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**VICKIE & JACK FARBER  
VISION RESEARCH CENTER**

**STANDARD OPERATING  
PROCEDURES**

**FOR**

**CLINICAL RESEARCH**

**June 10, 2021**

**VICKIE & JACK FARBER VISION RESEARCH CENTER (VJF-VRC)  
RESEARCH STANDARD OPERATING PROCEDURES (SOPs)**

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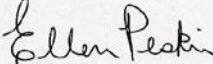
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 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>		<b>SOP # SP 01</b>	
		<b>Title: Policies on Standard Operating Procedures (SOPs)</b>	
		<b>Effective Date: Sept 15 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 2</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	Related SOPs:
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To describe the standard format for writing and maintaining the clinical research SOPs at the Wills Eye Hospital (WEH). This procedure is intended to comply with Food and Drug Administration (FDA) Federal Regulations and the International Conference on Harmonization (ICH) Good Clinical Practices (GCPs).

**SCOPE:** This SOP applies to all staff conducting clinical research at the WEH.

**RESPONSIBILITY:** The Vickie and Jack Farber Vision Research Center is responsible for preparing SOPs pertaining to clinical research. Each SOP will designate who is responsible for oversight of the SOP, performing the activities, or other procedural responsibilities.

**DEFINITIONS:**

**Standard Operating Procedure (SOP):** The International Conference on Harmonization (ICH) defines a SOP as “detailed written instructions to achieve uniformity of the performance of a specific function.” (ICH GCP 1.55). Unlike a study-specific Manual of Procedures, SOPs are general processes common to all studies.

**Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

**International Conference on Harmonization (ICH):** A joint initiative by the European Union (EU), Japan and the United States that established the ICH GCP Guideline to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

**Benefits of SOPs:** SOPs are intended to create operational efficiencies. Implementation of SOPs provides common processes among all studies, provides a degree of accountability for study team members and prevents noncompliance on a systematic level.

**PROCEDURES:**

**1. SOP Format:**

- Title: The title should be descriptive and accurate
- Purpose/Introduction: The purpose describes why the SOP is being written.



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- Scope: The scope of the SOP describes the range of activities to which the SOP applies.
- Responsibilities: This identifies the individuals accountable for oversight of the SOP, performing the activities, or other procedural responsibilities.
- Procedures: This includes a list of described tasks or step-by-step procedures necessary for completion of the activity, if applicable.
- Citations/References: List of sources cited in the SOP.

**2. SOP Implementation:**

- Each SOP will be prepared and implemented by the VJF Vision Research Center at WEH.
- When a SOP is finalized and approved by the Vice Chair for Research, a hard (paper) copy will be available in the Vision Research Center in an SOP binder maintained by the Manager of Clinical Research. An electronic version will be sent to all research personnel in Wills services and will remain available online for all research employees to access when needed.
- Each service designates a member of the research staff who ensures that current research staff in the service read and sign the SOP Acknowledgement Form (attached). The Acknowledgement form will be scanned and sent to the Manager of Clinical Research and stored on a secure server. The hard copy will be maintained in a binder in the clinical service. Research SOPs will be included in the onboarding process for new research staff, who will sign the Acknowledgement Form and return it to the designated person in the service.


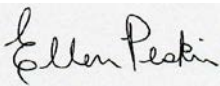

**3. SOP Revisions:**

- Each SOP will be reviewed every 2 years, unless changes in regulations occur or revisions to procedures are required sooner.
- Each revision will be labeled as a revision with an effective date listed.
- Previous versions of the SOP will be archived by the Vision Research Center.
- In the event of an FDA audit, the FDA may audit a study against the SOP that was in effect at the time of study conduct.

**Responsibility:** Wills Vice Chair for Research and the Manager of Clinical Research is responsible for ensuring compliance with this SOP.

**Citations:**

ICH E6 1.55 Standard Operating Procedures

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>		<b>SOP # HS 01</b>	
		<b>Title: Required Elements of Informed Consent Documents for Research Participation</b>	
		<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 6</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	Related SOPs: #HS 02: Obtaining Informed Consent for Study Participation #HS 03: Obtaining Assent/Consent from Minor Research Participants and Parents/LAR/Guardians #ST 01: Responsibilities of the Study Team
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To describe the essential components of an informed consent form for participation in a clinical study and guidance from the Wills IRB on how to address them.

**SCOPE:** This procedure applies to all staff involved in obtaining IRB approval for a study and to those who obtain informed consent from research participants.

**INTRODUCTION:** No research procedures, including procedures conducted solely for the purpose of determining eligibility for research and drug washout periods, can be initiated without first obtaining approval by the IRB to perform the study and without an IRB-approved informed consent form. The most common reason for delay of IRB approval of a protocol is a poorly written consent form. Although sponsors of research studies generally provide a template form for the clinical sites to modify, the form must be in compliance with the Wills IRB mandates in addition to federal regulations.

The elements of the consent form are specifically regulated in 45 CFR Part 46 [sections 116](#), and [117](#) and 21 CFR Part 50 section [20](#), [25](#), as well as outlined in the Good Clinical Practice (ICH) Guidelines (GCP) [section 4.8 Informed Consent of Trial Subjects](#). The IRB is responsible for reviewing the consent form to ensure that the proper elements are present, the form is written in lay language, and no coercive or misleading statements are included. The investigator cannot employ the informed consent form until IRB approval has been received from the IRB of record.

## DEFINITIONS

**Informed Consent Form (ICF):** is a document used to inform potential research participants about a research study and what is involved in participation. A signed ICF is required for clinical research investigations to document a person's agreement to participate, unless an exemption has been issued by the Wills IRB. It is important to recognize that informed consent is an *ongoing* process that includes disclosure of information, a discussion regarding what research participation entails and the opportunity for research participants to express a voluntary choice to enroll in research. The consent form is used as a tool to help researchers during the consenting process.



**Institutional Review Board (IRB):** is a group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA and HHS/OHRP regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

**ELEMENTS OF THE INFORMED CONSENT FORM**

The Common Rule, FDA regulations and ICH GCP guidelines have been harmonized to contain the following requirements (45 CFR 46.116, 21 CFR 50.25, ICH GCP E6 4.8.10). The elements of the informed consent form required by Federal regulations and GCP guidelines are listed below, along with guidance from the Wills IRB on how to incorporate them in ICFs used at Wills.

- A statement that the study involves research
- An explanation of the purpose of the research
  - Wills IRB guidance: Include a research project title and a short, non-technical title, in easy to understand words.
- An explanation of the expected duration of the participant's involvement
- A description of the procedures to be followed, including all invasive procedures and treatments. If applicable, include aspects considered experimental.
  - Wills IRB guidance: The description must be in lay language and not just a repetition of technical details. Indicate whether the treatment or procedures have previously been used in humans or animals. Detail when (at which visits) the procedures will be done.
- A description of any reasonably foreseeable risks or discomforts including risk of being taken off therapy (placebo or wash-out periods) and risks of any procedures related to the research
  - Wills IRB guidance: Whenever possible, describe potential risks in terms of probability (e.g., 1%, 5%, etc.). Include a patient/participant denominator, if relevant data are available.
- A description of any benefit to the participant or to others which may reasonably be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
  - Wills IRB guidance: Do not include any financial or monetary compensation language under this heading. Doing so could potentially cause the institution to appear coercive, or unduly persuasive, in its recruitment process.



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- A disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous.
  - Wills IRB guidance: In therapeutic studies, explain the choices the participant has other than the study interventions. If alternative treatment is not applicable (e.g., studies of “normal” volunteers) state that the alternative is not to participate.
- For studies involving more than minimal risk, an explanation as to whether any treatment or compensation is available if injury occurs, and if so, what they consist of or where further information may be obtained.
  - Wills IRB guidance: The issue is compensation or payment for injury, loss of work, or pain. The IRB policy is that when the research is sponsored by for-profit organizations, such sponsors should provide for medical care, including hospitalization, at no cost to the patient, in the event of adverse effects. The term “compensation” is used in the consent form to refer to payment for injury and does not refer to any payments to patients for travel or inconvenience associated with participation in a study.

The following statements have been approved by the Wills IRB:

1. For studies sponsored by a “not for profit” agency, i.e., Department research funds, NIH, a Foundation, or other government funds:
 

“You may refuse to participate in this investigation or withdraw your consent and discontinue participation in this investigation without penalty and without affecting your future care or ability to receive alternative medical treatment at Wills Eye Hospital. In the event of physical injury or illness resulting to you (or your child) as a direct result of the experiments, treatment(s), and/or procedure(s) used in this investigation, comprehensive medical and/or surgical care (including hospitalization) is available and will be provided. However, Wills Eye Hospital cannot assure that this comprehensive medical and/or surgical care will be provided to the extent needed without charge, and the costs incurred for this care may ultimately be your responsibility. There is no compensation or payment for loss of work or pain.”
2. For studies sponsored by a for-profit organization:
 

“You may refuse to participate in this investigation or withdraw your consent and discontinue participation in this investigation without penalty and without affecting your future care or ability to receive alternative medical treatment at Wills Eye Hospital. In the event of physical injury resulting to you as a direct result of the experiments, treatment(s), and/or procedure(s) used in this investigation, medical care (including hospitalization) is available, and any costs beyond that provided by your health insurance carrier will be covered by (INAME OF CORPORATE SPONSOR). No other financial compensation is available.” [NOTE: Failure of a sponsoring company to provide such coverage may have





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an impact on the wording of this indemnification as well as the risks section of the consent form and will therefore require additional administrative review.]

- An explanation of whom to contact (and contact information) for answers to pertinent questions about the research, the research participant's rights, and in the event of a research-related injury
  - Wills IRB guidance: Include telephone numbers. The IRB does provide a phone number for patients who wish information about the IRB (215-440-3145).
- A statement that participation is voluntary and that refusal to participate will involve no penalty or loss of benefits.
  - Wills IRB guidance: This section must include a statement that refusal of the patient to participate in the research will not affect his or her medical care.
- A statement that the participant may discontinue at any time without penalty or loss of benefits.
  - Wills IRB guidance: Indicate the consequences, if any, of a participant's decision to withdraw from the research and describe the procedures taken for orderly termination of.
- A statement that published results will not identify the participant
- A statement that refers to the trial's description on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (if applicable)
  - Wills IRB mandates the following language: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

When relevant, the informed consent must also include the following elements:

- A statement that the research may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) which are currently unforeseeable.
  - Wills IRB mandates the following language: "Exposure to investigational drugs may be hazardous to a fetus carried by a mother who is receiving an investigational drug or agent. Therefore, adequate birth control measures must be taken by all participants, and their sexual partners, while participating in this study. If you are a woman of childbearing potential, you will have a pregnancy test before being allowed to participate in this study. This requires that blood be drawn from a vein in your arm (i.e., \_\_\_\_ tsp.) one or two days prior to the start of the treatment program. The results of the pregnancy test must be made available to you prior to the start of the treatment program. Presently, you are not pregnant and should not plan to become pregnant while participating in this study. You have been advised to routinely practice a medically accepted method of birth control. Such methods will be discussed with you by





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your physician. Should you become pregnant during the course of this study, you should notify your study doctor immediately.”

Describe any reproductive effects that the investigational drug may have on male sperm production.

- A statement describing the extent, if any, to which confidentiality of records will be maintained
  - Wills IRB guidance: Include a statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and that notes the possibility that the Food and Drug Administration (FDA), National Institutes of Health (NIH), Wills Eye Hospital internal audit, Wills Eye Hospital Institutional Review Board, or another sponsor may inspect the records
- Anticipated circumstances under which participation may be terminated without regard to the participant's consent
- A statement that the participant will be told of significant new findings or information that may be relevant to the participant's continued willingness to continue in the study
- Approximate number of participants involved in the study overall and at Wills
  - Wills IRB guidance: Include the number of participants who will be enrolled in the study overall and at Wills.
- Signatures: Participant's name, signature, and date; signatures of the investigator and a witness.
  - Wills IRB guidance: The signatures cannot be on a page by itself. However, they may be on the reverse side of a page. Participant will receive a signed copy of the consent form.

*These elements, if applicable, are specific to ICH E6 Guidelines:*

- Probability for random assignment to each treatment
  - Wills IRB guidance: Random assignment will be explained in lay terms, e.g. “You will be assigned by chance, like the flip of a coin.”
- The anticipated prorated payment, if any, to the participant



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In addition to the above elements, the Wills IRB mandates the inclusion of the following:

A final statement that says, "I have read and understand I will receive a signed copy of this (*fill in #*)-page informed consent form."

For additional IRB guidance on informed consent forms, refer to the Wills Eye IRB Policy and Procedures Manual located at <https://www.willseye.org/wp-content/uploads/2018/03/WEH-IRB-Policy-Procedures-Manual.pdf>

**CITATIONS:**

21 CFR 50.25 Elements of Informed Consent

21 CFR 56.109 IRB Review of Research

21 CFR 312.60 General Responsibilities of Investigators


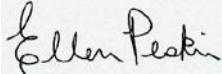
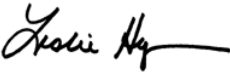
45 CFR 46.116 General Requirements for Informed Consent

45 CFR 46.117 Documentation of informed consent

45 CFR 164.512(i) Uses and disclosures for which an authorization or opportunity to agree or object is not required.

Good Clinical Practice (ICH) Guidelines (GCP) [section 4.8 Informed Consent of Trial Subjects](#).

