Regulatory Documents in Clinical Research

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Why Regulatory Documents are Required for Clinical Trials

- Regulatory documents are submitted to track and evaluate the ethical and procedural conduct of a trial and the quality of the data that is produced

- Regulatory documents demonstrate the compliance of the Investigator, Sponsor and IRB/IEC with the standards of Good Clinical Practice and with all applicable regulatory requirements

Regulatory File Document Guidelines

- Investigators must maintain 1 file for each study, and all essential documents must be in the file
- Must be established at beginning of each study
- Updated throughout life of study
- Source for Guidelines
  - ICH/GCP at www.ich.org
  - 21 CFR 11, 50, etc. at www.fda.gov
  - 45 CFR 46 at http://ohrp.osophs.dhhs.gov

Initial Minimum Required Documents

- For IND studies
- Form FDA 1572
- Final signed/dated Protocol & Amendments
- IRB approved Informed Consent Form
- IRB approved advertisements
- IRB Approval Letter for protocol, amendments, informed consents, advertisements, etc.
- IRB membership list or assurance number and compliance statement

Initial Minimum Required Documents

- CVs for Principal Investigator (PI) and Sub-Investigators
- Laboratory Certifications and Normal Ranges
- Investigator's Statement of Financial Disclosure for PI and Sub-Investigators
- Documentation of satisfactory site assessment (or waiver)
- Documentation of Protocol Training
- Signature Log

Form FDA 1572

- Contract between FDA and Investigator
- Contains logistics such as names and addresses
- Section 9
  - Commitments of the Investigator
  - http://www.fda.gov/opacom/morechoices/fdaforms/cder.html

Form FDA 1572

- Signed/dated by Principal Investigator
- List names of all Sub-investigators
- Location of all sites where are subjects seen
- Section 4: List Clinical Laboratories ONLY
  - Research laboratories must be identified in protocol
- Hand signed/dated on a double-sided form
- Keep ORIGINAL at site

Investigator Agreements

- Non-IND studies generally have an Investigator of Record (IOR) agreement
- Sometimes referred to as the "investigator statement"
- What is the PI "agreeing" to do?

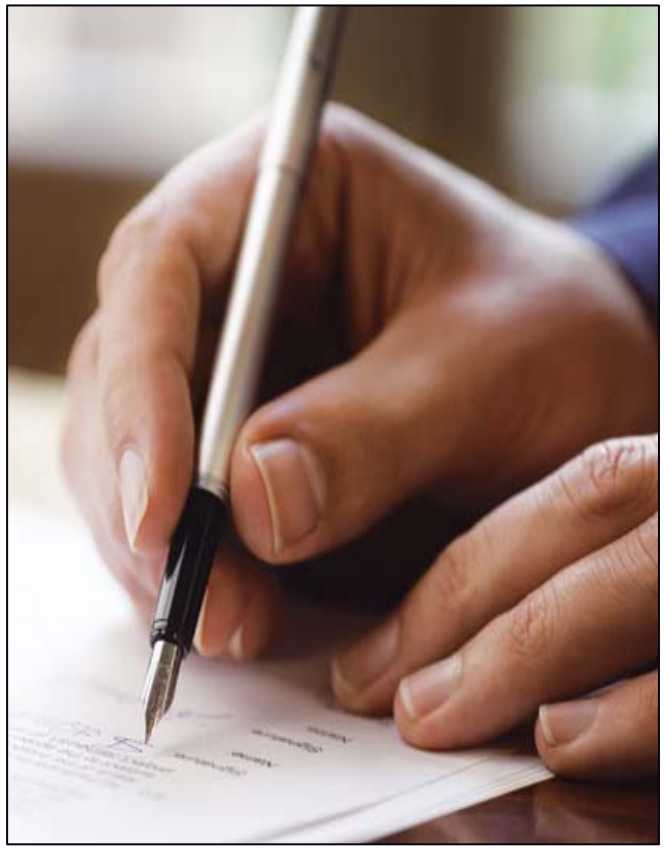
Commitments of the PI/IOR

- Comply with protocol
- Ensure compliance of IRB and consent process with 45CFR 46
- Report AEs
- Accurate record keeping and access
- No changes to study without permission of Sponsor and IRB

Financial Disclosure (IND Studies Only)

- Required for anyone listed on 1572
- Documents any potential conflicts of interest regarding:
  - Compensation
  - Equity
  - Proprietary information

Delegation of Responsibilities/Signature Log



- Who is required to be on this form?
- What's the purpose?

