Responsibilities of the Principal Investigator Part 2: Implementation of a Clinical Research Protocol

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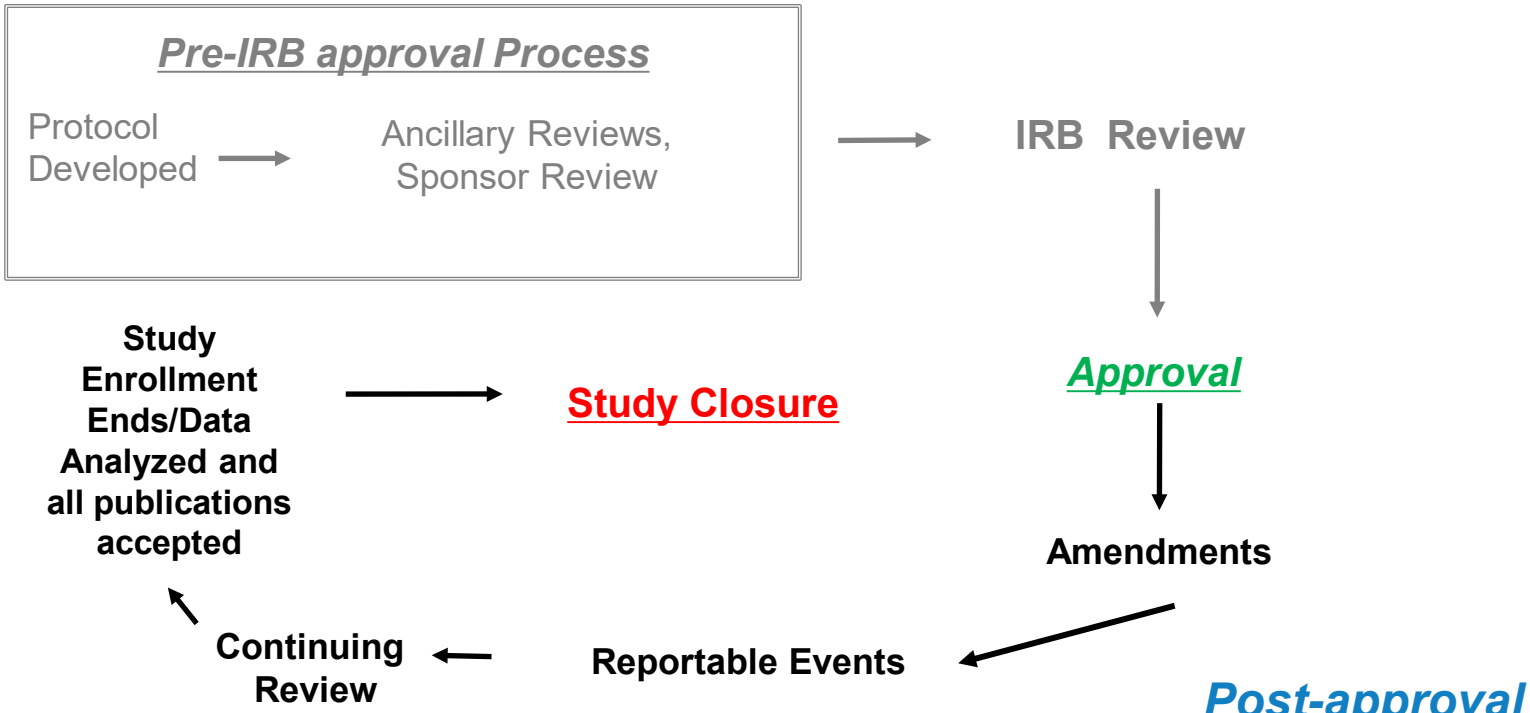
Protocol Life Cycle



Agenda

- NIH IRP HRPP Policy
- Regulations and Guidances
- Delegation and Supervision
- Informed Consent
- Data and Safety Monitoring Plan (DSMP)
- Maintaining Essential Documents

Investigator Responsibilities (Policy 300)…

- All investigators are expected to conduct themselves according to the highest standards of professional conduct and integrity and to adhere to the ethical principles that address the protection of human subjects in research.
  - (See *Policy 100 NIH Intramural Research Program's Human Research Protection Program*.)
- All NIH investigators will comply with federal law, regulation and policy, including NIH policy, and will conduct the research in compliance with the IRB approved protocol.

