes:

Risks and risk control measures	Monitoring methods [e.g. on-site, centralized (off-site)]	Methods for documenting and communicating monitoring results
Escalation process if continuous or egregious non-compliance	Aspects of investigation needing special attention	Processes to be monitored and data to be verified in source documents

Investigation Site Selection (6.8)

Identify criteria necessary for successful conduct of clinical investigation prior to start of site qualification, e.g.:

- Facilities required
- Principal investigator's qualifications
- Type of environment (e.g. home-based vs hospital)



Principal investigator(s) qualifications and investigation site(s) adequacy verified and documented in investigation site selection report

Agreements (6.9)

Written agreement between sponsor and principal investigator(s)/investigation site(s) and other relevant parties (e.g. laboratories, CROs) should be signed and dated by all parties

Agreement should detail responsibilities of each party

Agreement should identify instances where parties share regulatory responsibilities with sponsor

Labeling (6.10)

The device, IFU and packaging should state device is exclusively for use in a clinical investigation. In US, investigational label as per 21 CFR 812.5:

Frestedt incorporated

Clinical Investigation Conduct (7)
General (7.1)

- Conducted in accordance with CIP
- Not to commence until EC and/or regulatory approvals are obtained

https://www.flickr.com/photos/41284017@N08/8002885292

Investigation Site Initiation (7.2)

Initiation visit for each investigation site or an investigator meeting shall be conducted and documented by sponsor or monitor at start of the clinical investigation.

- Log with names, initials, signatures, functions and designated authorizations for principal investigator and members of investigation site team
- This may be done by telephone or other means

Investigation Site Monitoring (7.3)

- Conduct of clinical investigation monitored according to monitoring plan
- All monitoring activities documented

Adverse Events and Device Deficiencies (7.4)

7.4.1 AE or device deficiencies potentially indicating a serious health threat are evaluated by sponsor. May require a specific reporting process according to regulatory requirements.

7.4.2 All AE and any new information are documented in a timely manner and reported as specified (see AE Categorization). All AE are reported in interim and final reports.

Adverse Events and Device Deficiencies (7.4)- continued

7.4.3 Device deficiencies documented throughout clinical investigation and managed by sponsor as specified for control of non-conforming product. All deficient devices are returned for evaluation and reports submitted even if deficiency did not cause AE but could have caused serious AE

Adverse Events and Device Deficiencies (7.4)- continued

7.4.4 Arising risks during clinical investigation

a) Any person identifying risk potentially impacting safety informs principal investigator and sponsor

b) Sponsor shall perform risk analysis with principal investigator to determine if information is reflected in current risk assessment and risks remain acceptable. If unacceptable, and serious health threat identified, sponsor shall suspend trial immediately.

c) If a possible unacceptable risk, sponsor shall conduct risk assessment in compliance with ISO 14971 with possibility of 1) risks remain acceptable, 2) corrective actions found not affecting validity of investigation with revised benefit-risk may continue investigation, 3) if corrective actions affect validity of trial, trial is to be terminated, 4) if no corrective actions may be applied, investigation is to be terminated.

Clinical Investigation Documents (7.5)

- Amendments are made as needed throughout investigation following written procedures with documentation reviewed and approved as specified.
- Subject identification log maintained at each investigation site with an identification code linked to their private information
- Source documents are maintained by investigation site team throughout clinical investigation

Additional Members of the Investigation Site Team (7.6)

New members added to investigational site teams will only start their assignment after receiving adequate training and training is documented.

https://www.agcareers.com/uploads/Grain%20Buyer.png

Subject Privacy and Confidentiality of Data (7.7)

- Confidentiality observed by all involved parties and data is secured against unauthorized access.
- Privacy of subjects is preserved in all reports and publications.

Document and Data Control (7.8)

Traceability of Documents and Data

All documents produced and maintained ensuring reliability, integrity, control and traceability including all versions of documents. Source documents are verified and signed.

Recording of Data

Data on CRFs from source documents and discrepancies explained in writing. All CRFs are signed and dated.

Electronic Clinical Data Systems

Written procedures are used to describe system validation, data collection, security, backup and recovery. Ensure no deletion of entered data and changes can be followed via an audit trail.