Wills Eye IRB Policy and Procedures Manual

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER</b> <b>VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR</b> <b>CLINICAL RESEARCH</b>		<b>SOP # HS 02</b>	
		<b>Title: Obtaining Informed Consent from Study Participants</b>	
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<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: September 1 2020	<b>Related SOPs:</b> # HS 01: Required Elements of Informed Consent Documents # HS 03: Obtaining Assent/Consent from Minor Research Participants and Parents/LAR/Guardians #ST 01; Responsibilities of the Study Team #ST 02: Required Training for Clinical Research Staff
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: September 1 2020	

**PURPOSE:** To describe the procedures for obtaining and documenting informed consent from adult study participants or their legal authorized representative (LAR).

**SCOPE:** This procedure applies to all staff involved in obtaining informed consent from research participants.

## DEFINITIONS

**Legally authorized representative (LAR):** an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

**Experimental product:** a product that requires an Investigational New Drug application (IND) or Investigational Device Exemption (IDE) approval by the FDA.

**Informed Consent:** A process by which a subject voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. The Informed Consent Form (ICF) may also be referred to as Informed Consent Document (ICD) or Patient Consent Form (PCF).

**Informed Consent Form (ICF):** is a document used to inform potential research participants about a research study and what is involved in participation. A signed ICF is required for clinical research investigations to document a person's agreement to participate, unless an exemption has been issued by the Wills IRB. It is important to recognize that informed consent is an *ongoing* process that includes disclosure of information, a discussion regarding what research participation entails and the opportunity for research participants to express a voluntary choice to enroll in research. The consent form is used as a tool to help researchers during the consenting process.

**Institutional Review Board (IRB):** A group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.



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**Principal Investigator (PI):** A Principal Investigator is the lead researcher on a study. She/he is the primary individual responsible for the preparation, conduct, and administration of a research study in compliance with applicable laws and regulations and institutional policy governing the conduct of sponsored research.

**Study Coordinator:** A Study Coordinator is a person responsible for conducting clinical trials using good clinical practice under the auspices of a Principal Investigator

**Witness:** A witness is a person who participates in the informed consent process if the participant or the participant's LAR cannot read. The witness reads the ICF and any other written information supplied to the participant.

**INTRODUCTION:** It is the responsibility of the Principal Investigator (PI) to ensure that informed consent is properly obtained in accordance with the regulations 21 CFR 50 Parts 20 and 27, 45 CFR 46 Parts 116 and 117, and outlined in the ICH Good Clinical Practice (GCP) Guidelines section 4.8 Informed Consent of Trial Subjects. In research that does not involve an experimental product, this activity may be delegated to a research coordinator or other research staff who are knowledgeable about the research, the study population, the participant's alternative choices, and informed consent regulations. Ultimately, however, the PI has primary responsibility for the study and remains accountable for the actions of any research staff to whom the responsibility of obtaining informed consent has been delegated. No research procedures, including procedures conducted solely for the purpose of determining eligibility for research and drug washout periods, can be initiated without first appropriately obtaining informed consent with an IRB approved consent form.

**WHO MAY OBTAIN INFORMED CONSENT?**

For consent to be truly informed, the person obtaining consent must have sufficient background, education, experience, and knowledge of the study to answer the questions of potential participants. The Principal Investigator may designate consent procedures to be performed by qualified and experienced members of the study team at his or her discretion. The Informed Consent Form template assumes that a Principal or Co-Investigator will conduct the consent interviews. When the duty of conducting the consent interview is given to another member of the study team who is not an Investigator, this fact should be noted on the signature lines of the final page of the consent form.

Staff delegated by the Principal Investigator (PI) to obtain informed consent are responsible for:

- Understanding and following this SOP.
- Being adequately trained and qualified to obtain informed consent, as determined by the PI, by education, training, experience, and knowledge of the trial.
- Conducting the informed consent process with the potential participant. He/she will inform the potential participant that participating in the study is voluntary, and that the potential participant has a good understanding about the study procedures/study agents.



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- Conducting the consent process in a private setting free of coercion and undue influence. The possible study benefits will not be overstated nor will the risks be understated. Extra time will be taken to ensure understanding of these issues, as necessary.
- Delivering all required information in a manner that is understandable to the participant.
- Confirming that the potential participant comprehends the information.
- Documenting the informed consent process, as applicable, including documenting the process in the chart notes.

The PI is responsible for:

- Ensuring staff delegated the task of obtaining informed consent are adequately trained and qualified by education, training, experience, and have knowledge of the trial prior to the staff performing the delegated task.
- Ensuring that staff delegated the task of obtaining informed consent are listed on the study-specific Delegation Log prior to the staff performing the delegated task.
- Ensuring that all applicable staff have received the appropriate training, follow this SOP, and are compliant with all applicable CFR regulations and ICH Guidelines.
- Ensuring applicable SOPs are kept in the Regulatory binder.

**REQUIRED TRAINING FOR STAFF INVOLVED IN THE INFORMED CONSENT PROCESS:**

- Each staff member receives CITI training in Human Subjects Protection and Good Clinical Practice
- Each staff member receives or has direct access to applicable SOPs.
- All SOP training is documented and tracked in the study regulatory binder and with the IRB
- New staff are trained on applicable SOPs within 30 days of employment.
- Staff members whose duties fall within this SOP scope are retrained within 14 days of the approval of each SOP revision.

**PROCEDURES FOR OBTAINING INFORMED CONSENT FROM POTENTIAL PARTICIPANTS**

1. The PI or staff delegated by the PI to obtain informed consent will meet with the potential participant to obtain consent.
2. The consent discussion will occur a private, quiet, coercion-free setting and staff delegated by the PI to obtain consent will explain all aspects of the study.

- If the initial discussion with the potential participant to introduce the study is via the telephone, IRB approval must be obtained to mail or email a sample consent form to the potential participant for review prior to the consenting process and study appointment.
3. At the start of the first study visit, before any data are collected, the IRB-approved informed consent form will be reviewed with the potential participant, each section will be addressed thoroughly and the main points will be highlighted. The person obtaining consent must clearly explain the following:
    - background and purpose of the study
    - voluntary nature of participation
    - commitment entailed
    - risks of participation
    - benefits of participation
    - alternatives to participation
    - who to contact with questions (and their contact information)
  4. During the discussion, the potential participant, their LAR (if applicable) or anyone the potential participant designates will be encouraged to ask questions or express any concerns he/she/they may have.
  5. Potential participants must be given sufficient time to comprehend the research and read the Informed Consent Form.
  6. After all informed consent materials have been reviewed, and all questions/concerns have been addressed, the person obtaining consent should evaluate the potential participant's understanding by asking open ended questions about the study and addressing any misperceptions. Possible questions include:
    - *Can you describe the study in your own words?*
    - *What more would you like to know?*
    - *Would you please explain to me what we are asking you to do?*
    - *What are your concerns?*
  7. After the potential participant demonstrates that he/she fully understands the material in the informed consent form and wants to participate in the research, he/she will be asked to sign and the date the informed consent form.
  8. After observing the signature, the person authorized to obtain consent will print his/her name, date, and sign the informed consent form.



9. Signatures and dates will be entered in ink, and date blocks will be completed by each signatory. Any errors made to the informed consent form must be corrected per GCP.
10. A copy of signed consent form will be given to the participant. The original will be filed in the participant's study binder/folder and stored in a locked file/cabinet, preferably in a locked room.
11. The IRB-approved form must be signed and dated by the participant prior to his/her participating in any study-related activities, unless consent is waived by the IRB.
12. Document the informed consent process (see below).

**Documentation of Informed Consent**

A note in the chart and/or research record documenting the Informed Consent Process is designed to provide documentation of the informed consent process, as well as serve as a record in the event that the ICF is missing from the study records. The note should include the following information:

- Name of study and subject
- Date of consent
- Statement that the benefits, risks, commitment and alternatives were discussed
- Presence of any family members, friends, or witnesses

A sample informed consent note may look like the following:

On 3/10/2020, I reviewed the research protocol [study title] with [patient's name]. [He/she] was given an opportunity to read the consent form and was given ample time to ask questions and have them answered. The study's purpose, procedures involved, voluntary nature, risks and benefits were discussed with him/her. He/she indicated his/her decision to participate and signed the consent form. I provided him/her with a copy of the signed informed consent and HIPAA authorization form. The informed consent form was signed prior to any study related procedures, outside of standard of care, were performed.

**Waiver of Informed Consent**

In specific circumstances, the IRB may waive part or all of the informed consent process upon request. For example, an investigator may want to conduct a retrospective study of existing, identifiable laboratory specimens or scans without obtaining informed consent. To request a waiver of informed consent, the investigator must demonstrate in a letter to the IRB that all of the following five conditions are met:

1. The research involves no more than minimal risk to the health of the participant,
2. The waiver will not result in more than minimal risk to privacy/confidentiality,





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3. It is not practical to do the study without the waiver,
4. The study results would have direct clinical significance for patients whose data is used
5. The research is not practicable without access to identifiable data

**CITATIONS:**

21 CFR 50.25 Elements of Informed Consent

21 CFR 56.109 IRB Review of Research

21 CFR 312.60 General Responsibilities of Investigators

45 CFR 46.116 General Requirements for Informed Consent

45 CFR 46.117 Documentation of informed consent

45 CFR 164.512(i) Uses and disclosures for which an authorization or opportunity to agree or object is not required.

Good Clinical Practice (ICH) Guidelines (GCP) [section 4.8 Informed Consent of Trial Subjects](#).



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CLINICAL RESEARCH

SOP # HS 03

Title: Obtaining Assent/Consent from  
Minor Research Participants and  
Parents/LAR/Guardians

Effective Date: September 15, 2020

Revised Date: Jan. 22, 2022

Next Review Date: Sept. 15, 2022

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**Author:** Ellen Peskin  
Manager of Clinical  
Research

Signature:

Signature Date:  
August 15, 2020

Related SOPs:  
# HS 01: Required Elements of  
Informed Consent Documents  
# HS 02: Obtaining Informed  
Consent from Study  
Participants  
#ST 01: Responsibilities of the  
Study Team  
#ST 02: Required Training for  
Clinical Research Staff

**Approved by:**  
Leslie Hyman, PhD.  
Vice Chair for Research

Signature:

Signature Date:  
August 15, 2020

**PURPOSE:** To describe the procedures for obtaining and documenting assent/informed consent from a minor study participant or their legal representative. The consent process continues throughout the child's participation in the study.

**SCOPE:** This procedure applies to all staff involved in obtaining informed assent, parental permission, and consent when children are research participants.

**INTRODUCTION:** Children (minors) are considered a vulnerable research population and, as such, require additional protections when they are potential research participants. Subpart D of both 45 CFR 46 (DHHS) and 21 CFR 50 (FDA) require certain additional protections for children involved as participants in research. These regulations require that adequate provisions are made for soliciting the assent of all children involved in research when the children are capable of providing assent, and obtaining parental/legally authorized representative/guardian's permission, as applicable.

Permitted Categories for Research with Children

As per U.S. Federal regulations (45 CFR 46 and 21 CFR 50, Subpart D), permissible research involving children are limited to those activities that meet one of four categories, based on the level of risk and potential for benefit to the individual participant. These categories are:

1. Research not involving greater than minimal risk (§46.404 and §50.51);
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants (§46.405 and §50.52);
3. Research that involves more than minimal risk and presents the prospect of no direct benefit to individual participants, but generalizable knowledge (societal benefit) (§46.406 and §50.53); or
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (§46.407 and §50.54)



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**DEFINITIONS (PER §46.102/§46.402/§50.3)**

*Children:* persons who have not attained the legal age for consent to treatments or procedures involved in the research to be conducted. In Pennsylvania, the age of majority is 18 years.

*Assent:* a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. To take part in the assent process, children must be mature enough to understand the trial and what they are expected to do. In Pennsylvania, children under the age of 7 years are not able to provide to assent. Some children as young as 7 years old may be able to participate in the assent process, but this varies depending on the child.

*Guardian:* an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

*Legally authorized representative (LAR):* an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

*Emancipated Minor:* persons under the legal age of 18 who because of their unique circumstances (e.g. emancipated minors, self-sufficient minors, etc.), may have the legal rights of adults, including the right to consent to treatments or procedures involved in research. Such individuals would not meet the definition of children as defined at §46.402 and §50.3. Hence, parental/LAR/guardian permission (or waiver) is not required for these minors. Under these circumstances, minors with legal documents confirming their emancipation may provide their own informed consent to participate in the research.

*Minimal risk:* the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

*Parent:* a child's biological or adoptive parent.

*Permission:* the agreement of parent(s) or guardian to the participation of their child or ward in research.

**RESPONSIBILITIES**

**Staff delegated by the Principal Investigator (PI) to obtain informed assent/consent are responsible for:**

- Understanding and following this SOP.
- Being adequately trained and qualified to obtain informed assent/consent, as determined by the PI, by education, training, experience, and knowledge of the trial.
- Conducting the informed assent/parental permission/consent process with the child and his/her parent/LAR/guardian. He/she will inform the child and his/her parent(s)/LAR/guardian that



participating in the study is voluntarily, and that the potential participant and his/her parent(s)/guardian has a good understanding about the study procedures/study agents.

- Obtaining from each child assent or consent (for children who can consent on their own behalf), and informed permission from the parent(s)/LAR/guardian prior to initiation of study procedures.
- Conducting the assent/consent process in a private setting free of coercion and undue influence. The possible study benefits will not be overstated nor will the risks be understated. Extra time will be taken to ensure understanding of these issues, as necessary.
- Delivering all required information in a manner that is understandable to the child and his/her parent(s)/LAR/guardian.
- Confirming that the child and his/her parent(s)/LAR/guardian comprehends the information.
- Documenting the informed assent/consent process, as applicable, including documenting the process in the chart notes.