…Investigator Responsibilities…

- When the NIH IRB is the Reviewing IRB, all investigators will follow the policies of the NIH IRB (NIH HRPP policies).
- When an external IRB is the Reviewing IRB, in addition to NIH policies, NIH investigators will also comply with the applicable policies and procedures of the external IRB.

…Investigator Responsibilities…

- Know when an activity constitutes non-exempt human subjects research and assure IRB approval has been granted when required before performing human subjects research;
- Ensure that informed consent is obtained from each human subject and documented before conducting human subjects research, consistent with the IRB-approved protocol and according to *Policy 301 Informed Consent*, unless the requirements for consent or documentation of consent have been waived or altered by the IRB;

…Investigator Responsibilities…

- Ensure the accuracy, completeness, legibility, and timeliness of the data;
- Follow internal policies for the appropriate documentation of research related tests and procedures; and
- Be responsive to subject concerns and complaints consistent with *Policy 104 Managing Research-Related Complaints from Research Subjects*.

…Investigator Responsibilities

- Investigators conducting research regulated by the Food and Drug Administration (FDA) must comply with FDA requirements and NIH policy.
  - *Policy 500 Research Involving Drugs, Biological, and Nutritional Products*
  - *Policy 501 Research Involving FDA Regulated Devices*
  - *Policy 502 Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices (Test Articles)*

PI Responsibilities…

- Designate other investigators
- Ensure sufficient resources are allocated to the research
- Comply with the determinations of the Reviewing IRB
- Conduct research only after the following conditions have been met:
  - IRB approval is obtained
  - All other necessary institutional approvals have been obtained (*Policy 106 Ancillary Reviews*), if applicable
  - Appropriate agreements have been executed with outside entities, if applicable

…PI Responsibilities…

- For research involving the use or disclosure of identifiable private information or biospecimens, subjects' privacy and confidentiality is protected in compliance with relevant laws, regulations, policies, and the terms of the informed consent or other documents. (*Policy 107 Privacy and Confidentiality).*
- Ensure proper arrangements for IRB oversight when conducting non-exempt human subjects research at a non-NIH site, or with a non-NIH institution, including when seeking single IRB review for multi-site research (whether by the NIH IRB or an external IRB). *Policy 105 IRB Reliance*.

…PI Responsibilities…

- Ensure that, when Continuing Review is required by either regulation or by the IRB, submission of the required documents for IRB review occurs with sufficient time to allow for IRB review and approval prior to the expiration of the current IRB approval and with sufficient time for response by the PI to any stipulations of the IRB. (*Policy 205 Requirements for IRB Submissions)*
- Alternatively, for those studies that do not require continuing review, ensure timely submission to the IRB of amendments, progress reports, reportable events and any documentation required by other NIH policies, and also that the study is closed with the IRB upon completion of the research. (*Policy 204 Levels of IRB Review and Criteria for IRB Approval of Research*.)

…PI Responsibilities…

- Report Unanticipated Problems (UPs), non-compliance or other research events to the IRB and, as necessary, to sponsors or other regulatory agencies in accordance with requirements set forth in *Policy 801 Reporting Research Events*.
- Maintain a regulatory file with current and accurate records of all study documentation as required by applicable regulatory requirements.
  - *NIH Manual Chapter 1743 – Managing Federal Records*
  - *NIH Intramural Records Retention Schedule*
  - *NIH Privacy Act Policy*

…PI Responsibilities…

- Cooperate with NIH oversight, authorized federal regulatory agencies, and sponsors, including for: investigations, monitoring, audits, and actions.
  - Provision of certain documents to auditors or monitors may be privileged and not appropriate for disclosure, consult with appropriate NIH offices (e.g., OHSRP, OGC, ORSC or IC Privacy Officer) as needed.

