Good Clinical Practice: A Ground Level View

Jeanna Julo, BA, BA, CCRP
Assistant Director, Clinical Data Management & Quality Controls,
Auditing & Training
Clinical Research Administration
Research Institute, University of Kansas Medical Center
Principles of GCP

• Rights and well-being of the human participants are **PRIMARY** to all other considerations
• Ethical principles should dictate conduct of clinical trials
• Risk to benefit ratio should be evaluated, protocol must be scientifically sound and clearly written
• Study must have IRB approval
Principles of GCP

• Individuals conducting the trial should be qualified by training and experience
• Freely given informed consent must be obtained prior to the conduct of any study procedures
• Clinical trial information should be recorded to allow accurate reporting, interpretation and verification, and should be maintained throughout the trial and after closure
• Medical care, medical decisions should be the responsibility of the physician
• ICH = International Conference on Harmonization
So how does this translate to the real world experience of running a clinical trial?
Having the Right People

• Principal Investigator (ICH E6 4.1)
  – Qualifications should be documented (Curriculum Vitae, current licensure, certifications or specialized training)
  – Trained in the protection of human subjects, and aware of (and compliant with) GCP and applicable regulations
  – Required to maintain a list of those personnel to whom the PI has delegated significant trial-related duties (the study team)
Having the Right People

• Study Team
  – (Co/Sub-Investigators (including residents, Fellows, Nurse Practitioners, PharmDs, etc.))
  – Study Coordinators
  – Research Assistants

These individuals are bound by the same requirements to have sufficient qualifications and training, with the same documentation needed
Having the Right People

• Training Requirements
  – Human Subjects Protection Training, including privacy protection (per institutional requirement or as provided by study sponsor)
  – GCP Training (may be a component of human subjects protection training)
  – Protocol-specific training
Having the Right People

• Delegation of Responsibilities
  – PI may delegate study-related duties to study team members
    • Role must be clearly defined
    • Start and end dates
    • Documentation of qualifications, training, and IRB approval of each member prior to their participation or performance of any study related tasks
      – Delegated tasks must be appropriate to team member’s qualifications – i.e., physical examinations should be delegated only to MD/NP credentialed per institutional policy
Having the Right Resources

• Enough potentially eligible subjects

• Time!
  – The investigator should have adequate time to properly oversee study conduct – an investigator stretched too thin spells trouble

• Space (clinic, inpatient rooms, etc.)
  – The investigator/study team should have the necessary facilities available to conduct each visit or procedure required, in the time frames dictated by the protocol
Having the Right Resources

• **Staff**
  – There should be sufficient support staff to ensure the ability to enroll subjects, complete study procedures and record data, and handle the day-to-day operations of the trial

• **Ancillary services**
  – The investigator should have the ability to access all necessary services for the trial (non-invasive imaging, laboratory services, etc.) within the time frames dictated by the protocol
Having the Right Resources

• Equipment and Materials
  – Specific lab materials required by protocol (-80 freezer, refrigerated centrifuges, etc.)
  – Access to dry ice
  – Storage for investigational products meeting the sponsor’s requirements
  – High-speed internet access, copier, fax

Sometimes it’s the little things...
Following the Right Processes

• Standard Operating Procedures
  – While GCP and 21 CFR do not mandate that study sites establish SOPs, they are a best practice to ensure compliance with both
    • Should accurately and clearly outline process for completing tasks
    • All members of the study team should be familiar with SOPs and training should be documented
    • Should be reviewed regularly for any necessary revisions, and re-training of staff should be documented
Following the Right Processes

• Human Subject Protection
  – Enroll only suitable patients
    • Ensuring that patients meet the inclusion/exclusion criteria prevents enrollment of patients who may be at higher risk of adverse events
    • Not just medical criteria – patients with a history of treatment non-compliance make poor study subjects and may face greater risk due to failure to follow study requirements
  – Obtain informed consent prior to conduct of study activities (ICH E6 4.8.8)
Following the Right Processes

• Human Subject Protection
  – The investigator is responsible to ensure that trial subjects receive adequate medical care for any adverse events related to the trial, and to refer the patient for appropriate medical care for any incidental findings of conditions requiring treatment that the investigator becomes aware of during the course of the study (ICH E6 4.3.2)
  – Communication with the subject’s primary care physician regarding study participation is strongly recommended (best practice!) (ICH E6 4.3.3)
Following the Right Processes