**The PI is responsible for:**

- Ensuring staff delegated the task of obtaining informed assent/consent are adequately trained and qualified by education, training, experience, and have knowledge of the trial prior to the staff performing the delegated task.
- Ensuring that staff delegated the task of obtaining informed assent/consent are listed on study-specific Delegation Log prior to the staff performing the delegated task.
- Ensuring that all applicable staff have received the appropriate training, follow this SOP, and are compliant with all applicable CFR regulations and ICH Guidelines.
- Ensuring applicable SOPs are kept in the Regulatory binder

**REQUIRED TRAINING FOR STAFF INVOLVED IN THE INFORMED CONSENT PROCESS:**

- Each staff member receives CITI training in Human Subjects Protection and Good Clinical Practice
- Each staff member receives or has direct access to applicable SOPs.
- All SOP training is documented and tracked in the study regulatory binder and with the IRB
- New staff are trained on applicable SOPs within 30 days of employment.
- Staff members whose duties fall within this SOP scope are retrained within 14 days of the approval of each SOP revision.



## GENERAL PROCEDURES

### Parental Consent

Sections §46.408 and §50.55 of Subpart D require that adequate provisions be made for soliciting the consent of parents/LAR/guardian of each child involved in a research study. For studies with greater than minimal risk, parental permission should be obtained before the child is asked to assent. The IRB may find that the permission of one parent is sufficient. At a minimum, the federal requirements for consent indicated below must be met but the IRB may determine that more stringent requirements are appropriate.

### **.Permission from Parents or Guardians**

<b>Regulatory Category of Permitted Research with Children</b>	<b>One Parent's or Both Parents' Permission Required?</b>
Minimal Risk ( <u>45 CFR 46.404, 21 CFR 50.51</u> )	<b>One parent</b> /legal guardian <i>may</i> be sufficient
Greater than Minimal Risk, Direct Benefit to Participant ( <u>45 CFR 46.405 21 CFR 50.52</u> )	<b>One parent</b> /legal guardian <i>may</i> be sufficient but IRB must determine whether one or two is required
Greater than Minimal Risk, No Direct Benefit to Participant but Likely to Yield Generalizable Knowledge about Participant's Condition ( <u>45 CFR 46.406 21 CFR 50.53</u> )	<b>Both parents</b> /legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.
Greater than Minimal Risk, No Direct Benefit to the Participant, but Results May Alleviate Serious Problems of Children's Health or Welfare ( <u>45 CFR 46.407 21 CFR 50.54</u> )	<b>Both parents</b> /legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.

### **When One Parent's Permission Is Sufficient**

For research that falls into risk-benefit Category 1 [45 CFR 46.404 21 CFR 50.51] or 2 [45 CFR 46.405 21 CFR 50.52], the IRB may determine that permission from only one parent is sufficient. Research that falls into Category 3 [45 CFR 46.406 21 CFR 50.53] or 4 [45 CFR 46.407 21 CFR 50.54] requires permission from both parents, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child [45 CFR 46.406 or 407, 21 CFR 50.55(e)].

**IMPORTANT NOTE:** When there is only one living parent or guardian or one parent has sole custody after a divorce, the investigator may determine that single-parent or single-guardian permission is sufficient.

### **When Parents Disagree**

If there are two parents available to give permission but they disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. This



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applies to all permissible categories; even if only one parent's signature is required, when both parents are involved in the decision, they must agree for the child to be enrolled. If a parent who was not involved or available for the original consent later becomes involved or available, the two parents must then agree.

Children Who Reach the Legal Age of Consent While Enrolled in a Study

Informed consent is an ongoing process throughout the duration of a research study. When a child who was enrolled in research with parental/LAR/guardian permission reaches the legal age of consent, the participant's participation no longer requires parental/LAR/guardian permission. Informed consent must then be obtained from the now-adult participant to continue research participation, unless the IRB determines that the requirements for obtaining informed consent can be waived.

Consent Process for Emancipated Minors

Emancipated minors with legal documents confirming their emancipation may provide their own informed consent to participate in the research.

Documentation of Informed Assent/Consent

The IRB approved form must be signed and dated by the parent(s)/LAR/guardian prior to the child's participating in any study-related activities, unless permission is waived by the IRB/EC for non-IND studies.

**When Assent Is Not Required**

Assent must be obtained from children unless:

- The child is under 7 years of age
- A child 7 years of age or older who is not capable of assenting.
- The child might benefit from the treatment or procedure being studied in the trial.
- The treatment or procedure that may benefit the child is only available in clinical trials.
- Even if assent is not required, children still benefit from going through the assent process. Doing so can help children feel more in control and engaged in the trial. It shows that they have a say in what happens to them and that their questions and input are valued.



**SPECIFIC PROCEDURES FOR OBTAINING PERMISSION/CONSENT FROM PARENTS/  
LAR/GUARDIANS**

1. Staff delegated by the PI to obtain informed consent will meet with the child's parent(s)/LAR/guardian to obtain permission. If the child is unable to provide assent, the parent(s)/LAR/guardian must provide consent for the child's participation.
2. The consent discussion will occur a private, quiet, coercion-free setting and staff delegated by the PI to obtain consent will explain all aspects of the study.
3. The IRB-approved informed consent form will be reviewed with the child's parent(s)/LAR/guardian and each section will be addressed adequately and the main points will be highlighted. During the discussion, child's parent(s)/LAR/guardian will be encouraged to ask questions or express any concerns he/she/they may have.
4. After all informed permission/consent materials have been reviewed, and all questions/concerns have been addressed, the person obtaining consent will verify understanding of the study and informed consent process with the child's parent(s)/LAR/guardian.
5. After the parent(s)/LAR/guardian demonstrates that he/she fully understands the material in the informed permission/consent form, and allows the child to be in the study, he/she will be asked his/her to sign and the date two separate informed consent forms (one to be offered to the parent(s)/LAR/guardian and the other for the research records).
6. After witnessing the signature, the person authorized to obtain consent will print his/her name, date, and sign both informed consent forms.
7. Signatures and dates will be entered in ink, and date blocks will be completed by each signatory. Any errors made to the informed assent form must be corrected per GCP.
8. A copy of the permission/consent form will be offered to the child's parent(s)/LAR/guardian. The other signed copy will be filed in the participant's study binder/folder and stored in a locked file/cabinet, preferably in a locked room.

**SPECIFIC PROCEDURES FOR OBTAINING ASSENT FROM CHILDREN:**

1. In determining whether children aged 7 or older are capable of assenting, the ages, maturity, and psychological state of the children involved should be taken into account. An assent process that takes into account the child's experience and level of understanding assures an element of cooperation and a feeling of inclusion on the part of the child, and also illustrates the investigator's respect for the rights and dignity of the child in the context of research.
2. Staff delegated by the PI to obtain informed assent/consent will meet with the child and the parental/LAR/guardian(s) in a private, quiet, coercion-free setting and explain all aspects of the research.





3. An IRB-approved assent form, developed for the appropriate age range of the child for his or her easier comprehension, will be reviewed with the child. The child should be given an explanation, at a level appropriate to the child's age, maturity and condition, of the procedures to be used, their meaning to the child in terms of discomfort and inconvenience, and the general purpose of the research.
4. During the discussion, the child and his/her parent/LAR/guardian(s) will be encouraged to ask questions or express any concerns he/she may have. Staff will answer all questions and discuss all concerns before moving on to the next section of the form.
5. After all assent materials have been reviewed, and all questions/concerns have been addressed, the person delegated by the PI to obtain consent will verify understanding of the study and informed assent process with the participant.
6. Staff will listen carefully to all questions and/or concerns expressed by the child and take as much time as needed to discuss these thoroughly. If the child does not seem to understand the study even after answering questions, or he/she seems hesitant, site staff will not proceed with signing the assent form. The child will be thanked for his/her time and will be provided with the phone number and requested to call the study site clinic if he/she have further questions.
7. It may take several sessions before the research team feels that the child has a clear understanding of what the trial involves. Only after the child demonstrates a full understanding of the material in the informed assent form and chooses to take part, he/she will be asked to sign and date two separate informed assent forms (one to be offered to the child and the other for the research records).
8. After the child has signed the assent form, the person who is conducting the informed assent discussion will print his/her name, date, and sign both informed assent forms.
9. If the child will not assent to participate, he/she cannot be enrolled even if the parent/LAR/guardians(s) has provided permission/consent.
10. Signatures and dates will be entered in ink, and date blocks will be completed by each signatory. Any errors made to the informed assent form must be corrected per GCP.
11. One signed copy of the Assent for will be given to the child or to the child's parent/LAR/guardian. The other signed copy will be filed in the participant's study binder/folder and stored in a locked file/cabinet, preferably in a locked room.

**CITATIONS**

21 CFR 56.109    IRB Review of research  
45 CFR 46.109



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21 CFR 50.25 Elements of Informed Consent

21 CFR 56.111 Criteria for IRB Approval of Research  
45 CFR 46.111

21 CFR 312.54 Emergency Research under §50.24 of this chapter  
21 CFR 312.60 General Responsibilities of Investigators

21 CFR 312.62 Investigator Recordkeeping and Record Retention  
45 CFR 46.116 General Requirements for Informed Consent


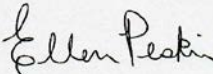
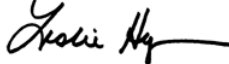
FDA Internal Compliance Program Guidance Manual, 1994: 7348.811: Clinical Investigators

FDA Information Frequently Asked Questions, A Guide to Informed Consent Sheets, October, 1995  
Documents, Informed Consent and the Clinical Investigator

The Belmont Report and Declaration of Helsinki

May 9, 1997 International Conference on Harmonisation: Good Clinical Practice: Consolidated  
Guideline

FDA website: [U S Food and Drug Administration Home Page](#) OHRP website: [HHS - Office for  
Human Research Protections](#) ICH website: [ICH](#)

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER</b> <b>VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR</b> <b>CLINICAL RESEARCH</b>		<b>SOP # SD 01</b>	
		<b>Title: Essential Study Documents</b>	
		<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 5</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	Related SOPs: #SD 02: Source Documents in Clinical Trials #SD 03: Retention of Research Records
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To define essential study documents and to describe the organization, content and retention of essential study records at Wills Eye Hospital to comply with Federal regulations.

**SCOPE:** This SOP applies to all clinical studies conducted at the Wills Eye Hospital (WEH).

**RESPONSIBILITY:** Principal Investigators, Co-Investigators, Research Coordinators and the Manager of Clinical Research is responsible for ensuring compliance with this SOP.

**INTRODUCTION:** Investigators and coordinators conducting clinical research at the WEH shall maintain a complete set of files pertaining both to specific participants (Subject Files and Source Documents) and to regulatory documentation, including study approvals, IRB correspondence and all significant correspondence for each study conducted.

Documentation shall be maintained per this SOP as required by federal regulations, in alignment with the FDA and ICH E6, Essential Documents and as stipulated in the study protocol, if applicable.

## DEFINITIONS

**Confidentiality:** Prevention of disclosure, other than to authorized individuals, of a sponsor's proprietary information or of a study participant's identity.

**Documentation:** All records, in any form (including, but not limited to written, electronic, magnetic, and optical records and scans) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

**Essential Documents:** According to ICH E6 8.0, essential documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. Refer to the appended document for a list of all essential documents per ICH.

**Inspection:** The act by a regulatory authority of conducting an official review of documents, facilities, records, and other resources deemed by the authority to be related to the clinical trial.



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**Investigator’s Brochure:** A collection of all relevant information known prior to the start-up of a clinical research study involving an investigational product(s). It includes the pre-clinical data such as chemical, pharmaceutical, toxicological, pharmacokinetic and pharmacodynamic data in animals and humans as well as the results of earlier trial.

**Note-to-File:** A description of the protocol-specific method of accomplishing a process. This document can also be used to describe the reason for a discrepancy, missing data or missing documentation and can include information regarding the location of central files.

**“Part 11”:** Title 21 CFR Part 11 is the part of Title 21 of the Code of Federal Regulations that establishes the United States Food and Drug Administration regulations on electronic records and electronic signatures.

**Quality Assurance (QA):** Planned and systematic actions established to ensure that the trial is performed and the data are generated, documented, and reported in compliance with GCP and the applicable regulatory requirement(s).

**Regulatory Binder/File:** Contains essential documents required to conduct a clinical study and is often the first document reviewed during audits and inspections. Referred to synonymously as Study Files, Investigator Files or Investigator Binder, it includes a record of all data pertinent to the conduct of the investigation and includes evidence of required reviews and approvals. The materials included in this file and a suggested organizational format are attached to this document.

**Source Documents:** Source documents include, but are not limited to, medical records, laboratory reports, output from automated instruments, images, subject diaries and study case report forms. The study CRFs often require information that is beyond the scope of usual chart notes or that is collected or formatted specifically for the trial. In these instances, the CRF is the source document when the data are recorded directly onto the CRF. (For more information on study source documents, see VJF VRC SOP #SD 02 Source Documents in Wills Clinical Trials.)

**PROCEDURES:**

1. For each clinical study, the study coordinator or regulatory coordinator will create an electronic file (preferred) in a designated Part 11 compliant storage area. If unavailable or if mandated by a study sponsor, a paper binder will be created.
2. The coordinator maintains and updates essential documentation as necessary, adding appropriate documents as they are generated or received. For significant e-mail correspondence, only the latest and final chain including any final actions or decisions should be printed and retained.