…PI Responsibilities

- Ensure, when is leaving the NIH:
  - Proper arrangements are made for continued IRB oversight for any investigator who wishes to continue the research or continue to perform data analysis of identifiable data
  - Data and specimens are transferred to/retained by the departing investigator only with appropriate permissions, forms, and IC oversight; and
  - PI who is leaving, to revise the protocol and obtain IRB approval of a new PI who is suitably qualified to be responsible for the conduct of the research.

Laws, Regulations and Guidances

- Laws
  - Legislative Branch (Congress)
  - Published in the United States Code (USC)
- Regulations
  - Executive Branch (Departments & Agencies)
  - Code of Federal Regulations (CFR)

BINDING

- Guidances
  - Agencies

Not Binding

Selected Regulations

- Title 45 Part 46
  - HSP regulations for HHS funded research
- Title 21: FDA regulations
  - Part 11: Electronic records and signature
  - Part 50: Protection of human subjects
  - Part 54: Financial disclosure by clinical investigators
  - Part 56: Institutional review boards
  - Part 312: Investigational New Drug application
  - Part 812: Investigational Device Exemption

Selected Guidance Documents

- OHRP: *Investigator Responsibility Frequently Asked Questions*
- FDA: *Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects*
- *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines*
  - *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)* (2016)

PI Delegation & Supervision

- PI can delegate certain study-related tasks to other investigators and study staff
- When tasks are delegated:
  - PI is responsible for providing adequate supervision of those to whom tasks are delegated
  - PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the study

Individuals Who Are Delegated Tasks

- Are qualified by education, training, and experience to perform the tasks
  - Includes appropriate licensing and/or certification
  - Appropriate credentialing per hospital policy
- Receive adequate training on how to conduct the delegated tasks was provided
- Provided with an adequate understanding of the study

Delegation of Tasks (DOT) Log

- Log that allows PI to note delegation of research related tasks
- Completed prior to the initiation of any study-related tasks and procedures
- Updated as staff leave or are added
- Separate log for each study
- Include who will be able to cover for PI

Example Delegation Log

Site Delegation of Tasks Log / Signature Log

Site: _____ Protocol Number _____ Study Title: _____

The purpose of this form is to serve as the 'Site Signature Log' and assure that the individuals performing study related tasks/procedures are appropriately trained and authorized by the Principal Investigator to perform the task/procedure. The PI will sign and date the log after discussing with the individual the tasks he/she is being delegated. Once the individual no longer has delegated responsibilities, the PI will enter the end date and initial and date the entry. This form should be completed prior to the initiation of any study-related tasks/procedures. *The original form should be maintained at the site in the study regulatory/study binder. This form should be updated during the course of the study as needed.* **Study Roles include: Principal Investigator, Research Nurse, Associate Investigator, Data Manager, Nurse Practitioner, Regulatory Specialist**

	Assume PI Responsibilities when PI is Unavailable	Obtain Informed Consent	Eligibility Assessment	Perform History and Physical Exam	Review of Labs	Prescribe Study Agent	Oral Drug Accountability	AE Assessment (severity /relationship to research)	Expedited Event Reporting	Protocol Specimen Shipping	Case Report Form (CRF) completion	Data/CRF QA	Regulatory Document /Binder Maintenance	**Other** (please specify):	**Other** (please specify):			
Name:	The PI is responsible for the study design and conduct including all delegated tasks.															Dates of Responsibilities Format: mm/dd/yy		
Study Role: Principal Investigator	Signature:					Initials:		Date (mm/dd/yy):			PI Signature: N/A				Date (mm/dd/yy): N/A	Start:	End:	PI Initials/ Date at End
Name:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Dates of Responsibilities Format: mm/dd/yy		
Study Role:	Signature:					Initials:		Date (mm/dd/yy):			PI Signature:				Date (mm/dd/yy):	Start:	End:	PI Initials/ Date at End