• IRB Review & Ongoing Communication (ICH E6 4.4)
  – Full IRB Approval of the study and materials (protocol, investigator’s brochure, consent forms, recruitment materials, etc.) must be obtained prior to screening/enrolling subjects
Following the Right Processes

• IRB Review & Ongoing Communication (ICH E6 4.10)
  – Progress reports (at least annually)
  – Updated documents and new information must be submitted to the IRB for review and approval prior to implementation
    • Protocol Amendments
    • Revised Investigator’s Brochure(s)
    • Consent form revisions
    • DSMB reports
    • Any new information or changes significantly affecting the conduct of the trial and/or increasing the risk to subjects
Following the Right Processes

• Informed Consent (ICH E6 4.8)
  – Consent forms should use plain language (8th grade reading level recommended)
  – Must be IRB-approved, and the PI/study team should ensure that the correct version is utilized (common error)
    • ICH E6 4.8.10 addresses all components required to be present in the informed consent document
    • IRB review will ensure that all necessary elements are present prior to issuing approval
Following the Right Processes

• Informed Consent (ICH E6 4.8)
  – Subjects must be allowed ample time and opportunity to ask questions about participation prior to making their decision

• Additional considerations if patient is part of a vulnerable population:
  – Unable to consent on their own behalf (cognitive issues, emergency situation)
  – Minor child
  – Non-English speaking

• Investigators should consult with their IRB to ensure that all regulations are being followed when recruiting these patients
Following the Right Processes

• Informed consent is an ongoing process, not a “one and done”
  – Investigator is required to provide subjects with any new information that could affect their willingness to continue participation
  – Re-consenting to occur when changes are made to the consent form which affect:
    • Length of participation, number or type of procedures to be performed, change in risk or benefit
Following the Right Processes

- Protocol Compliance (ICH E6 4.5)
  - The investigator’s commitment to conduct the study in accordance with the protocol and any additional requirements imposed by the IRB is documented via several mechanisms:
    - Protocol Signature Page
    - FDA Form 1572 (for FDA-regulated drug studies)
    - Statement of Investigator (for FDA-regulated device studies)
Following the Right Processes

• Protocol compliance (ICH E6 4.5)
  – Means that all procedures required by the protocol must be completed and recorded in the source documentation
  – Visits, procedures, and tests required by the protocol are performed within the time frames specified by the protocol
  – Visits, procedures, tests are all performed by personnel who: appear on the delegation log, have been approved to participate by the IRB, have been appropriately trained on the study and their role
Following the Right Processes

- Protocol compliance (ICH E6 4.5)
  - Deviations from the protocol must be documented and explained
  - Deviations may be made to eliminate immediate hazard(s) to trial subjects, and should be reported to the IRB, the sponsor, and (if required) to the regulatory authorities (ICH E6 4.5.4)
Following the Right Processes

• Investigational Product accountability (ICH E6 4.6)
  – The investigator is responsible to ensure that the product is only used in accordance with the approved protocol
  – This is usually delegated by the investigator to a pharmacist or other appropriate individual (study coordinator, research nurse)
  – This person responsible to maintain records of receipt, storage, dispensing/disposition of unused product, and reconciliation of all product received from the sponsor
Following the Right Processes

• Investigational Product accountability (ICH E6 4.6)
  – Records should include dates, quantities, batch/serial numbers, expiration dates if applicable, and the unique code numbers assigned to each product/trial subject.
  – In addition, the patient records should document that the subjects were provided the doses specified by the protocol and training on the use of the product
Following the Right Processes

• Investigational Product accountability (ICH E6 4.6)
  – Storage requirements may vary with study sponsor, but generally include:
    • Secure storage accessible only to delegated personnel (locked cabinet/storage room)
    • Environmental controls (temperature monitoring, refrigerated/frozen storage)
Following the Right Processes

• Investigational Product accountability (ICH E6 4.6)
  – Studies involving investigational devices have similar accountability and storage requirements
Following the Right Processes

- Randomization and Blind Maintenance (ICH E6 4.7)
  - Adhering to randomization assignments and maintaining the study blinding are critical to the integrity of the study data
  - In a blinded trial, any unblinding (whether accidental or in response to an SAE) should be thoroughly documented and reported to the sponsor, IRB (per their reporting requirements)
Following the Right Processes