Investigational Device Accountability (7.9)

- Access to devices is controlled and only used in the clinical investigation following the CIP.
- Physical location of all devices documented
- Records shall be kept on:

a) name of person received, used, returned or disposed of device
b) date of receipt, identification and quantity of devices
c) expiry date if applicable
d) date(s) of use
e) subject identification
f) date device returned or explanted from subject
g) return date of unused, expired or malfunctioning devices

Accounting for Subjects (7.10)

- All subjects accounted for and documented
- If subject discontinues, the reason(s) shall be recorded
- Investigator may use existing data on the subject and may ask for permission to obtain follow-up information

https://www.flickr.com/photos/144152028@N08/33772074972

Auditing (7.11, Annex J)

- Audits may be conducted to evaluate compliance to CIP, written procedures, ISO 14155 and applicable regulatory requirements
- Audits may cover all involved parties and are separate from quality control or routine monitoring functions
- Auditors shall be independent of the clinical investigation
- Audit results are documented and communicated to relevant parties.

Suspension, Termination, and Close-Out of the Clinical Investigation (Section 8)

8.1 Completion of clinical investigation may be pre-specified by the plan or terminated early

Completion coincides with:

- Last visit of the last subject
- When follow up is complete

Suspension or Premature Termination (8.2)

May suspend entire investigation or single site

- May be suspended or terminated by: sponsor, principal investigator, EC or regulatory authority
- Justify in writing and inform all parties
- Reasons for suspension or termination:
  - Suspicion of unacceptable risk
    - Suspend for risk assessment, terminate if risk is unacceptable
  - Serious or repeated deviations by investigator
- Sponsor is responsible for obligations to participants

Resuming After Temporary Suspension (8.2.2)

After problem analysis and corrective actions in place:

- Inform principal investigators (PI), ECs and regulatory authorities (when applicable)
  - Provide with reasoning and supporting data
- ECs and regulatory authorities (when applicable) must concur BEFORE clinical investigation resumes

https://commons.wikimedia.org/wiki/File:Red-approved.gif

Routine Close-Out (8.3)

Close-out activities:

- PI records and sponsor's file complete and up to date
  - Case Report Forms (CRF) complete, Adverse Event (AE) status documented
  - Record retention and archival arrangements in place
- Remaining materials disposed of
  - Devices, samples, other materials
- All identified issues resolved
- All parties notified
  - EC, regulatory body (if applicable), study database

Clinical Investigation Report (8.4)

Report for all clinical investigations should follow Annex D

- Include: device information, methodology, clinical investigation design, clinical investigation protocol (CIP) deviations, data analysis, results compared to investigation objectives
- Report covers all participants at all sites
  - No identifiable participant information
- Sponsor and PI or coordinating investigator sign-off
  - Report provided to all PIs, EC and regulatory authorities
- Results updated in clinical investigation database and published

Clinical Investigation Report (Annex D)

Annex D outlines a detailed format for the clinical investigation report to follow and specifies the content required for the report

Risk Assessment and Conclusions (8.5)

Risk information should be formally reviewed; data and conclusions should be updated in risk analysis and clinical evaluation documents

Document Retention (8.6)

- Both sponsor and PI are responsible for maintaining clinical investigation documents
  - Custody may be formally transferred if necessary

- CIP, IB, CRF and final reports should be kept in the manufacturer's Quality Management System (QMS) and incorporated in the device technical documents (when possible)

Essential Clinical Investigation Documents (Annex E)

- Tables E.1- E.3 include lists of documents to maintain
  - Includes document names, purposes, who needs to keep them, where to find them in ISO 14155
- Regulatory bodies may require a list of all documents
  - Record location of essential documents
  - Version histories required
  - Easy to search and retrieve

Sponsor Responsibilities (9)

- Ensure quality, planning, conduct, monitoring, management and regulatory approval of studies

Clinical Quality Management (9.1)

- Create and maintain quality procedure documents
- Maintain compliance records
- if applicable, ensure auditing requirements are met per ISO 14155
- Document and justify significant exceptions to ISO 14155 requirements

Clinical Investigation Planning and Conduct (9.2)