PI Supervision & Involvement

- Adequate supervision and involvement in the ongoing conduct of the study

PI Supervision

- Develop a plan for supervision and oversight even for individuals who are highly qualified and experienced
  - Routine meetings with the research team reviewing the progress of the study and updating any changes
  - Process for correcting problems identified by the research team or others
  - Documenting the performance of delegated task
  - Process to ensure informed consent process is being conducted per regulations and institutional policies
  - Process to ensure accurate data collection
  - Process for dealing with monitoring/auditing results
  - Process to ensure research team complies with the protocol and reporting requirements to IRB and if applicable, the sponsor

PI Involvement

- Document involvement in the ongoing conduct of the study
  - PI responsibilities for plan for supervision and oversight
  - Medical record documentation
    - When to document?
  - Team meeting minutes including attendees, discussion and PI decisions
  - Involvement in developing, implementing, and evaluating CAPA plans

Informed Consent: PI Responsibilities

- Ensure that informed consent is obtained consistent with regulations and institutional policies
- PI may delegate other qualified persons to obtain consent from prospective subjects

PI Delegation of IC

- Familiar with the protocol, research, clinical experience, and qualifications
  - Have the ability to assess participant's capacity to consent
- Have appropriate training in human subjects research protections and obtaining proper IC (*Policy 103*)
- Observe PI + PI observe designee
- Investigators delegated to obtain IC should be noted in the IRB protocol application (i.e., study personnel) and on the delegation log

PI Delegation Exception

- Visiting Fellows, IRTAs and CRTAs serving as Associate Investigators may observe or participate in the informed consent process only if they are under the direct and constant supervision by a qualified NIH federal employee investigator. These trainees may not sign the informed consent document.

HRPP Applicable Policies

- Policy 301: Informed Consent
- Policy 400: Research Involving Pregnant Women, Human Fetuses and Neonates
- Policy 401: Research Involving Prisoners
- Policy 402: Research Involving Children
- Policy 403: Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation
- Policy 404: Research Involving NIH Staff

FAQs: Everything you need to know about consent

Help with Capacity Assessment at the Clinical Center

- NIH Ability to Consent Assessment Team (ACAT)
  - Determine individual's ability to consent
  - Can be reached at 301-496-9675 or 301-496-2429
  - Members of NIMH Human Subjects Protection Unit (HSPU) and CC Bioethics Department

- Resources
  - NIH Medical Administrative Series Policy 87-4 (Research Involving Adults Who Are or May be Unable to Consent)
    - Note: Due to the firewall, MAS policies can only be accessed through VPN or on site.

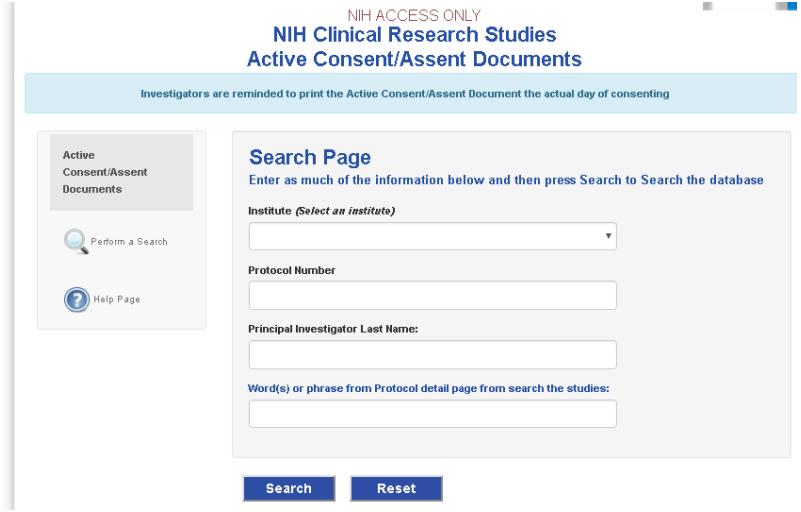
NIMH Human Subjects Protection Unit (HSPU)