3. Regulatory documents should be filed in chronological order in a standardized format. The preferred organizational structure is appended to this document. A Regulatory Log is recommended to track most current study related documentation such as protocol amendments and changes in informed consent documents.
4. Retain copies of the original and all amendments to the documents (e.g., protocol, investigator’s brochure, informed consent form(s)).
5. All newsletters, Monitoring Visit Letters and any significant correspondence addressed to the study staff must be initialed and dated by the appropriate personnel as evidence of review prior to filing the documents.
6. Prior to scheduled monitor and/or auditor visits, the study coordinator should review the contents of regulatory files for completeness.
7. At the end of the study, the study coordinator should review the regulatory file for accuracy. Missing documents should be retrieved and inserted, and discrepancies noted by creating a note-to-file. If the document cannot be found or replaced, a note-to-file explaining why the document is missing should be placed in the regulatory file. If a document is temporarily stored outside of the regulatory file, create a note-to-file indicating the document’s location.
8. After the study is completed and the file is reviewed completely, the regulatory file must be stored in a secure place and made available in the event of a regulatory audit.
9. Refer to the sponsor/funding agency’s contract/agreement to determine the required regulatory document retention guidelines.

**ORGANIZATION OF ESSENTIAL STUDY DOCUMENTS:**

Essential Study Documents are to be organized into three sections, 1) the Regulatory file/binder and 2) individual subject files and 3) IP records (if appropriate). Individual subject files are maintained separately from the regulatory file.

**Document Requirements\*:**

A. Original or copies of the following documents must be sent to the sponsor:

- Original final signed protocol
- Original final signed amendments
- Final signed FDA form 1572 from each Investigator
- Current CVs from each Investigator (and Sub-Investigators when requested)
- Amended FDA form 1572 as available
- Financial disclosure documentation



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- Lab certification, and normal lab values for each lab used
- Copy of IRB approval for original protocol, advertisements, and informed consent/HIPAA forms and all amended versions of each document
- Copy of IRB progress reports and final report
- Originals of all Case Report Forms (CRFs) and any other data forms including lab test data for the study
- Original or copy of test article log for investigational test article, concomitant medications, and equipment. Copies of test article shipment and retrieval documents
- Information on any adverse events at WEH including IRB submissions when reported as required by IRB
- Copies of any abstracts or manuscripts regarding the results of the study
- Copy of IRB final report letter

**\*A full list of essential study documents is appended to this document**

**B. Study Subject Record Requirements**

An accurate record for each study subject must be maintained. These records include, but are not limited to, the following documents:

- Signed Informed Consent forms
- CRFs
- Medical history records
- Physical examination results
- Laboratory test results
- Clinic notes
- Other source documents

**C. Investigational Product (IP) Record Requirements**

The individual responsible for receiving, dispensing and accounting for the IP (Investigator, study coordinator or Pharmacist) maintains accurate and complete accounting of all IP received, disbursed, and returned to the sponsor. These records must be kept with other study records and retained as required by the sponsor and FDA.

**Retention of Study Documents**

Refer to SOP #SD 03 Retention of Research Documents for Wills' policy on research records retention.



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**Applicable Regulations and Guidelines**

FDA 21 CFR 11—Electronic Medical Records

FDA 21 CFR 50—Protection of Human Subjects

FDA 21 CFR 312.60—General Responsibilities of Investigators

FDA 21 CFR 312.62—Investigator Recordkeeping and Record Retention

FDA 21 CFR 312.68—Inspection of Investigator’s Records and Reports

FDA 21 CFR 812.140(a)—Investigator Records

ICH E6 8.0 Essential Documents for the Conduct of a Clinical Trial



# Wills Eye Hospital Vision Research Center Regulator Binder Template

## 📁 Correspondence

### 📁 IRB Correspondence

#### 📁 Initial IRB Submission & Approvals

- 📁 Submission Materials
- 📁 Correspondence
- 📁 Approval letter

#### 📁 Subsequent IRB Submissions and Approvals

- 📁 Submission Materials
- 📁 Correspondence
- 📁 Approval letter

#### 📁 IRB/HIPAA Approved ICF, Advertising, Other written info

- 📁 ICF/HIPAA Tracking Log
- 📁 Outdated ICFs- DO NOT USE

#### 📁 IRB Final Report/Closeout and Approval

- 📁 Submission Materials
- 📁 Correspondence
- 📁 Approval/Acknowledgement Letter

#### 📁 IRB Letter of Assurance

- 📁 Approvals from Other Reviewing Entities (Letter of approval, receipt of submission or Correspondence with any other reviewing committees relevant to the study)

#### IBC

- 📁 Others?

- 📁 Sponsor/CRO Correspondence (Relevant communication between Site, CRO or sponsor regarding study administration, conduct, subject mgmt., protocol violations and AEs. Includes CTA, letters, faxes telephone discussions and emails.)

- 📁 General Correspondence (Communication between clinical personnel, pharmacy, etc. regarding study administration, conduct, subject mgmt., protocol violations and AEs. Includes letters, faxes telephone discussions and emails.)

- 📁 Protocol Deviation Reports

## 📁 Study Documents

- 📁 Protocol

- 📁 Current Protocol & Protocol Signature Page

- 📁 Protocol Tracking Log

- 📁 Protocol Amendments (Description of changes to the protocol, including revision date and version number)

# Wills Eye Hospital Vision Research Center Regulator Binder Template

- 📁 Outdated Protocol Versions
- 📁 Investigator's Brochure/Safety Information
- 📁 Product Labeling and Handling Instructions
- 📁 Certification of analysis (if applicable)
- 📁 Laboratory Documents (if applicable)
  - 📁 Current Lab Certification (CLIA & CAP)
  - 📁 Lab Manual
  - 📁 Normal Lab Values
  - 📁 Record of Retained /Stored Samples (if applicable)
- 📁 Investigational Product Handling and Accountability
  - 📁 IP Certificate of Analysis
  - 📁 IP Shipment Receipts
  - 📁 IP Product Accountability Log
  - 📁 IP Destruction Documentation
  - 📁 IP Supply Correspondence
- 📁 Research Personnel
  - 📁 CVs, Licenses, FDA 1572, Financial Disclosure
    - 📁 Clinician CVs & Licenses
    - 📁 Coordinator CVs
    - 📁 Technician CVs (if needed)
    - 📁 Physician Licenses
    - 📁 Financial Disclosures
  - 📁 Human Subjects Training Certificates
  - 📁 GCP Certificates
  - 📁 HIPAA Training Certificates
  - 📁 IATA Certification (if required)
  - 📁 Signature and Delegation of Responsibility Log
  - 📁 FDA Form 1572
  - 📁 Study Certification documents
    - 📁 Investigator Certification
    - 📁 Coordinator Certification
    - 📁 Technician Certification
    - 📁 Photographer Certification

Wills Eye Hospital  
Vision Research Center  
Regulator Binder Template

📁 Safety and SAE Reports

- 📁 SAE Reports, PI to Sponsor
- 📁 SAE Reports to IRB
- 📁 Safety reports, IRB interim or annual
- 📁 Safety Reports, Sponsor to PIs
- 📁 DSMC Summary Reports (if applicable)

📁 Subject Logs

- 📁 Screening Log
- 📁 Subject Enrollment Log
- 📁 Subject Identification Code List

📁 Monitoring Reports

- 📁 Monitor Signature Log & Visit Record
- 📁 Study Initiation Report
- 📁 Interim Monitoring Reports
- 📁 Close-Out Report

📁 Study Closeout

- 📁 Site Close-Out Checklist

## **8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL**

### **8.1 Introduction**

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

### **ADDENDUM**

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

## 8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	<b>INVESTIGATOR'S BROCHURE</b>	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	<b>SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)</b>	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	<b>INFORMATION GIVEN TO TRIAL SUBJECT</b> <b>- INFORMED CONSENT FORM</b> (including all applicable translations)	To document the informed consent	X	X
	<b>- ANY OTHER WRITTEN INFORMATION</b>	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
	<b>- ADVERTISEMENT FOR SUBJECT RECRUITMENT</b> (if used)	To document that recruitment measures are appropriate and not coercive	X	
<b>8.2.4</b>	<b>FINANCIAL ASPECTS OF THE TRIAL</b>	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
<b>8.2.5</b>	<b>INSURANCE STATEMENT</b> (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
<b>8.2.6</b>	<b>SIGNED AGREEMENT BETWEEN INVOLVED PARTIES</b> , e.g.: <ul style="list-style-type: none"> <li>- investigator/institution and sponsor</li> <li>- investigator/institution and CRO</li> <li>- sponsor and CRO</li> <li>- investigator/institution and authority(ies) (where required)</li> </ul>	To document agreements	<ul style="list-style-type: none"> <li>X</li> <li>X</li> <li></li> <li>X</li> </ul>	<ul style="list-style-type: none"> <li>X</li> <li>X</li> <li>(where required)</li> <li>X</li> <li>X</li> </ul>

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.7	<p><b>DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b></p> <ul style="list-style-type: none"> <li>- protocol and any amendments</li> <li>- CRF (if applicable)</li> <li>- informed consent form(s)</li> <li>- any other written information to be provided to the subject(s)</li> <li>- advertisement for subject recruitment (if used)</li> <li>- subject compensation (if any)</li> <li>- any other documents given approval/ favorable opinion</li> </ul>	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s)	X	X



	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.8	<b>INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION</b>	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	<b>REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL</b> (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	<b>CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)</b>	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	<b>NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and/or ranges of the tests	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.12	<b>MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS</b> - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X  (where required)	X
8.2.13	<b>SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)</b>	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	<b>INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b> (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	<b>SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b>	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.16	<b>CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED</b>	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	<b>DECODING PROCEDURES FOR BLINDED TRIALS</b>	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.18	<b>MASTER RANDOMISATION LIST</b>	To document method for randomization of trial population		X (third party if applicable)
8.2.19	<b>PRE-TRIAL MONITORING REPORT</b>	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	<b>TRIAL INITIATION MONITORING REPORT</b>	To document that trial procedures were reviewed with the investigator and the investigator's trial staff ( may be combined with 8.2.19)	X	X

### 8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.1	<b>INVESTIGATOR'S BROCHURE UPDATES</b>	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	<b>ANY REVISION TO:</b> <ul style="list-style-type: none"> <li>- protocol/amendment(s) and CRF</li> <li>- informed consent form</li> <li>- any other written information provided to subjects</li> <li>- advertisement for subject recruitment (if used)</li> </ul>	To document revisions of these trial related documents that take effect during trial	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.3	<p><b>DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b></p> <ul style="list-style-type: none"> <li>- protocol amendment(s)</li> <li>- revision(s) of:                             <ul style="list-style-type: none"> <li>- informed consent form</li> <li>- any other written information to be provided to the subject</li> <li>- advertisement for subject recruitment (if used)</li> </ul> </li> <li>- any other documents given approval/favorable opinion</li> <li>- continuing review of trial (where required)</li> </ul>	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s).	X	X
8.3.4	<p><b>REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:</b></p> <ul style="list-style-type: none"> <li>- protocol amendment(s) and other documents</li> </ul>	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	<b>CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB- INVESTIGATOR(S)</b>	(see 8.2.10)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.6	<b>UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	<b>UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS</b> - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	<b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT</b>	(see 8.2.15.)	X	X
8.3.9	<b>CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS</b>	(see 8.2.16)		X
8.3.10	<b>MONITORING VISIT REPORTS</b>	To document site visits by, and findings of, the monitor		X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.11	<b>RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS</b> <ul style="list-style-type: none"> <li>- letters</li> <li>- meeting notes</li> <li>- notes of telephone calls</li> </ul>	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	<b>SIGNED INFORMED CONSENT FORMS</b>	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	<b>SOURCE DOCUMENTS</b>	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	<b>SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)</b>	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	<b>DOCUMENTATION OF CRF CORRECTIONS</b>	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	<b>NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS</b>	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X



	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.17	<b>NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION</b>	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	<b>NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION</b>	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	<b>INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)</b>	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	<b>SUBJECT SCREENING LOG</b>	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	<b>SUBJECT IDENTIFICATION CODE LIST</b>	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.22	<b>SUBJECT ENROLMENT LOG</b>	To document chronological enrolment of subjects by trial number	X	
8.3.23	<b>INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE</b>	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	<b>SIGNATURE SHEET</b>	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
8.3.25	<b>RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)</b>	To document location and identification of retained samples if assays need to be repeated	X	X

#### **8.4 After Completion or Termination of the Trial**

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.1	<b>INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE</b>	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	<b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION</b>	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	<b>COMPLETED SUBJECT IDENTIFICATION CODE LIST</b>	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	<b>AUDIT CERTIFICATE</b> (if available)	To document that audit was performed		X
8.4.5	<b>FINAL TRIAL CLOSE-OUT MONITORING REPORT</b>	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.6	<b>TREATMENT ALLOCATION AND DECODING DOCUMENTATION</b>	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	<b>FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)</b>	To document completion of the trial	X	
8.4.8	<b>CLINICAL STUDY REPORT</b>	To document results and interpretation of trial	X (if applicable)	X



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH

SOP # SD 02

Title: SOURCE DOCUMENTS IN  
CLINICAL RESEARCH

Effective Date: September 15, 2020

Revised Date: N/A

Next Review Date: Sept. 15, 2022

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**Author:** Ellen Peskin  
Manager of Clinical  
Research

Signature:

Signature Date:

August 15, 2020

Related SOPs:

#SD 01: Essential Study  
Documents

#SD 03: Retention of Research

**Approved by:**  
Leslie Hyman, PhD.  
Vice Chair for Research

Signature:

Signature Date:

August 15, 2020

**PURPOSE:** To define the different types of source documents used for clinical trials and provide guidance for ensuring complete and accurate source documentation for data collected in clinical trials conducted at the Wills Eye Hospital (WEH)

**SCOPE:** This document applies to all Wills research staff involved in collecting, recording and documenting data from or about research participants.