Delegation of Responsibility Log/Signature List

Study:

Investigator Name		*Site Number*		*Page Number*	

Name and Title of Site Staff Use Block Capitals	**Signature**	**Initials**	**Responsibilities*** (See below)									**Involved From** DD-MMM-YY	**Involved To** DD-MMM-YY	**PI Initials**
			A	B	C	D	E	F	G	H	I			
			A	B	C	D	E	F	G	H	I			
			A	B	C	D	E	F	G	H	I			
			A	B	C	D	E	F	G	H	I			
			A	B	C	D	E	F	G	H	I			
			A	B	C	D	E	F	G	H	I			
			A	B	C	D	E	F	G	H	I			

DELEGATION OF RESPONSIBILITIES CODES		*NOTES FOR COMPLETING THIS FORM*
A. Obtaining consent *B. CRF entries* *C. Dispensing Medication* *D. Physical Examination* *E. Phlebotomy* *F. Essential Documents*	*G. IP Receipt/Return* *H. Query Resolution* *I. Authorized Signatory for resolved queries* *J. Other_____*	• *Please PRINT CLEARLY when completing this form* • *Please enter all dates in the DD-MMM-YY format (e.g., 21-JAN-01)* • *Use 'Involved From' and 'Involved To' to record staff changes during the study* • *Enter a new line and applicable dates when responsibilities change* • *PI should initial each line as individuals are assigned responsibilities*
***Delete those which do not apply**		

Principal Investigator Signature (Close Out):_____ Date:_____

Curriculum Vitae (CV)

- All investigators and sub-investigators (listed on 1572 or IOR agreement) must submit a current CV and/or other relevant documents
  - Evidence of qualification to conduct the trial and to provide medical supervision of subjects
  - CV should be updated to reflect significant changes

Medical Licenses

- PI is responsible for maintaining the current licensure for all sub-investigators/study staff
- Maintain a copy of current medical licenses for the PI and all sub-investigators listed on the Form FDA 1572 in the regulatory file

Federal Wide Assurance (FWA)

- Obtained by Institution:
  - Maintain a record of FWA number
  - Expiration date
- Website for obtaining this information:
  - http://ohrp.cit.nih.gov/search/asearch.asp#ASUR

IRB/IEC Regulatory Documents

- Investigator submits:
  - Protocol
  - Amendments
  - Informed consent
  - Any other information given to the subject to the IRB for review and approval
- The IRB reviews:
  - Investigator Brochure
  - Safety Reports
  - Protocol Deviations
  - Unanticipated problems
  - Grant applications

Protocol/Protocol Amendments

- Retain original IRB/IEC approved protocol and any approved revisions/amendments
  - Draft protocols that were not submitted do not need to be maintained
  - Remember to include version numbers and dates!!

Consent Forms

- Include a copy of original IRB approved consent and any subsequent IRB approved revisions/amendments
- Other consent forms:
  - Screening consents
  - Future use consents
  - Translated consents

Advertisements and Subject Information Materials

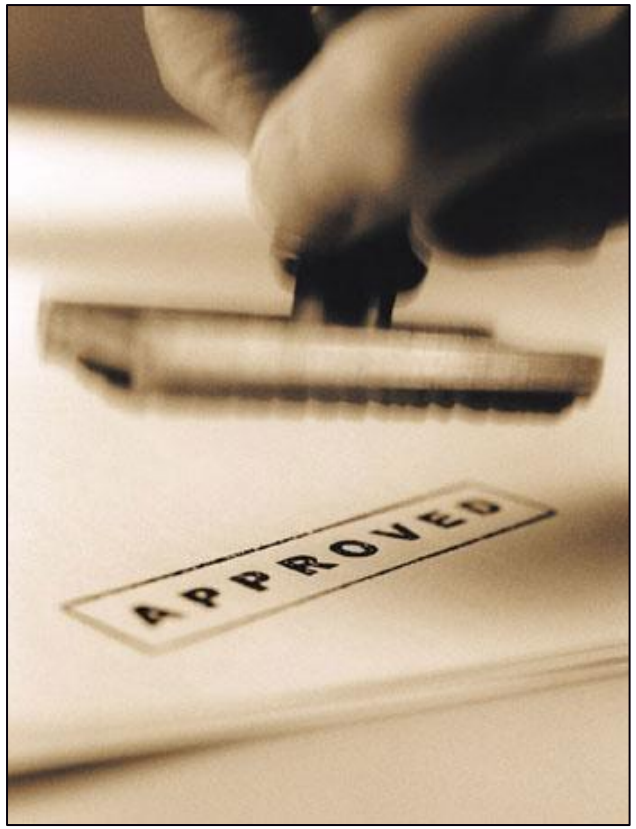
- Types:
  - TV
  - Radio
  - Newspaper
  - Internet
  - Flyers
- IRB approval must be obtained prior to the use of any study advertisement including revisions to advertisements