- Clinical Research Advocates (CRAs) to assess, develop and implement human subjects' protections for potentially vulnerable participants enrolling in research
- Services:
  - Capacity assessment
  - Ability to assign a surrogate
  - Surrogate decision-maker assessment
  - Consent and assent monitoring
  - Consultation
  - Training and education

HSPU Phone 301-232-2984
Pager 102-11158
FAX 301-402-6872
nimhhspu@mail.nih.gov

Where to find IRB Approved IC/Assent Documents

https://clinicalstudies.info.nih.gov/Search.aspx



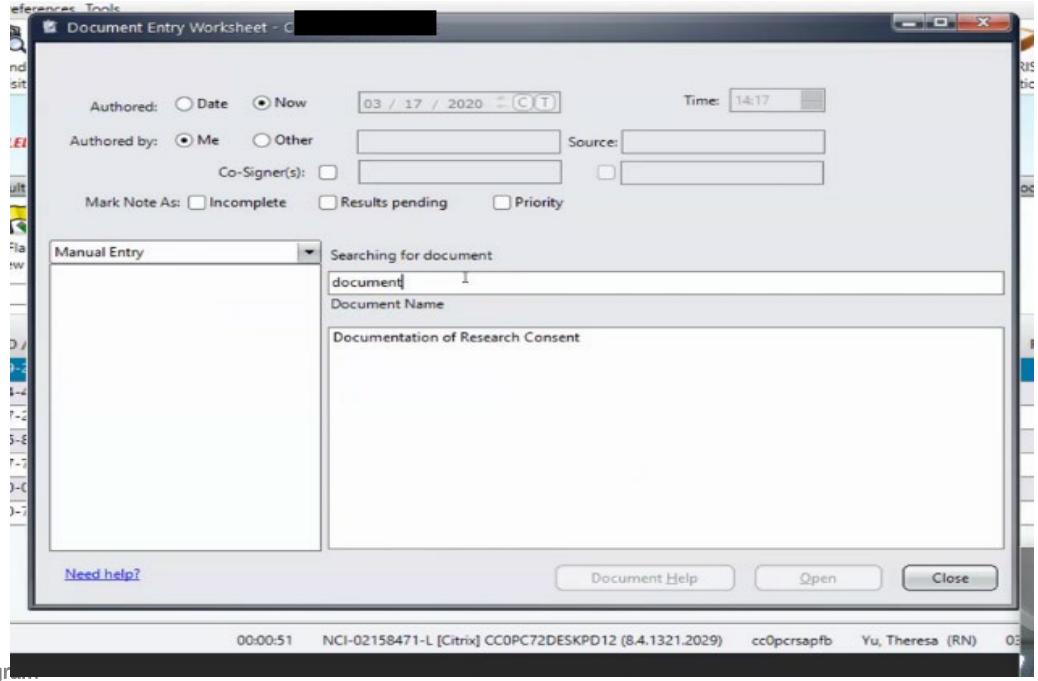
https://irbo.nih.gov/confluence/display/ohsrp/Short+Form+Consents