**RESPONSIBILITY:** Principal Investigators, Co-Investigators, Clinical Research Coordinators and the Manager of Clinical Research is responsible for ensuring compliance with this SOP.

**INTRODUCTION:** All study-mandated activities are conducted in strict adherence to a specified protocol. Data generated from these activities must be accurately noted or collected in source documents.

**DEFINITIONS:**

**Case Report Form (CRF):** A paper or electronic questionnaire specifically used in a clinical trial to collect data from participating clinical centers on each study participant.

**Logs:** Records that document that certain procedures essential for study conduct have been followed. These include but are not limited to temperature control logs, investigative product inventory logs, and instrument calibration logs.

**Medical Record:** The systematic documentation of a patient's medical history and care across time within one particular health care provider's jurisdiction.<sup>1</sup> The medical record includes, among other information, physician notes, relevant family and patient medical histories, test results, and medication history entered over time by health care professionals including paper and electronic records.

**Note-to-File:** A description of the protocol-specific method of accomplishing a process. This document can also be used to describe the reason for a discrepancy, missing data or missing documentation and can include information regarding the location of central files.

**Source Document:** A document in which data collected for a clinical trial, medical record or other purpose is first recorded.<sup>1</sup> Note that the four documents defined above are each source documents.



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**DESCRIPTION OF SOURCE DOCUMENTS IN CLINICAL TRIALS CONDUCTED AT WILLS**


Source documents include, but are not limited to, medical records, laboratory reports, output from automated instruments, images, subject diaries and study case report forms. The study CRFs often require information that is beyond the scope of usual chart notes or that is collected or formatted specifically for the trial. In these instances, the CRF is the source document when the data are recorded directly onto the CRF. Good Clinical Practice guidelines recommend the identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) to be considered to be source data.<sup>2</sup> Several different sources of data, recorded directly onto the CRFs and associated study documents, can serve as source documents in clinical trials. Examples include:

- Responses to questions on study-specific CRFs about symptoms, signs, or other personal characteristics using specified wording with quotation marks around the question to ensure consistency when study personnel question the patient.
- Results of clinical examinations that the examiner either records directly or dictates to another study staff member to document on the CRF.
- Information referring to the conditions, settings, time, and results of examinations and measurements performed under a study protocol. This information may be recorded on separate CRFs or study logs.
- Standard pre-existing questionnaires (e.g., NEI VFQ, SF-36) that are self-administered by the study participant or administered to the participant by study personnel.

Particular types of information are generally **not** recorded directly on the CRFs. In these instances, associated documents and the CRF are not considered the source. However, such information may be attached or transcribed onto the CRF. Examples include:

- Results of tests received via printed or electronic report from a laboratory or reading center
- Items referring to past medical history that are obtained through chart review.

In some instances, information captured on the CRF may be obtained from medical record review or from participant report (e.g., past medical history). In these cases, the study protocol should clearly state which data would be considered as the primary source for study documentation. For example, data can be accepted based on participant report alone or may require verification from the medical chart. If verification from the medical chart is requisite, the protocol should specify the time frame for which the medical chart should be reviewed for this information (e.g., previous 10-year period). If the history for a particular condition is considered positive by either participant report or medical record, the data recorded on the CRF should indicate a positive history.

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER</b> <b>VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR</b> <b>CLINICAL RESEARCH</b>	<b>SOP # SD 02</b>	
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### **Resolution of discrepancies between source and other documents**

In general, if there are discrepancies between data on the CRF (as the primary source document) and other documents available for review (e.g. medical records from a non-study medical provider, correspondence among care providers) data from the source document should be considered as correct. However, there may be some instances when the designated source document does not provide the information required to complete the CRF. For example:

1. If the medical record contains data that contradict the data entered on the CRF, the study coordinator will work with Site Visitor/Monitors to resolve the discrepancy ASAP by seeking out additional information from the participant, study investigator, or other health care providers, as relevant and assessing the likelihood that the source document is in error (e.g., a date in the source document is listed as 2091, when the medical record indicates that the visit took place in 2019). All changes to the medical record, CRF or database will be documented in accordance with good clinical practice, as described below.
2. If the medical record contains data that have been omitted from the study CRF, the CRF and database will be updated with the data from the medical record by the study coordinator, or another study staff member who has been trained and certified to record study data in accordance with good clinical practice.

### **PROCEDURES:**

#### **A. Maintenance of Source Document**

1. To ensure that the most recent version of approved source documents are used during a study visit, the coordinator must replace the outdated version with the new version in a file/notebook of current CRFs. (This is sometimes handled by the sponsor in a study-wide website.)
  - Maintain all previous CRF versions in a binder unless handled by the sponsor in a study-wide website.
  - Be sure to destroy all hard copies of blank, outdated forms immediately to avoid errors.
2. File in the participant's study file all results of laboratory reports, diagnostic test results, etc. as they become available and after they are reviewed.
3. If visit worksheets are used to collect data that are recorded in the CRF, the worksheets must be dated and signed by the recorder and retained as part of the source document.



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## B. Ensuring Complete and Accurate Source Documentation

1. All CRFs and other study related documents must be completed and corrected only by trained and study-certified coordinators. The study coordinator is responsible for the completeness and accuracy of all study documents, unless they are masked to some data as mandated by the study protocol.
2. During each study visit, a worksheet or flow sheet indicating all the protocol-specific exams, tests, evaluations and assessments scheduled for the visit should be completed and reviewed for completeness and accuracy. Note any out-of-range clinical values per protocol as well as any investigator assessment as clinically significant findings.
3. Transcribe data from the visit into the CRF/eCRF or data entry system as soon as possible but no longer than 3 days after the visit. If data are received at a subsequent time (e.g., lab results or data from reading centers), enter them onto the CRF as quickly as possible after receipt. Ensure documentation is available to verify that equipment have been calibrated within established calibration parameter timelines and that applicable certificates have not expired, if applicable. If such documentation does not already exist in the Clinical Service, develop and maintain a log.
4. Review for accuracy the inventory of investigational product and study supplies that are needed a) to perform study-related procedures, b) to record data during the visit or c) to be given to the participants.
5. If a study-related procedure was not completed per protocol, note the reason it did not occur. If a procedure was performed in another location, follow up with the appropriate person to capture the data and note on the CRF when and by whom the procedure was done. The Study Coordinator has the responsibility to ensure that documentation is completed appropriately by the person performing the study-related procedure.
6. If corrections must be made to source documents, use a blue or black ink pen to cross out the incorrect entry with a single line so that the original entry is still visible. The corrected entry is written next to the original entry and the correction is dated with the current date and initialed by delegated staff. **Do not obliterate the original entry, or backdate corrections or use white out.** Corrections may be made by the study coordinator or by other study staff certified to perform and record results for a particular procedure (e.g., a technician certified to perform refraction may record and correct refraction results on the appropriate CRF).
7. If a note of explanation is needed to clarify source documentation, record the information clearly, making sure the note does not obliterate any data entries. This may be written directly on the source documents, on paper attached to the source document or in a note to file (and indicated on the source document). The notation must be signed and dated





VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

**STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH**

**SOP # SD 02**

**Title: SOURCE DOCUMENTS IN  
CLINICAL RESEARCH**

**Effective Date: September 15, 2020**

Revised Date: N/A

Next Review Date: Sept. 15, 2022


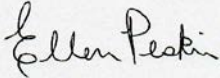

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8. Collect all test results and images as soon as possible. Review and record the results as instructed per protocol as soon as possible and document the review.
9. Follow up on all outstanding test results until all data for the study visit are obtained or the reason for incompleteness is documented.
10. Record all adverse events (AEs) in source documents. Refer to and follow the study protocol and IRB policies with regard to specific reporting requirements.
11. File source documents from the visit in the subject study record.

**CITATIONS:**

<sup>1</sup>“Personal Health Records: CMS Publication No. 11397” April 2011

<sup>2</sup> FDA GUIDANCE FOR INDUSTRY: E6 Good Clinical Practice: Consolidated Guidance, section 6.4.9. (<http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf> accessed on August 5, 2013).

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER</b> <b>VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR</b> <b>CLINICAL RESEARCH</b>		<b>SOP # SD 03</b>	
		<b>Title: Retention of Research Records</b>	
		<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 3</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	<b>Related SOPs:</b> SD 01 Essential Study Documents SD 02 Source Documents in Clinical Trials SC 03 Study Close-Out Processes
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To delineate Wills Eye Hospital's policy regarding the retention of research files to ensure compliance with Federal regulations.

**SCOPE:** This SOP applies to all research studies conducted at the Wills Eye Hospital (WEH).

**RESPONSIBILITY:** Principal Investigators, Research Coordinators and the Manager of Clinical Research are responsible for ensuring compliance with this SOP.

**INTRODUCTION:** Research records are the accumulated historical documentation of all research activity. All research yields a large cache of documentation, and a thoughtful, well-executed system for managing these documents is a requirement of federal regulations and international standards. Research records exist in various forms, including paper, electronic, and images.

The Principal Investigator (PI) is ultimately responsible for ensuring proper record maintenance. The PI often delegates this responsibility to the Clinical Research Coordinator or Fellow.

## DEFINITIONS

**HIPAA:** The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a federal law designed to provide privacy and security standards to protect patients' medical records and other health information provided to health plans, doctors, hospitals and other health care providers. The law pertains to both physical and on-line records.

**Regulatory Binder/File:** Contains essential documents required to conduct a clinical study and is often the first document reviewed during audits and inspections. Referred to synonymously as Study Files, Investigator Files or Investigator Binder, it includes a record of all data pertinent to the conduct of the investigation and includes evidence of required reviews and approvals.

## MANDATORY RETENTION PERIODS

Requirements for document retention varies by funding source, regulatory authority local regulations and WEH policies. If a study is subject to multiple regulations, records must be retained for the longest required amount of time. Note that records may be stored in a remote, secure location during the retention period if 1) the records are retrievable and 2) the regulatory authority or sponsor has determined in writing that the records may be archived.



## WILLS EYE HOSPITAL POLICY

WEH requires the retention of all study files for a **minimum of six (6) years** after the study is closed by the IRB. This policy meets or exceeds all the requirements listed below.

### FDA Regulated Research:

- For Investigational New Drug (IND) research, the FDA requires that investigators retain records **for 2 years** following the date a marketing application is approved. If no application is to be filed or if the application is not approved, retain records **for 2 years** after the investigation is discontinued and FDA is notified. See [21 CFR 312.57](#) and [21 CFR 312.62](#).
- For Investigational Device Exemption (IDE) research, the FDA requires the investigators maintain records “for a period of **2 years** after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol”. See [21 CFR 812.140](#)

**DHHS/NIH Funded Research:** DHHS regulations require that financial records shall be retained for **at least 3 years** from the submission of the final expenditure report. See [45 CFR 75.361](#). IRB records must be retained for **at least three years** after the completion of research. See [45 CFR 46.115\(b\)](#) and [21 CFR 56.115\(b\)](#)

**HIPAA regulations** require that any HIPAA-regulated information, authorizations, waivers, etc. must be maintained for **at least 6 years** after completion of the study.

**Department of Veterans Affairs:** Study records must be retained for **6 fiscal years**, calculated from end of the fiscal year after final action, completion of study, or when expired/superseded.

**Private Sponsors:** The Clinical Trial Agreement should specify the number of years study documentation must be retained. The sponsor may require that records be retained for a longer period of time than other regulations. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

### GENERAL TIPS FOR RECORD RETENTION

- Keep research records in a locked file cabinet to ensure security and confidentiality.
- When the study is over, review the contents of regulatory files and subject records for completeness.
- Store records on site in a locked room until it has been determined from the sponsor or regulatory authority that files can be archived. Label storage boxes clearly and completely including protocol number, description of contents (i.e. subject files xx-xx, regulatory documents, etc.), number of boxes as 1 of X, 2 of X, etc.



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

**STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH**

**SOP # SD 03**

**Title: Retention of Research Records**

**Effective Date: September 15, 2020**

Revised Date: N/A

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- Arrange to archive all patient files and source documents for the number of years agreed upon in the contract with sponsor.
- Maintain lists for tracking archived research records.
- Obtain authorization from the sponsor prior to record destruction and maintain an accurate list of destroyed records.

**DIGITAL RECORDS (E.G., ELECTRONIC FILES, DIGITAL RECORDINGS, ETC.)**

Digital files containing human subjects' research data must be stored in password-protected files that reside on Wills-maintained servers and have regular and secured back-up. Sensitive data must also be encrypted, stored, and when authorized for destruction, must be securely destroyed. Consult with the Wills IT department before storing any HIPAA-protected research data electronically. The record retention period for electronic records are identical to data contained in paper files.

**Applicable Regulations and Guidelines**

21 CFR 56.115(b) IRB records

21 CFR 312.57 Recordkeeping and record retention

[21 CFR 312.62 Investigator recordkeeping and record retention](#)

21 CFR 812.140(d) Records

[45 CFR 46.115\(b\)](#) IRB Records

[45 CFR 75.361](#). Retention requirements for records

45 CFR 164.530 (j)—Administrative Requirements

ICH E6 4.9 Records and Reports



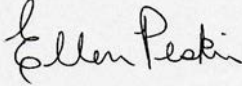

VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH

SOP # ST 01

Title: Responsibilities of the Research  
Team

Effective Date: September 15, 2020

Revised Date: N/A	Next Review Date: Sept. 15, 2022	Page 1 of 4	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	Related SOPs: #ST 02: Required Training for Research Personnel #ST 03 Policy on Form FDA 1572 #SC 02 Study Start-Up Processes #SC 03 Study Close-Out Processes
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To identify all members of the research team, to define their roles and responsibilities as well as to record written procedures for the delegation of tasks and responsibilities within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH).