• Data Integrity (ICH E6 4.91, 4.9.2, 4.9.3)
  – Data entered into the study case report forms must be:
    • Accurate (typos are common!)
    • Complete – all required fields complete, or incomplete fields explained
    • Legible (in cases of paper CRFs – increasingly less common)
    • Timely (don’t sit on your data for days and days!)
Following the Right Processes

• Data Integrity (ICH E6 4.91, 4.9.2, 4.9.3)
  – Data entered into the study case report forms must be:
    • Consistent with the source documentation
    • Discrepancies must be explained
      – Notes to file are your friend – explain, explain, explain!
Following the Right Processes

• Data Integrity (ICH E6 4.91, 4.9.2, 4.9.3)
  – What if changes are needed to the case report form?
    • If paper, single line through the original entry, initialed, dated, and explained
    • Electronic data capture systems maintain an audit trail
Following the Right Processes

• Reporting Requirements in Addition to IRB
  – To Sponsor
  – Safety Reporting
Following the Right Processes

• Reporting to Sponsor (ICH E6 4.10)
  – Annual reports of study status at site
    • The annual report to the IRB, which is copied to the sponsor, satisfies this requirement
  – Protocol Violations, Deviations
  – Adverse Events, Serious Adverse Events, Unanticipated Adverse Device Events
Following the Right Processes

• Reporting to Sponsor (ICH E6 4.10)
  – Changes in personnel
  – Financial disclosures (at study start, ad hoc reporting of changes, at study closure)
  – Final study report
    • The closure report to the IRB, which is copied to the sponsor, satisfies this requirement
Following the Right Processes

• Safety Reporting (ICH E6 4.11)
  – All serious adverse events should be reported to the sponsor immediately upon the investigator/study team becoming aware of the event
    • Immediate reports should be followed as soon as possible by more detailed information (written report, source documents such as medical records with PHI redacted)
    • Some SAEs may not require reporting, based on the protocol and/or investigator’s brochure
  – Sponsor will perform required reporting to FDA
Following the Right Processes

• Safety Reporting (ICH E6 4.11)
  – If the investigator holds the IND (sponsor-investigator), it is the investigator’s responsibility to report the event to the FDA
Following the Right Processes

- Safety Reporting (ICH E6 4.11)
  - Adverse events and/or abnormal lab results identified in the protocol as critical to safety evaluations should be reported to the sponsor per their requirements and within their mandated time frames
Following the Right Processes

- Record Keeping (ICH E6 4.9.4, 4.9.5)
  - Patient Records
  - Regulatory / critical documents binder
  - Long term storage
Following the Right Processes

• Record Keeping (ICH E6 4.9.4, 4.9.5)
  – Patient Records
    • Wet-ink original signed consent forms
    • Copies of medical records documenting study procedures/activities should be maintained in the site study records
    • Electronic medical record use increasing
      – Printed “shadow charts” frequently used by study sites both throughout the trial and for long-term storage
Following the Right Processes

• Regulatory / Critical Documents Binder (ICH E6 8.1, 8.2, 8.3, 8.4)
  – Three primary components
    • Documents needed before the trial can start
    • Documents generated during the course of the trial
    • Documents required after completion or termination of the trial
  – The “Story of the Study” in three-ring binders, must include all required items from sponsor’s trial master file
Following the Right Processes

• Regulatory / Critical Documents Binder (ICH E6 8.1, 8.2, 8.3, 8.4)
  – Maintaining these records is generally delegated to either the study coordinator or a regulatory specialist
• Some items listed in ICH E6 8 may be filed separately from main critical documents binder (investigational product records, financial and contractual records)
Following the Right Processes

To be on file before enrollment begins...

- Investigator’s Brochure
- Signed protocol and amendments
- Sample Case Report Forms
- Informed consent, any other written information given to subjects, and any advertising materials
- Insurance statement (where required)
- Documentation of IRB approval of study and related materials
- IRB Roster, FWA number
- FDA correspondence
- CVs and medical licensure (as applicable) for PI and study team
- FDA Form 1572 (for drug studies), Statement of Investigator (for device studies)
- Financial Disclosure Forms for PI and study team
- Laboratory certifications and normal ranges
- Master randomization list
- Documentation of pre-study site evaluation visit by sponsor
- Documentation of site initiation visit by sponsor, including protocol, investigational product handling, and CRF training for PI and study team
- Delegation of Authority / Signature Log showing identities, roles, delegated tasks, and signatures of study staff
Following the Right Processes

To be maintained during the study...