Documentation of IC Process

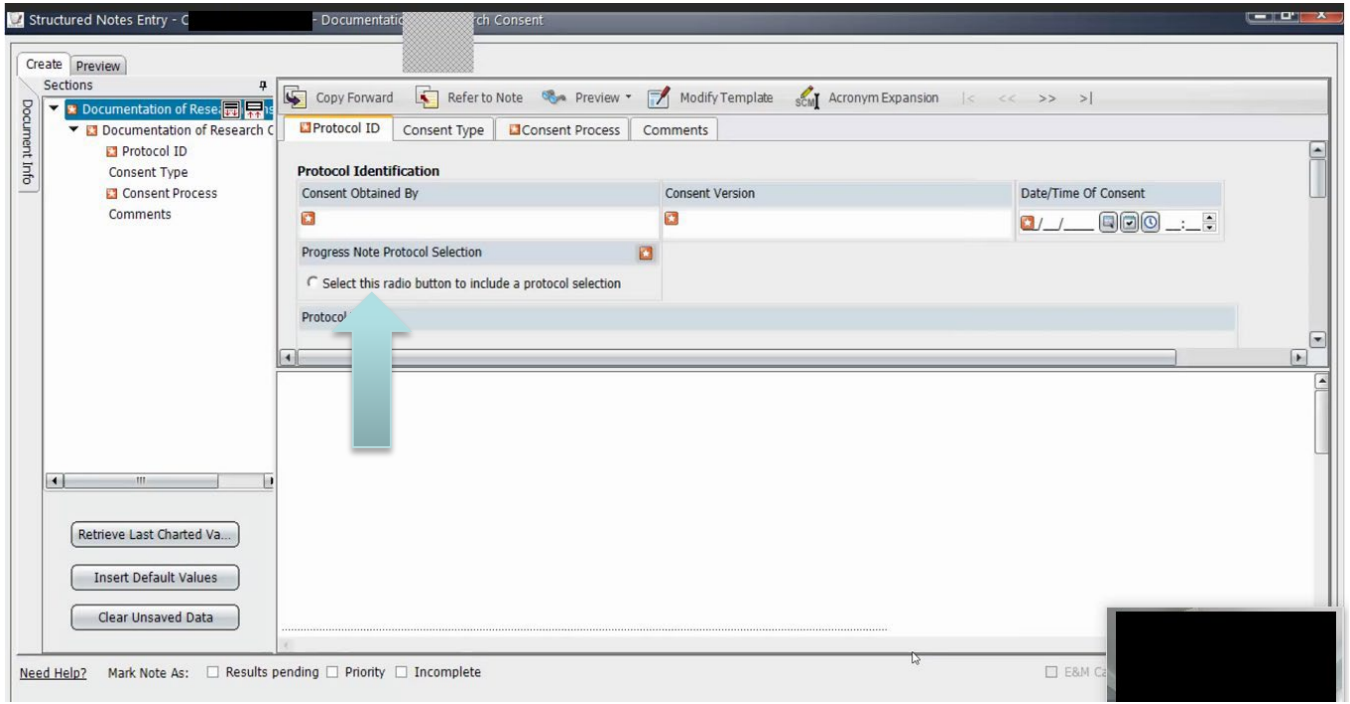
- Specific statement in medical record addressing the informed consent process
- Should be done by all who discussed the study with the subject
- Typically note will include a statement that:
  - A copy of IC document was given to the individual prior to signing
  - All questions were reviewed and answered to individual's satisfaction
  - A copy of the signed IC document was given to the participant
- CRIS has an IC process template progress note