**SCOPE:** This SOP applies to all clinical research personnel and research support staff involved in supervising, managing, conducting or supporting study related activities at the Wills Eye Hospital (WEH).

**RESPONSIBILITY:** The Principal Investigator (PI) and all members of the research team are responsible for having a clear working knowledge about their specific duties. The PI may delegate authority to trained and/or licensed members of the research team; however, the PI is ultimately responsible for the conduct of the study.

**DEFINITIONS:**


**ALCOA:** An acronym used in clinical research meaning “attributable, legible, contemporaneous, original and accurate”. ALCOA+ puts additional emphasis on the attributes of being complete, consistent, enduring and available, which more specifically states implicit basic ALCOA principles.

**Conflict of Interest (COI):** A COI exists in research when an investigator’s or other study team member’s self-interests have the potential to compromise his/her professional judgment and objectivity in the design, conduct or reporting of research.

**Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.


**Good Documentation practices:** The practice of ensuring that source documents are reliable, accurate and adequate to help ensure that study results are built on the foundation of credible and valid data. ALCOA+ criteria are key attributes for good documentation practices.

**International Conference on Harmonization (ICH):** A joint initiative by the European Union (EU), Japan and the United States that established the ICH GCP Guideline to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>	<b>SOP # ST 01</b>	
	<b>Title: Responsibilities of the Research Team</b>	
	<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 2 of 4</b>

## RESPONSIBILITIES OF CLINICAL RESEARCH STAFF


1. **Principal Investigator (PI):** The PI is responsible for assuming overall authority and accountability for the ethical and scientific conduct of a clinical study in accordance with all applicable federal and state laws and regulations and with institutional policy. The PI promotes GCP in the conduct of clinical studies by assuming the following essential roles and responsibilities:
  - 1.1. Protects the rights and welfare of participants subjects
  - 1.2. Protects the private health information (PHI) of research participants
  - 1.3. Discloses applicable COIs as required by the Institutional Review Board (IRB)
  - 1.4. Conducts study activities in compliance with IRB requirements after IRB approval and in accordance with the approved protocol, except where necessary to eliminate apparent immediate hazards to participants
  - 1.5. Accurate and prompt reporting of all adverse events as required by the IRB and the sponsor
  - 1.6. Obtains informed consent from each study participant
  - 1.7. Assures the validity of the data reported to the sponsor
  - 1.8. Assures good documentation practices are used for documentation of study-related procedures, processes and events
  - 1.9. Assures the proper use and storage of investigational products
  - 1.10. Ensures privacy and security of research data
  - 1.11. Maintains adequate and accurate records and make records available for inspection to external and internal monitors. Meet with auditors (FDA, sponsor and internal) at the conclusion of their audits to review findings and to implement changes to correct weaknesses or deficiencies.
  - 1.12. Assures delegation of responsibilities is appropriate and documented and that individuals recruited as members of the research team are appropriately licensed and/or trained. Delegating the work, however, does not relieve investigators of their responsibility. They ultimately bear the responsibility for all work conducted in the trial.
  
2. **Co-Investigator (Co-I)/Sub-investigator (Sub-I):** The Co-I/Sub-I (e.g., attending physician, resident, research fellow) has the following roles and responsibilities:
  - 2.1. Designated and supervised by the investigator to perform all or some of the functions of the PI, however, the PI has ultimate responsibility for the conduct of a research project.
  - 2.2. Plays a key role in study scientific development and conduct in collaboration with the PI
  - 2.3. Obligated to ensure that study design and conduct is compliant with applicable laws, regulations and institutional policies governing human subjects research.

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**3. Study Coordinator:** Responsible for managing all aspects of the day-to-day conduct of the clinical trial with in-depth knowledge of the protocol and GCP per federal regulations and ICH. Responsibilities include, but are not limited to, the following:

- 3.1. Manages the business aspects of studies, including collaborative development of study budgets with the Manager of Sponsored Projects and the Manager of Clinical Research.
- 3.2. Assures protocol compliance through a thorough understanding of the protocol.
- 3.3. Leads study start up activities.
- 3.4. Develops organizational aids and checklists to facilitate patient recruitment and the collection of complete and accurate study data.
- 3.5. Designs appropriate recruitment strategies and tracks study enrollment.
- 3.6. Maintains the regulatory and study files for each research project
- 3.7. Prepares regulatory documents as needed for the FDA (e.g., Form 1571, 1572) and IRB
- 3.8. Communicates with the IRB as appropriate.
- 3.9. Screens and enrolls study participants.
- 3.10. Schedules and maintains study visits with participants.
- 3.11. Obtains informed consent and signed personal health information (PHI) Authorization/HIPAA forms from study participants before performing any study related procedures, along with the PI and other investigators.
- 3.12. Assures proper handling of the investigational product (IP).
- 3.13. Assures proper handling and accurate processing of samples (e.g. blood and tissue).
- 3.14. Tracks participant compliance with the research drug, device or procedure.
- 3.15. Completes source documents and case report forms (CRFs) in an accurate and timely manner.
- 3.16. Tracks, reports and monitors adverse events and deviations as appropriate.
- 3.17. Ensures routine communications among study staff including regularly scheduled and ad hoc meetings, calls, etc.
- 3.18. Prepares for and participates in site monitoring visits and other quality assurance activities of the sponsor, the FDA, other regulatory agencies.
- 3.19. Trains and supervises other clinical research personnel as appropriate.
- 3.20. Protects all research data in accordance with WEH privacy and security requirements.
- 3.21. Oversees study closure
- 3.22. Meets with the representatives of the sponsor to discuss planned and ongoing studies.



 <b>WILLIE AND JACK FARBER VISION RESEARCH CENTER</b>  <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>	<b>SOP # ST 01</b>	
	<b>Title: Responsibilities of the Research Team</b>	
	<b>Effective Date: September 15, 2020</b>	
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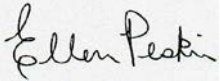

**4. Other members of the research team (Research Assistant, Regulatory Coordinator, etc.) will:**

- 4.1. Conduct clinical research studies according to federal and local regulations and guidelines, Good Clinical Practices, IRB policies, and departmental/division SOPs.
- 4.2. Assure the safety and welfare of study participants by being knowledgeable about ongoing study protocols and investigational products.
- 4.3. Comply with federal regulations governing disclosure of personal, professional or financial conflicts of interests in a research study that may impact upon its conduct, evaluation or outcome.
- 4.4. Maintain confidentiality of all clinical trial related information, including patient records.
- 4.5. Fulfill job responsibilities specific to each job title for each study according to federal regulations and guidelines and the WEH job description.
- 4.6. Assure that the PI and Study Coordinator are informed in a timely manner of all study-related activities.
- 4.7. Maintains the regulatory and study files for each research project.
- 4.8. Prepares regulatory documents as needed for the FDA (e.g., Form 1571, 1572) and IRB
- 4.9. Communicates with the IRB as appropriate.

**REFERENCES**

- 21 CFR 312.53 Selecting Investigators and Monitors
- 21 CFR 312.60 General Responsibilities of Investigators
- 21 CFR 312.61 Control of the Investigational Drug
- 21 CFR 312.62 Investigator Recordkeeping and Record
- 21 CFR 312.64 Investigator Reports
- 21 CFR 312.66 Assurance of IRB Review
- 21 CFR 312.68 Inspection of Investigator's Records and Reports
- 21 CFR 312.69 Handling of Controlled Substances
- 21 CFR 54 Financial Disclosure by Clinical Investigators
- January 1988 Guidelines for the Monitoring of Clinical Investigations
- FDA Information Sheets October 1998 - Frequently Asked Questions, Continuing Review After Study Approval, Recruiting Study Subjects, Payment to Research Subjects, Screening Tests Prior to Study Enrollment, A Guide to Informed Consent, Sponsor- Investigator- IRB Interrelationship
- May 1997 - International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline



 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>		<b>SOP # ST 02</b>	
		<b>Title: Required Training for Clinical Research Staff</b>	
		<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 4</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	Related SOPs: # ST 01: Responsibilities of the Study Team #ST 03: Policy on Form FDA 1572
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To delineate the training required by all Wills Eye Hospital (WEH) staff, residents and fellows engaged in clinical research

**SCOPE:** This document applies to all clinical research staff, residents and fellows involved in the implementation, conduct and coordination of clinical research studies at the WEH.

**RESPONSIBILITY:** Principal Investigators, Co-Investigators, Research Coordinators and the Manager of Clinical Research are responsible for ensuring compliance with this SOP.

**INTRODUCTION:** All studies conducted at WEH comply with the principles of the International Conference on Harmonization (ICH) and Guideline for Good Clinical Practice (GCP). The purpose of this Standard Operating Procedure (SOP) is to ensure that clinical research personnel have documented training to ensure expertise in the conduct of clinical research to meet and exceed the internationally recognized guidelines.

**DEFINITIONS:**

**Clinical Research Personnel:** Members of a clinical research team vary by study. Clinical research personnel include the Principal Investigator, Co-Investigators, Study Coordinators, Regulatory Coordinator and anyone listed on the FDA1572 form or as key personnel on a grant proposal.

**International Conference on Harmonization (ICH):** A joint collaboration between the United States, European Union (EU) and Japan that established the ICH GCP Guideline aimed to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities of these jurisdictions. See <https://www.ich.org/>.

**Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

**HIPAA:** The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a federal law designed to provide privacy and security standards to protect patients' medical records and other health



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH

SOP # ST 02

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Revised Date: N/A

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information provided to health plans, doctors, hospitals and other health care providers. The law pertains to both physical and on-line records.

**Principal Investigator (PI):** A Principal Investigator is the lead researcher on a study. She/he is the primary individual responsible for the preparation, conduct, and administration of a research study in compliance with applicable laws and regulations and institutional policy governing the conduct of sponsored research.

**Study Coordinator:** A Study Coordinator is a person responsible for conducting clinical trials using good clinical practice under the auspices of a Principal Investigator

**PROCEDURES**

**I. REQUIRED TRAINING OF ALL RESEARCH STAFF:**

All of the training listed below must be completed and documented before any research activities can commence. Training must be completed within 60 days of hire or when a staff person is new to research.

**A. Training in the Vickie and Jack Farber Vision Research Center’s Standard Operating Procedures (SOPs)**

All new clinical research personnel will be given the research SOPs as part of their on-boarding package. Prior to commencement of any clinical research activities at the WEH, new clinical research personnel will acknowledge in writing to having read and understand the VRC Standard Operating Procedures and will comply with them. Training will be documented on a Research Personnel Training Log that is maintained by the Manager of Clinical Research.

**B. CITI (Collaborative Institutional Training Initiative) Training\***: CITI training can be accessed at <http://www.citiprogram.org>. When creating an account, state your affiliation as Jefferson Hospital.

1. Biomedical Research Certification (includes HIPAA) 7 modules
  - Full complement required only once (refresher courses required every 3 years)
2. Good Clinical Practice (GCP) 14 modules
  - Refresher course required every 3 years (per NIH, January 2017)
3. Responsible Conduct of Research (Conflict of Interest): 3 modules
  - Refresher course every 4 years

\*Training determined by the Wills IRB to be equivalent to CITI is acceptable.



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
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SOP # ST 02

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Revised Date: N/A

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**C. Additional Mandatory Training (As Needed):** Anyone working on behalf of WEH with a reasonable expectation of exposure to blood, body fluid, tissue, investigational products or sharps or who will ship biohazards must complete the appropriate training (e.g., IATA, blood borne pathogen handling) offered at Jefferson Hospital within 90 days of acquiring said duties. For information on available training at Jefferson, contact the Manager of Clinical Research in the Wills VJF-VRC. Current documented training from another institution in these areas is acceptable.

**D. Additional Training for Study Coordinators**

Additional Required CITI Module: Study coordinators must complete the Clinical Research Coordinator (CRC) training. Training determined by the Wills IRB to be equivalent to the CITI CRC module is acceptable.

Certificates of Training Completion: After successfully completing each training, download and retain the certificate of completion. Email a copy of the certificate to the Manager of Clinical Research in the Vickie and Jack Farber Vision Research Center (epeskin@willseye.org).

**II. ADDITIONAL RECOMMENDED TRAINING**

The following offerings are available through the Jefferson Clinical Research Center (JCRC) and are open to Wills clinical research team members. Contact the Manager of Clinical Research in the VRC for information about when trainings are offered and their cost.

**A. Investigators:**

Attending the “Investigator Training: A Competency-Based Approach to Principal Investigator Responsibilities Conference” an all-day training offered by the Association for Clinical Research Professionals (ACRP) at Jefferson Hospital approximately twice a year. The training provides a practical application of clinical research competencies as they relate to the role of the principal investigator and site staff.

**B. Study Coordinators:**

1. Clinical Research Coordinator Workshop: a two-day workshop designed to deepen understanding and improve performance of safe, ethical and compliant clinical tasks that includes a comprehensive review of the best practices, skills, and tools necessary to implement successful clinical research that incorporates GCP guidelines.
2. Clinical Research Fundamentals: A full-day course targeted toward clinical research personnel that are new to clinical research (18 months or less) to enhance the understanding of the role and responsibilities of the research coordinator by providing foundational knowledge.
3. Jefferson Clinical Research Forums: A monthly lunchtime forum that provides educational offerings to research coordinators.