Submission Letter/Package/IRB/IEC Approval

- Includes:
  - Full copies of original IRB-approved Protocol, subsequent approved revisions/amendments to Protocol.
- Maintain entire packets together in the file
  - Including submission letter/package, responses,comments, and final IRB approval
- Everything should have a Version Number and date

IRB Approval Letter

- At minimum: (per GCP guideline 3.1.2)
  - Protocol name and number
  - Approval date
  - List of approved documents



Periodic Reports/Annual Renewals
Final Reports

- Submitted by the Principal Investigator to IRB:
  - New safety information
  - DSMB reports
  - Annual renewals
  - Final report
- Maintain all approvals with what was submitted

Local Regulatory Approvals

- Local, state and/or special authorizations relating to the protocol should be maintained
  - Must have documentation of National approval for conduct of a study done outside the United States
  - Approvals must be collected/renewed per local regulations

Study-Specific Procedures or Manual of Procedures

- May include:
  - Lab Procedures, Lab Specimen/Test Article handling and/or preparation instructions, and Protocol-specific instructions
  - Each Study Specific Procedure (SOP) or Manual of Procedures (MOP) must have Version Number and Date
- All versions must be maintained in the regulatory file !!

Additional Documents

- Copies of Study Drug shipment and receipt records
- Site visit log
- CRF guidelines
- Subject screening, enrollment and identification logs
- Site initiation, monitoring, and close-out reports
- Study Drug accountability records
- Unblinding procedures, if applicable
- Communication/Correspondence

Case Report Forms (CRFs)

- Paper Case Report Form (CRF)
  - Maintain a complete copy of the Case Report Form
  - The Protocol will identify data to be recorded on the CRF and considered to be source data
  - ALL documents must have Version number and date

Laboratory Normal Reference Ranges and Accreditations

- Must maintain current lab normal ranges used by all clinical labs for study data
  - Laboratory name and date of the document must be provided
- Must maintain a copy of all labs current certifications

Lab Normals and Accreditations

- Domestic laboratory certifications should include:
  - CLIA accreditation and CAP or JCAHO, or
  - CLIA certification of compliance (stand alone), or
  - Dept. of Health cert. (if CLIA-exempt state)
- Research Labs (no accreditation required)
- CLIA exemptions for certain tests
- Non-US labs - include national equivalent of certification

Additional Documents

- Continuing IRB/IEC review
- SAE notifications to the IRB/IEC and reports
- Any amendments to protocol, consent forms, and IRB/IEC documentation
- Updates to Investigator team list
- CVs for new investigators or staff
- Revised Form FDA 1572
- Any IND safety reports/Investigator Brochure updates

Test Article Accountability Records

- The following documentation MUST be included with the Essential Documents:
  - Shipping Receipts
  - Receipt date, quantity
  - Lot numbers
  - Copy of test article label

Test Article Accountability Records

- Record showing all UNUSED test article has been returned to designated central repository or manufacturer, or destroyed as per the IND sponsor's instructions
  - Should include date of shipment (or destruction), quantity, and lot number of the returned or destroyed study material

Test Article Accountability Records

- Physical inventories are recommended on a monthly basis during active enrollment and on a regular basis thereafter
- Copy of Test Article Sample label (ICH GCP 8.2.13)
- Copy of any drug purchased locally, vaccine, diluent or placebo label

Test Article Accountability Records

- Disposition of any unused vials remaining at end of the study will be determined by DMID
- Transfer of Test Article from one study to another is not allowed
- For blinded studies, expiry dates and lot numbers are confidential and are not entered onto the accountability log

Test Article Accountability Records

- Accurate records must be kept documenting the date & amount of test article dispensed to subjects, the amount used, and if applicable, the date and quantity of the study drug returned by subjects

Investigator's Brochure/Package Insert

- Must be available to all study staff
  - This is the site's reference to potential reactions and side effects
  - IND safety reports must be filed with the Investigator's Brochure
  - Any other informational letters issued by the manufacturer must be filed with the Investigator's Brochure

Computer/Electronic Records

- 21 CFR part 11
  - Electronic signatures
  - Passwords
- Electronic Case Report Form (eCRF)
- Can any regulatory documents be kept/stored electronically?