Consent Note in CRIS

- Structured Note Titled: *Documentation of Research Consent*

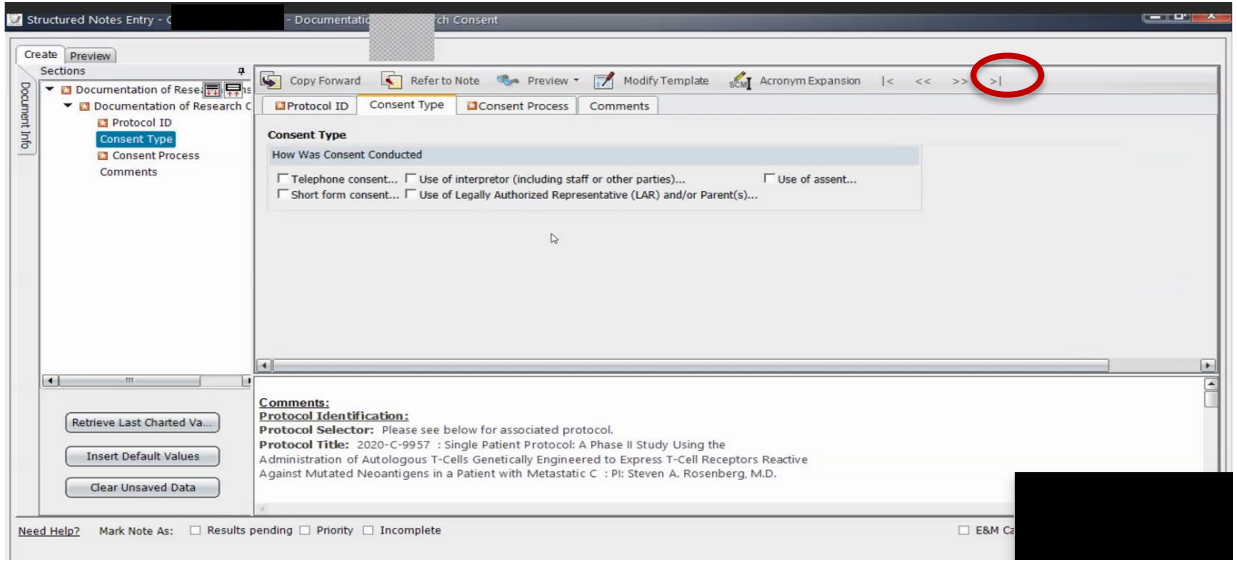


Consent Note: Sections of the Note



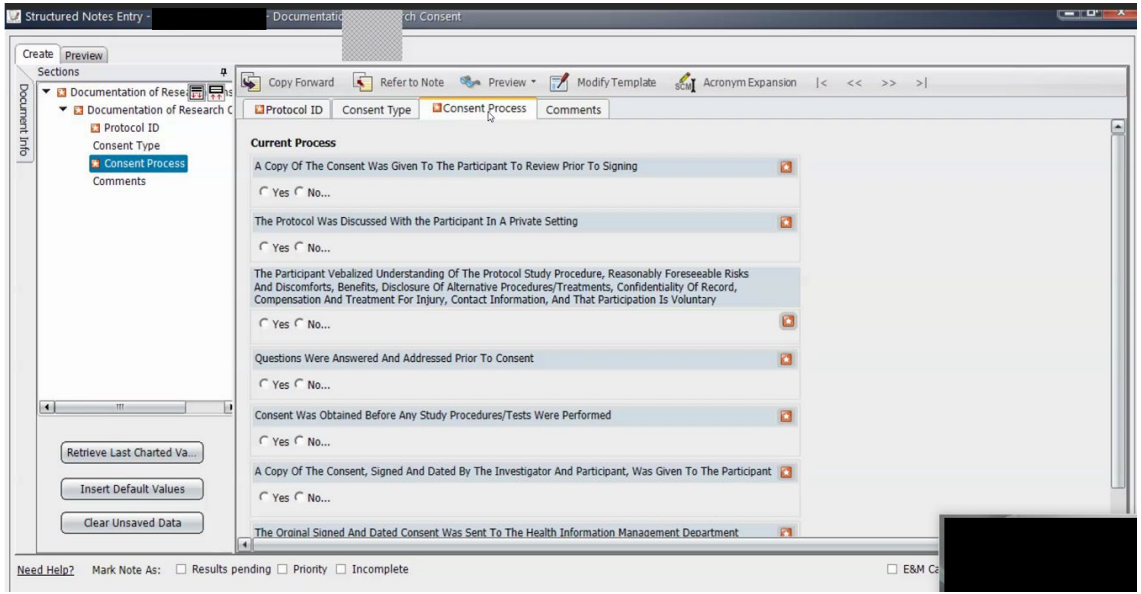
Consent Note: Consent Type

- Select specific consent situation, if applicable
  - If none apply, click on tab or “>” to advance to Consent Process