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4. Professional Certification: Coordinators are encouraged to become certified as a research professional. Certification programs are offered by the Association of Clinical Research Professionals (ACRP) and the Society of Clinical Research Associates (SoCRA). More information about certification and other resources is available at the organizations' websites: [www.socra.org](http://www.socra.org) or [www.acrpnnet.org](http://www.acrpnnet.org).

### **III. MEMBERSHIP IN PROFESSIONAL RESEARCH ORGANIZATIONS (RECOMMENDED)**

It is strongly recommended that clinical research personnel join and participate in professional research organizations that are dedicated to advancing the field of clinical research. Suggested organizations include the Society for Clinical Trials (SCT), Association of Clinical Research Professionals (ACRP) and the Society of Clinical Research Associates (SoCRA).



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH

SOP # ST 03 (v.2)

Title: POLICY ON FDA FORM FDA 1572  
STATEMENT OF INVESTIGATOR

Effective Date: June 10, 2021

Revised Date: 9/15/20

Next Review Date: June 10, 2023

Page 1 of 4

**Author:** Ellen Peskin  
Manager of Clinical  
Research

Signature:

Signature Date:

June 1, 2021

Related SOPs:

#ST 01: Required Training for  
Clinical Research Staff

#ST 02 Responsibilities of Clinical  
Research Teams

**Approved by:**  
Leslie Hyman, PhD.  
Vice Chair for Research

Signature:

Signature Date:

June 1, 2021

#SC 01 Study Feasibility  
Assessment

#SC 02: Study Start-Up  
Processes

**PURPOSE:** To assist the Wills Eye Hospital (WEH) research community in determining which members of the research team who perform activities on a clinical trial subject to FDA IND regulations should be listed on Form FDA 1572 as investigators and sub-investigators.

**SCOPE:** This document applies to investigators involved in the conduct of studies at the WEH operating under a Food and Drug Administration (FDA) IND (Investigational New Drug).

**RESPONSIBILITY:** Any person at WEH engaged in research being conducted under an IND.

**INTRODUCTION:** The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and to assure that he/she will comply with FDA regulations related to the conduct of a clinical investigations involving investigational drugs or biologics. The most recent version of the 1572 is available online at <https://www.fda.gov/media/71816/download>.

The 1572 has two purposes: 1) to provide the sponsor with information about the qualifications of the investigators and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the clinical investigation, and 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations.

Investigators must complete the form as accurately as they can. Investigators must be aware that making a willfully false statement is a criminal offense under 18 U.S.C. 1001. Submission of a deliberately false statement to the sponsor or to the agency can be taken into consideration in a disqualification proceeding.

**DEFINITIONS:**

**Delegation of Responsibility Log:** Also known as a Delegation and Signature Log, or Delegation of Authority Log, a log that documents is responsible for various activities in a research study. Every person involved with the study must be listed and their signature provided.



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH

SOP # ST 03 (v.2)

Title: POLICY ON FDA FORM FDA 1572  
STATEMENT OF INVESTIGATOR

Effective Date: June 10, 2021

Revised Date: N/A

Next Review Date: June 10, 2023

Page 2 of 4

**Investigational New Drug (IND):** The US Food and Drug Administration's IND program is the means by which an entity obtains permission to test experimental drugs in humans start human clinical trials before a marketing application for the drug has been approved. Regulations are primarily at 21 C.F.R. 312.

**Investigator:** The Code of Federal Regulations defines an investigator as the individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). When an investigation is conducted by a team of individuals, the Principal Investigator is the responsible leader of the team. The regulations do not require that an investigator be a physician. Sponsors are required to select investigators qualified by training and experience to investigate the drug/biologic. On the form 1572, documentation of investigators' qualifications is in the accompanying curriculum vitae (CV).

**Principal Investigator (PI)** – A Principal Investigator is the lead researcher on a study. She/he is the primary individual responsible for the preparation, conduct, and administration of a research study in compliance with applicable laws and regulations and institutional policy governing the conduct of sponsored research. In some situations, it is preferable to have more than one principal investigator responsible for a clinical investigation, especially when the study is conducted at multiple sites that are not in close proximity. The Principal Investigator(s) must sign the Form 1572. The FDA expects an investigator who has signed a 1572 to be available at each location to either personally conduct or supervise the study. This responsibility cannot be delegated to a sub-investigator.

**Sub-Investigator:** Although many people are involved in the performance of a clinical trial, a sub investigator is a person who makes a direct and significant contribution to the data. Sub-investigators may include but are not limited to physicians, residents, and research coordinators. Sub-investigators are not expected to complete a 1572 form.

**Determining Whether an Individual Should be Listed as a Sub-Investigator on the 1572:**

Section 6 of the 1572 requires a list of sub-investigators participating in the conduct of the research under the Investigator. The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data.

It is left to the discretion of the Principal Investigator or to the study sponsor to determine if individuals performing specific duties should be listed in Section 6. In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the 1572.

Individuals not likely to be listed as a sub-investigator include Wills Eye Hospital technicians, nurses, residents or office workers who provide ancillary or intermediate care as part of their normal duties, as well as regulatory coordinators.



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When larger laboratories with extensive staff are used in the study, only the lead performing the work for the study is required to be listed on the 1572. It is the responsibility of the Principal Investigator to ensure that his/her sub-investigators engaged in the research are qualified and trained to perform the study related activities assigned to them.

Examples of direct and significant contribution to the data include but are not limited to:

1. Obtaining Informed Consent
2. Conducting subject recruitment activities
3. Administration of investigational product/study drug (when different from routine care)
4. Perform critical trial-related procedures that contribute to the data
5. Perform research physical examinations
6. Evaluation of adverse and serious adverse events
7. Determination of eligibility

Example 1: If the protocol requires that each subject must visit an internist who will perform a full physical to qualify subjects for the study, that internist should be listed in Section #6.

Example 2: A research pharmacist who prepares test articles and maintains drug accountability would not need to be listed in Section 6 because the pharmacist would not be making a direct and significant contribution to the data.

**NOTE:** the determination of whether an individual is listed on the Form 1572 is independent from listing them on the Delegation of Authority Log). *All staff* who have been delegated *any task* related to the protocol should be listed on the log even if they are not included on the Form 1572.

#### WHEN SHOULD THE FORM BE SIGNED?

FDA Form 1572 must be signed before an investigator may begin participation in a clinical study conducted under IND regulations. The investigator should sign this form only AFTER receiving sufficient information to be informed about the study and to understand the regulatory commitments undertaken by signing the form. This typically means the investigator must have received, read, and understood the investigator brochure and protocol, and be familiar with the regulations before signing a 1572.





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As specified in Form-1572, IRB review and approval is required before a study can be initiated under an IND.

Financial Disclosure is required of everyone listed on the FDA-1572, specifically including the sub-investigators, pharmacists, coordinators, etc.

**REFERENCES**

21 CFR 312.2 Investigational New Drug Application, downloadable at

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312>

21 CFR 312.3(b) Definitions downloadable at


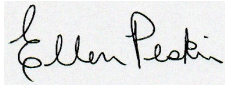

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3>

(21 CFR 312.53(a)): Selecting Investigators

18 U.S.C. 1001 downloadable at Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions – Statement of Investigator (Form FDA 1572) downloadable at

<https://www.fda.gov/media/78830/download>



 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>		<b>SOP # SC 01 (v2)</b>	
		<b>Title: Study Feasibility Assessment</b>	
		<b>Effective Date: June 10, 2021</b>	
Revised Date: 9/15/2020	Next Review Date: June 10, 2023	<b>Page 1 of 4</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date June 1, 2021:	Related SOPs: #SC 02: Study Start-up Procedures SUPERCEDES Sept 15, 2020 version
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: June 1, 2021:	

**PURPOSE:** To describe the procedures for assessing the feasibility of conducting a specific protocol at Wills Eye Hospital (WEH). Before agreeing to perform a clinical research study, the Principal Investigator (PI) and WEH must agree to the scientific, clinical, and ethical merits of the study, the financial impact to the institution, compliance with regulations, and the operational feasibility of conducting the study at WEH.

**SCOPE:** This SOP applies to all clinical studies under consideration for conduct at WEH.

**RESPONSIBILITY:** The PI, Research Coordinator, Financial Managers, Service Chiefs, and others who may be responsible for protocol review and study feasibility assessment.

**DEFINITIONS:**

**Confidentiality Disclosure Agreement (CDA):** A legal document a sponsor gives to an investigator that ensures confidentiality of proprietary information. A signed, study specific CDA may be required before a sponsor will provide its proprietary information, such as the study protocol, to an investigator. It is also referred to as a Non-Disclosure Agreement or Confidentiality Agreement.

**Contract Research Organization (CRO):** A person or an organization contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

**Feasibility Assessment:** To evaluate the possibility of conducting a clinical trial in a proposed location based on a list of questions. The answers will allow the PI to make an informed decision regarding the feasibility of the study at his/her site.

**Prescreening:** Activities undertaken before obtaining informed consent to determine initial eligibility for and interest in a study. Pre-screening may be performed over the telephone, in-person or on-line and **may not include** any research procedures.

**Protocol:** A document that describes the rationale, objectives(s), design methodology, statistical considerations, and organization of a trial.

**Recruitment:** The process that applies the study inclusion and exclusion criteria and is used by investigators to enroll appropriate participants into a research study.

**Sponsor:** An individual, company, institution, or organization that takes responsibility for and initiates a clinical research trial.



**INTRODUCTION:** Wills Eye Hospital is committed to promoting, fostering and conducting clinical research to advance the field of ophthalmic practice and patient outcomes. Major elements of success in clinical trial performance are ensuring that the trials selected are those that best match investigator interests, trials in which patients seen at Wills would be willing to enroll in sufficient numbers, require resources extant at WEH (or will be provided) and that don't compete for patients with other ongoing trials to each trial's detriment.

### PROCEDURES:

1. When a sponsor/CRO contacts an investigator or Service about a potential study, the investigator and Service Chief (if not the same person) will assess whether or not it would be feasible to conduct the protocol with the existing staff and resources. **Investigators are strongly encouraged to contact the Vickie and Jack Farber Vision Research Center for guidance when considering a new clinical trial.**
2. If a signed CDA is required to obtain the protocol and study documents from the sponsor/CRO for assessment review, the investigator must send the CDA to the legal counsel's office to review and execute the agreement. **The investigator may not sign the CDA on behalf of WEH.**
3. The PI, study coordinator and other appropriate site personnel will review the protocol and assess feasibility to perform the study at WEH. It is strongly recommended that the attached Clinical Trials Feasibility Form be completed during the review.

In assessing study feasibility, the following questions must be considered:

- Is the study important?
- Will the study results have the potential to advance knowledge and clinical practice?
- Does the sponsor plan to publish the data? Is there potential for Wills' investigators to be co-authors if desired?
- Why is the study of interest to the investigator(s)?
- Is the study ethically acceptable and based on good medical science?
- Does the study expose participants to undue risk?
- How complex are the study visit schedule and required tests and procedures? How burdensome to the participants?
- Does the investigator have sufficient time to properly conduct and complete the trial within the designated trial period?
- Are there available clinicians, clinical research and technician staff trained in all study procedures?
- What is the availability of required specialized equipment?



- Are there sufficient numbers of potential participants available and willing to meet enrollment goals? (See #4, below.)
- Are there any foreseeable barriers to participants completing the study?
- Do other studies at WEH compete for the same participants and resources?
- If collaborators are required (either in another Wills Service or at external entities such as laboratories, pharmacies, primary care physicians), has the investigator obtained collaborator assurances that they can perform the requisite service(s)?
- Is there sufficient funding from the sponsor for the site to complete the work required by the study?
- Do the study investigators have potential conflicts of interest with the sponsor or investigative product?

#### 4. Initiating Pre-Screening Activities During Study Feasibility Assessment

The Wills IRB allows researchers to conduct a record review of potential participants preparatory to research and prior to IRB approval. This prescreening process is crucial to establish whether adequate numbers of participants can be recruited into the study.

The following prescreening steps must be taken:

Based on the enrollment goal, length of study, recruitment, screening and enrollment period, the research team must apply the inclusion and exclusion criteria to 20-50 (if available) potentially qualifying patient charts/records of patients seen over a pre-specified period of time and determine the percentage of these patients who may actually qualify based on the specific criteria. The Vision Research Center will assist the research staff in this process, if desired. Steps include:

- Evaluating enrollment potential based on actual numbers of qualifying patients identified by reviewing electronic and paper records.
- If necessary and appropriate, identifying sources of potential participants from external practices.
- Considering potential transportation barriers.
- If recruitment timelines are short, considering the impact of holidays and vacations on recruitment potential.
- Considering the schedule of enrolling physicians (how many days per week on site, etc.)
- Establishing a proactive recruitment plan to maximize the likelihood of meeting the sponsor's timeline. Consider various recruitment methods (e.g., radio ads, letters, community presentations, print media, patient support groups, internet, flyers, posters, community education opportunities).
- Work with the Vision Research Center and Finance to estimate the cost of the recruitment strategy to ensure that these costs are recouped in the study budget.



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

**STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH**

**SOP # SC 01 (Ver. 2)**

**Title: Study Feasibility Assessment**

**Effective Date: June 10, 2021**

Revised Date: 09/15/2021

Next Review Date: June 10, 2023

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The results of the prescreening activity must be recorded on a prescreening log (template attached) that is stored on password protected, HIPAA compliant servers or in a locked filing cabinet.