- Investigator’s Brochure updates
- Protocol amendments
- Case Report Form revisions
- Revisions to the informed consent, any other written information given to subjects, and any new or revised advertising materials
- Updated IRB Rosters
- New FDA correspondence
- Updates to Delegation of Authority / Signature Log
- Subject screening log
- Enrollment log / subject identification code list
- Documentation of current IRB approval of study and related materials as well as acknowledgement of reportable events, annual reports, safety reports
- Updated CVs and renewed medical licensure (as applicable) for PI and study team
- Monitoring visit reports
- Revisions to FDA Form 1572 (for drug studies), Statement of Investigator (for device studies)
- Ad hoc Financial Disclosure reporting for PI and study team
- Updated laboratory certifications and normal ranges
- Relevant communications other than site visits (letters, email, numbered memoranda, etc)
Following the Right Processes
To be included after completion of the trial...

- Everything from the previous two slides
- Completed drug/device accountability records showing final disposition of all product (dispensed, returned, destroyed) should be included in study file – collect from pharmacist or other delegated personnel
- Completed subject identification code list
- Final trial close-out monitoring report
- Final report to the IRB
- Clinical study report (may not be received from the sponsor for several months following conclusion of site activities)
Following the Right Processes

• Long Term Storage (ICH E6 4.9.5)
  – All trial documents are required to be retained for at least 2 years after either the approval of the marketing application or the formal discontinuation of clinical development of the product.
  • This translates to 10-15 years in the real world
  • It is the sponsor’s responsibility to notify sites when records no longer need to be retained
Following the Right Processes

• Long Term Storage (ICH E6 4.9.5)
  – Carefully archive records
    • Label each container clearly with a unique identifier, study name, protocol number, PI information, and contents (i.e., Critical Documents, binders 1-3; subject records, pts 001-010; etc.), and mark that records are not to be destroyed or discarded without first contacting the investigator
    • Include sheet with last known patient contact information in each patient record
    • Maintain clear records of what has been archived in which container for easier retrieval if needed
Following the Right Processes

• Long Term Storage (ICH E6 4.9.5)

  – Tried-And-True Tip:

    • Don’t jump the gun when sending items to long-term storage – sponsors frequently will continue to request items from the critical documents binder after study closure at the IRB. Keeping things on-site for ~6 months after closure at the IRB will save record retrieval costs and inconvenience
Following the Right Processes

• Compliance monitoring (ICH E6 4.9.7)
  – The study sponsor will arrange for routine
    compliance monitoring of the study
  – If the investigator holds the IND/IDE, they are
    responsible for ensuring ongoing compliance
    monitoring of the study
Following the Right Processes

• Compliance monitoring (ICH E6 4.9.7)
  – Monitoring is risk-based, and lower-risk studies will have less frequent monitoring
    • Generally occur every 6 weeks in significant risk studies
    • Ensures that all reportable events are identified, that the investigator/study team are complying with the protocol, and that data is accurate and verified by source documentation
    • Monitors are permitted to access all trial-related materials and patient records including medical records
Following the Right Processes

• Trial Sponsor Audits
  – Study sponsor identifies sites at risk for FDA audit
    • Highest enrolling sites
    • Sites with higher numbers of adverse events, serious adverse events, or deviations than other sites
    • Intended to prepare those sites for potential audit
    • Generally performed by sponsor personnel other than the study monitor assigned to the site
Following the Right Processes

• FDA Audits
  – The FDA has the right to direct access to all requested trial records
  – Not fun, but not the end of the world – as long as the investigator and study team have followed GCP and the requirements of their IRB then the likelihood of major deficiencies being noted is slight
What it all boils down to...

• Thinking of patient rights and safety first and foremost
• Following your protocol
• Documenting EVERYTHING (research is such a good place for packrats...)
• When in doubt, asking your IRB or the study sponsor for guidance
THANK YOU!!!