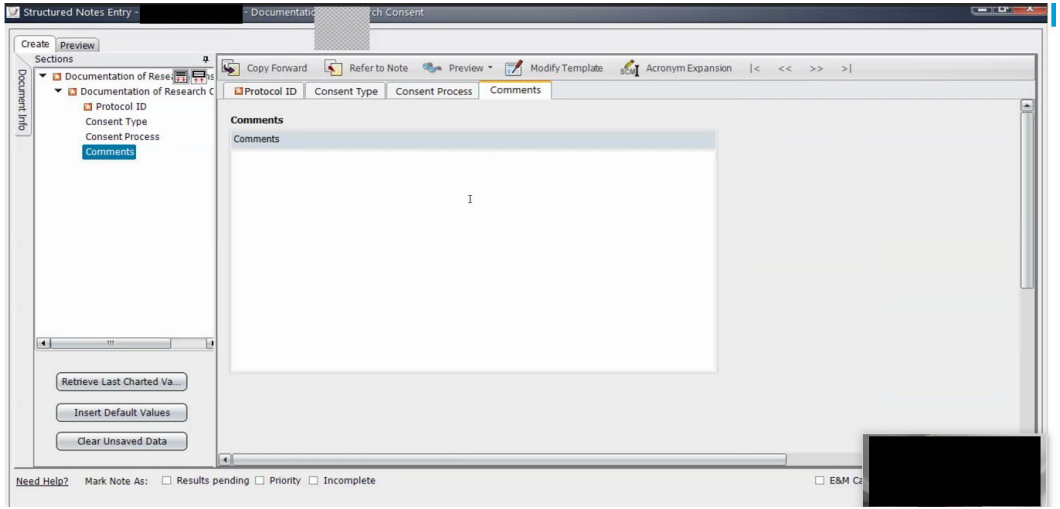
Consent Note: Consent Process

- Must select “Yes” or “No”
  - If “No,” text box will appear for explanation



Consent Note: Comments

- For additional information
- DO NOT repeat information from other section
- DO NOT include information about eligibility



Data and Safety Monitoring

- A formalized process for reviewing accumulated outcome data from an ongoing research study to ensure the continuing safety and welfare of current research subjects and those yet to be enrolled, as well as the continuing validity and scientific merit of the study.
- Data Safety and Monitoring Plan
  - A written description that prospectively identifies and documents monitoring activities, or that none are needed, to protect research participants and maintain study integrity and data validity
  - May also identify when to terminate a subject's participation (i.e. individual stopping rules) and/or the appropriate termination of a study (i.e. study stopping rules).
- All protocols submitted to an NIH IRB must include a Data Safety Monitoring Plan (DSMP) - Policy 503

Data and Safety Monitoring Entity

- Identified individual or group assigned to conduct interim monitoring of data from research activities:
  - PI
  - Coordinating or statistical center
  - Medical monitor
  - IC monitor
  - Independent Data and Safety Monitoring Board (DSMB) and other entities including:
    - Data and Safety Monitoring Committee (DSMC)
    - Data Monitoring Committee (DMC)

Data and Safety Monitoring Plan (DSMP)…

- Identify the data and safety monitoring entity (e.g., PI, medical monitor or DSMB).
- Commensurate with the level of risk and complexity of the study:
  - The schedule for reporting to the data and safety monitoring entity;
  - The frequency of assessments of data or events;
  - The stopping rules;
  - Plans for interim and/or futility analyses;
  - Procedures for communication between the PI, research team members, the study sponsor, the data and safety monitoring entity, the IRB, others at NIH and, as applicable, the coordinating or statistical center, FDA and other study sites.

…DSMP

- Needs to be outlined in the protocol
- Provide reports to the IRB at the time of continuing review or sooner

Essential Documents

- Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
- Demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and all applicable regulatory requirements
- May also be referred to as regulatory file/binder, study file/binder

Examples of Essential Documents

- All versions of the protocol and amendments
- All versions of the IC document
- All IRB approvals
- All continuing reviews
- IRB Correspondence
- IRB membership lists
- CVs
- Training Records
- Screening and Enrollment Logs
- Laboratory certifications and reference ranges
- All versions of the FDA Form 1572 or Investigator agreement, if applicable
- All copies of the Investigator Brochure
- Sponsor correspondence
- Monitoring logs
- Pharmaceutical/device information

Note: Includes more than the documents found in iRIS. A separate file/binder is needed.

Maintenance of Essential Documents

- PI is ultimately responsible for maintenance
- Task is often delegated to other members of the research team
- Various formats are acceptable
- Needs to be organized in a manner that allows specific documents to be found easily
- Important rule of thumb with filing is “consistency”


QUESTIONS?
COMMENTS?
CONCERNS?