- **Selection and training of clinical personnel**
  - define, establish, and allocate roles and responsibilities
  - select appropriately qualified principal investigators
- **Preparation of documents and materials**
  - prepare documents in accordance with Clauses 5-7
  - ensure documents are approved by relevant persons with dated signature
- **Conduct of clinical investigation**
  - accountability of investigational devices for entirety of trial

Clinical Investigation Planning and Conduct (9.2)

- **Monitoring**
  - accurate, complete and verifiable data
  - qualified in the field, knowledgeable on the use of the investigational device, trained
  - All monitoring activities shall be documented and reported to the sponsor
- **Safety evaluation and reporting**
  - responsible for AE classification and ongoing safety evaluation
- **Clinical investigation close-out**
  - ensure close-out activities are properly completed

Outsourcing of Duties and Functions (9.3)

- Sponsor may transfer duties and functions (e.g. monitoring) to external organization
- Sponsor responsible for verifying external organization adheres to written procedures

https://commons.wikimedia.org/wiki/File:Transfer-left_right.svg

Communication with Regulatory Authorities (9.4)

- Obtain regulatory authority approval/non-objection (including any amendments)
- report progress and status of investigation
- perform safety reporting
- report if investigational devices withdrawn from site due to safety or performance issues

Responsibilities of the Principal Investigator (10)

- PI is responsible for patient safety and oversight of all site activities

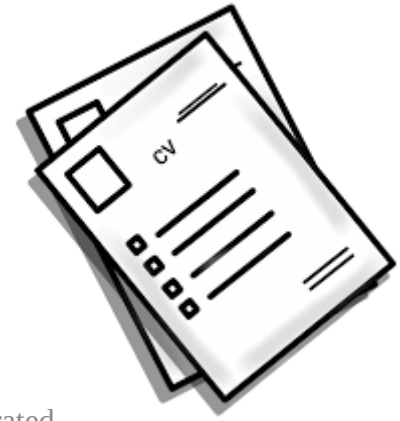
https://cdn.pixabay.com/photo/2017/02/01/12/23/cartoon-2030061_960_720.png

General (10.1)

- PI ensures investigation site team adequately trained and qualified
- maintains oversight of team activities
- ensures data integrity
- protects subjects' rights, safety, and well-being
- may delegate tasks to team members but retains responsibility

Qualification of the Principal Investigator (10.2)

- have the necessary education, training, and experience
- experience in field and trained in use of investigational device
- disclose financial and other potential conflicts of interest
- understand method of obtaining informed consent



Qualification of Investigation Site (10.3)

Has:

- enough eligible subjects
- investigation site team
- adequate facilities

https://nancyfootehigley.com/2009/11/30/monday-november-30-2009/

Communication with the EC (10.4)

- Provide copies of communications with EC to the sponsor
- Obtain written EC (and regulatory authority, if applicable) approval prior to study beginning
- Perform safety reporting
- Notify EC of deviations from the CIP
- Notify EC of study suspension or premature termination
- Notify EC of routine close-out of the clinical investigation

Informed consent process (10.5)

- Ensure informed consent process is compliant with ethical principles
- Ensure authorized designees conducting informed consent process are trained with training documented

Compliance with the CIP (10.6)

- Written PI acceptance of CIP
- PI conducts trial in accordance with the CIP
- Ensure proper documentation processes
- Ensure CRF reports and data sent to sponsor are accurate, complete and timely
- Ensure device accountability records are properly maintained

Compliance with the CIP (10.6)

- Facilitate monitoring and auditing activities performed by the sponsor
- Investigate instances of non-compliance and implement appropriate corrective and preventative actions
- Ensure retention of all records
- Sign final clinical investigation report

Medical care of subjects (10.7)

- Responsible for subject medical care of adverse events during and after study
- Inform subjects of significant study findings and the nature and possible causes of adverse events
- Provide subjects with procedures for potential emergency situations
- For subjects withdrawing prematurely, make reasonable efforts to determine reason while respecting the subject's rights

Safety reporting (10.8)

- Every adverse event and device deficiency should be recorded and assessed
- All serious adverse events and device deficiencies reported to the sponsor immediately per the CIP if may have led to serious adverse device effect
- Additional safety information should be provided to sponsor upon request