Subject Screening/Enrollment Log

- All subjects screened for the study must be on the screening/enrollment log
  - Subjects can not be screened until they have signed an informed consent document
- A study number or screening number must be used
- List reason why subject was not enrolled, when applicable

ID Code List

- Confidential document
- Remains at the site
- Study use only
  - Contains names of all subjects allocated study numbers upon enrollment
  - Contains subject contact information
  - Allows investigator/institution to reveal the identity of any subject

Collaborating Research Laboratories

- If identifiable samples are to be sent to collaborating laboratories for research, IRB approval must be obtained by your IRB and the collaborating IRB
  - Maintain documentation concerning the samples and IRB approval
- Remember, commercial laboratories are not considered to be collaborating research labs

Specimen Retention Records

- Maintain a record of the Protocol-specified retained body fluids/tissue samples (if any) to document the location and identification of retained samples if assays need to be repeated
  - Sites must consult with DMID regarding the relocation, destruction, or anonymization of any remaining clinical specimens once study is complete and final report has been submitted to FDA. Unused specimens must be destroyed or anonymized unless consent has been granted for future use of stored specimens.

Protocol Training

- All sites should maintain documentation of protocol training:
  - Prior to the start of the trial
  - At regularly convened team meetings
  - Any time new safety information is obtained

Protocol Deviations

- DEVIATION = Non-adherence to the Protocol
- May result in significant added risk to study subject
- Non-adherence to enrollment eligibility, safety surveillance, endpoint outcomes, test article handling/accountability
- Non-adherence to Good Clinical Practice
- Informed Consent issues

Protocol Deviations

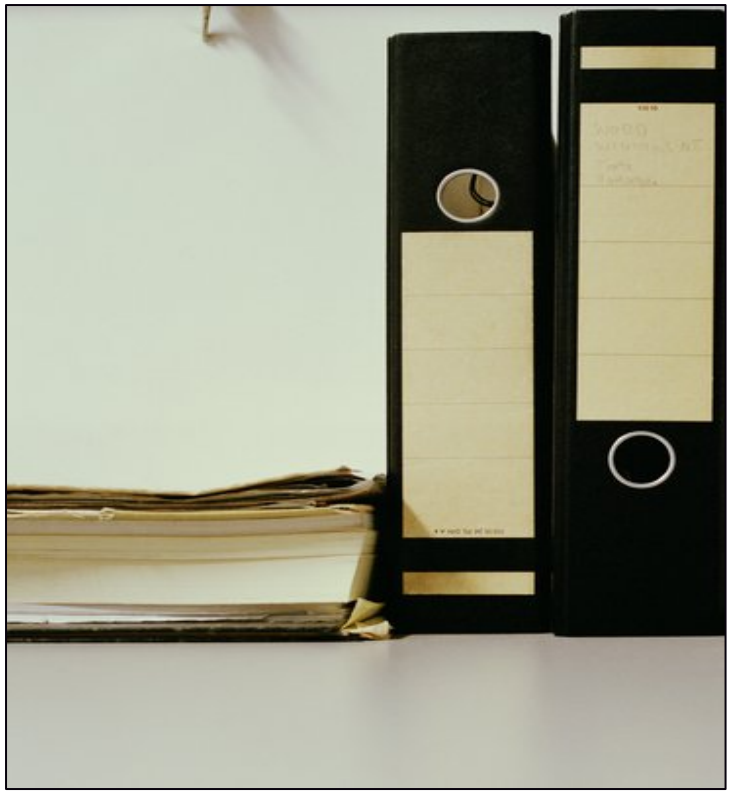
- Must be addressed in source documentation
  - Include reason, attempts to prevent or correct
- Deviation form
  - Completed for each protocol deviation
  - Must maintain a copy at site in the subject's source documents and in the regulatory file
- Notify IRB per IRB requirements

Serious Adverse Event Reporting

- Maintain copies of all SAE report forms in your regulatory binder
- SAEs determined to be causally related, serious, and unexpected MUST be reported immediately to the IRB, Sponsor and FDA (usually done by sponsor)
  - IND sponsor may also send sites IND safety reports
    - Must be submitted to the IRB
    - Are considered amendments to the IB
    - May require revision to informed consent

Temperature Log

- Maintain temperature log for all refrigerators/ freezers that hold study related materials
- Use a separate log for each refrigerator/ freezer study-related items



Monitor Log/Monitoring Reports

- List all study site visits made by external monitors and retain a copy of all site visit letters and reports

- This is proof that the site permits monitoring of their data

Correspondence and Notes to File

- Site Correspondence with DMID/Sponsor
- Internal Correspondence
- Notes to File
- Site Specific Information
- Clinical Database Validation