5. The sponsor may visit at an early stage of the process in order to see if facilities are adequate and to gauge the interest and qualifications of proposed study personnel. This visit is also known as Site Qualification Visit (SQV) or Pre-Site Qualification Visit (PSQV). Please contact the Manager of Clinical Research if such a visit is scheduled.
6. The investigator is strongly encouraged to collaborate with his/her research team to make decisions about participating in or initiating a new research study.
7. When it is determined that the protocol meets the above criteria, the PI or study coordinator will notify the sponsor/CRO of their willingness to participate in the study. All documents must be sent to the WEH Manager of Sponsored Projects and the Manager of Clinical Research to develop the study budget, in collaboration with the study team and sponsor.

**ATTACHMENT:** Clinical Trials Feasibility Form  
Template Prescreening Form

**REFERENCES**

45 CRF 164.512(i)(1)(ii) Reviews preparatory to research  
ICH E6 (R1) 2.2 Principals of ICH GCPs  
ICH E6 (R1) 4.2 Adequate Resources

## CLINICAL TRIALS FEASIBILITY ASSESSMENT

### 1. General information

**Name of Study:**

**Study Sponsor:**

**Clinical Service(s):**

**Principal Investigator:** (i.e., clinician responsible for the study at Wills):

**2. Importance of the study.** Briefly describe in the space below why it is important to do this study. Please consider that the study will use Wills resources and thus the criteria below should be reflected in your response

- Will the study advance the field?
- Will the study advance Wills standing in the field?
- Is this an innovative study that may lead to other advances?

**3. CDA Needed:**  Yes  No

Requested?  Yes  No

Received?  Yes  No

		Yes	No
<b>4.</b>	<b>Conflicts of Interest</b>		
	Are there known or perceived financial conflicts of interest between the study investigators or others at Wills and the study sponsor, or with a company that competes with the sponsor?	<input type="checkbox"/>	<input type="checkbox"/>
	<b>If yes, comment on how they can they be addressed</b>		
<b>5.</b>	<b>IRB</b>		
	Does the sponsor intend to use a central IRB?	<input type="checkbox"/>	<input type="checkbox"/>
<b>6.</b>	<b>Collaborators</b>		
	Will the study require subcontractors/outside vendors or collaborators?	<input type="checkbox"/>	<input type="checkbox"/>
	<b>6a. If yes</b> , have the collaborators, vendors etc. been identified?	<input type="checkbox"/>	<input type="checkbox"/>
	<b>6b. If yes</b> , please specify who are the collaborators/groups		
<b>7.</b>	<b>Recruitment</b>		
	What are the required site-specific recruitment goals? _____		
	What is the timeframe for recruitment? _____		
	What is the estimated number of potentially eligible patients at Wills? _____		
	<b>Provide documentation to support that Wills has a sufficient number of patients to meet recruitment goals in the required time period</b>		
	Will patients be interested in participating in this study?	<input type="checkbox"/>	<input type="checkbox"/>
	<b>If no, how will you successfully enroll for this study?</b>		
<b>8.</b>	<b>Retention and Adherence</b>		
	Given the number of follow-up visits, do you anticipate a higher-than-expected rate of missed follow-up visits or dropouts?	<input type="checkbox"/>	<input type="checkbox"/>
	<b>If yes, comment on why you expect a low rate of retention.</b>		

		Yes	No
<p>Given the protocol, do you anticipate a higher-than-expected rate of patient non-compliance with regard to study treatment?</p> <p><b>If yes, comment on why you expect a high non-compliance rate.</b></p>		<input type="checkbox"/>	<input type="checkbox"/>
<b>9 Study Procedures</b>			
<p>Can all of the evaluations be performed readily within the specified clinical service?</p> <p><b>9a. If No, can all of the evaluations be performed within WEH?</b></p> <p><b>9b. If No, will transportation be provided to off-site locations?</b></p> <p><b>9c. If all of the evaluations can be performed within WEH, will the Coordinator accompany the patient from the Clinical Service to another service (e.g., Diagnostic Services?)</b></p> <p>Are there any unique protocol procedures/requirements that will require additional training?</p> <p><b>If yes, specify plans for training and indicate if the sponsor will pay for the additional training.</b></p>		<input type="checkbox"/>	<input type="checkbox"/>
<b>10. Staff and Physical Resources</b>			
<p>Will additional staffing be required to perform all of the required evaluations?</p> <p><b>If yes, comment on the needs for additional staffing</b></p> <p>Does the service have the space required to conduct the study?</p> <p>Does WEH have all the required equipment to fulfill the study protocol?</p> <p><b>If no, comment on what equipment is required and whether the sponsor will purchase it.</b></p>		<input type="checkbox"/>	<input type="checkbox"/>
<b>11. Data Management</b>			
<p>Does the site have the resources and personnel to complete data collection, recording and data entry in a timely manner?</p> <p>Will special training, resources or technology be required for data management?</p> <p><b>If yes, please describe what new training, resources and technology are required and whether the sponsor will provide/pay for it.</b></p>		<input type="checkbox"/>	<input type="checkbox"/>

		Yes	No
<b>12. Investigational Product (IP) <input type="checkbox"/> Check here if not applicable and skip to #13</b>			
Is the IP dispensing/accountability complicated?		<input type="checkbox"/>	<input type="checkbox"/>
Does the IP require special handling or storage?		<input type="checkbox"/>	<input type="checkbox"/>
<b>If yes</b> , please explain the special handling/storage requirements			
Does the site have storage space and/or equipment to accommodate and monitor the IP?		<input type="checkbox"/>	<input type="checkbox"/>
<b>If no</b> , will the sponsor provide the necessary equipment?		<input type="checkbox"/>	<input type="checkbox"/>
Does the site require special staff to monitor, reconcile and/or dispense the IP?		<input type="checkbox"/>	<input type="checkbox"/>
<b>13. Risk/Benefit</b>			
Are the risks associated with study procedures/product(s) balanced by potential benefits?		<input type="checkbox"/>	<input type="checkbox"/>
<b>Comment on the risks/benefits:</b>			
Will our study participants benefit directly from the study?		<input type="checkbox"/>	<input type="checkbox"/>
<b>14. Budget</b>			
Do the projected study payments exceed the costs to Wills?		<input type="checkbox"/>	<input type="checkbox"/>
<b>If no</b> , explain why Wills should participate in the study (if you believe that Wills should do so).			
Will the Sponsor/CRO negotiate budgetary issues?		<input type="checkbox"/>	<input type="checkbox"/>
Is there potential for unanticipated expenses?		<input type="checkbox"/>	<input type="checkbox"/>
Is the Sponsor/CRO willing to amend the budget if amendments are made to the study design or protocol that require additional procedures or timelines for the site?		<input type="checkbox"/>	<input type="checkbox"/>
Will the Sponsor/CRO reimburse the site for pre-screening activities and screen-fails?		<input type="checkbox"/>	<input type="checkbox"/>
Will the Sponsor/CRO reimburse the site for outside medical record requests as needed for eligibility assessment or patient management?		<input type="checkbox"/>	<input type="checkbox"/>
Will the Sponsor/CRO reimburse for obtaining records related to SAEs?		<input type="checkbox"/>	<input type="checkbox"/>

\_\_\_\_\_  
Signature of person completing form

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date



## Pre-Screening Log

Protocol:

Investigator Name

**This log must be stored in a locked filing cabinet or on a password protected servers at all times. If sponsors request prescreening data, remove all patient identifiers before disclosing any data!**

	Patient Initials	Patient Date of Birth	Date of Prescreening	Prescreener Initials	Patient Meets Enrollment Criteria (Y/N)	If ineligible, enter reason (s)	Comments (list other factors that may impact participation)
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							


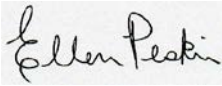

## Pre-Screening Log

Protocol:

Investigator Name

**This log must be stored in a locked filing cabinet or on a password protected servers at all times. If sponsors request prescreening data, remove all patient identifiers before disclosing any data!**

13.							
14.							
15.							
16.							
17.							
18.							
19.							
20.							
21.							
22.							
23.							
24.							
25.							

 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER</b> <b>VISION RESEARCH CENTER</b> <b>STANDARD OPERATING PROCEDURES FOR</b> <b>CLINICAL RESEARCH</b>		<b>SOP # SC 02</b>	
		<b>Title: Study Start-Up</b>	
		<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 5</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	<b>Related SOPs:</b> #SC01: Study Feasibility Assessment #SD01: Essential Study Documents #ST01: Responsibilities of the Study Team #ST02: Required Training for Clinical Research Staff
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** The purpose of this SOP is to describe activities that must be accomplished by study staff to initiate a new clinical research study at the Wills Eye Hospital (WEH).

**SCOPE:** This SOP applies to all new clinical studies to be initiated within the Wills Eye Hospital (WEH).

**RESPONSIBILITY:** The Principal Investigator (PI), Study Coordinator, Manager of Sponsored Projects and Manager of Clinical Research

#### **DEFINITIONS:**

**Clinical Trial Agreement (CTA):** A legally binding agreement that manages the relationship between a company providing funding and a protocol for a clinical trial and the institution who implements the protocol and provides study data. Among other issues, a CTA details sponsor and site responsibilities, payment terms and schedule, and policies on publication and intellectual property.

**Contract Research Organization (CRO):** A person or an organization contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

**Monitor:** An individual who acts on behalf of the sponsor to oversee the progress of a clinical trial, and to ensure that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

**Protocol:** A document that describes the rationale, objectives(s), design methodology, statistical considerations, and organization of a trial.

**Site Initiation Visit (SIV):** A visit performed by the sponsor to ensure that the investigators and study staff understand the study protocol, that all the operational steps are in place, and that everyone is clear and well trained in their specific roles and responsibilities. A trial initiation visit is conducted prior to the first patient being recruited into a study. The visit is usually conducted by the trial coordinator or monitor on behalf of the sponsor.

**Sponsor:** An individual, company, institution, or organization that takes responsibility for and initiates a clinical research trial.



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

**STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH**

**SOP # SC 02**

**Title: Study Start-Up**

**Effective Date: September 15, 2020**

Revised Date: N/A

Next Review Date: Sept. 15, 2022

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**INTRODUCTION:** Prior to enrolling the first subject, all regulatory and institutional requirements must be met and preparations for protocol procedures must be complete. In most cases, the sponsor requires a Site Initiation Visit before they will authorize the site to begin enrollment.

**PROCEDURES:**

1. Immediately after the study sponsor and the WEH PI mutually agree that the study should be conducted at Wills, the Principal Investigator or Study Coordinator sends the full study protocol, the template Informed Consent Form and a sponsor budget template (if available) to the Manager of Clinical Research and to the Manager of Sponsored Projects.
2. The Manager of Sponsored Projects creates a Time and Event Schedule spreadsheet that includes, in addition to the study visit procedures, other tasks associated with study start-up, conduct and closeout.
3. The Study Coordinator and Principal Investigator identify all personnel who will be involved in conducting the study (co-investigators, technicians, OR nurses, etc.).
4. The Study Coordinator (or PI) completes the Time and Event Schedule, and for each task identifies the person responsible for conducting the task, the time required to complete it, and whether the task is included in routine care.
5. If external entities are required to complete some tasks (e.g., a research pharmacy, outpatient lab at Jefferson, primary care physician), the study coordinator identifies and contacts the external entity to ensure their capacity and willingness to perform the study procedures and requests a budget.
  - The Manager of Sponsored Projects, the Manager of Clinical Research and the Wills Legal Counsel will develop and finalize a budget and agreement with the external provider.
6. While the contract is being negotiated and before it has been executed, the Study Coordinator prepares the following:
  - Informed consent document(s): The Study Coordinator modifies the documents for the WEH setting and sends them to the Wills legal counsel for review. The Wills approved document(s) must be sent to the sponsor/CRO for their review prior to IRB submission.
  - A list of all allowed and disallowed medications for the duration of the study (that will be updated, consulted and reviewed with study participants during every study visit).
  - A master Study Visit Schedule/Checklist for each subject visit specified in the protocol. Include all activities for each visit.



- Lab requisition forms for each visit (if applicable). These forms must be reviewed by the study sponsor/CRO for accuracy. If the Jefferson outpatient lab will be used, send the requisition form to the Lab Manager for review and formatting on Jefferson outpatient laboratory forms.
7. IRB Submission: If the sponsor is a for profit entity, the Wills IRB charges for study review. Thus, IRB submissions generally occur after the CTA is fully executed. IRB submissions may occur prior to CTA execution if the sponsor enters into a signed agreement to pay the IRB fee regardless of whether the CTA is ultimately executed.
  8. Submissions to other committees as required: If other reviews are required (e.g., Jefferson's Institutional Biosafety Committee (IBC)), the study coordinator must submit all documents as soon as IRB approval has been received. If there are questions about what additional approvals are required, contact the Wills IRB Administrator for guidance.
  9. Training/certification in specific study tasks: Generally, certification of study staff in specific study protocols occurs after the CTA has been fully executed. However, it is important that all study team members become familiar with the certification process and requirements while the CTA is under review to ensure that they can expeditiously begin the certification process immediately upon CTA execution.

### Site Initiation Visit (SIV)

The Initiation Visit may be conducted before IRB approval has been obtained. However, the IRB approval letter and final approved informed consent documents must be received prior to screening the first subject.

The objectives of the Site Initiation Visit are to:

- Verify that the site's study preparation procedures are completed
- Verify that all regulatory documents are in place
- Verify that investigational product is available so that training can begin
- Verify that study supplies are available so that training can begin
- Review the protocol, CRFs and other documents
- Review all regulatory requirements
- Provide recruitment and retention plan
- Provide the study monitoring plan
- Provide the site with all sponsor contact names and telephone numbers
- Confirm the sponsor's expectations on the conduct of the study
- Train all participating research personnel and ensure documentation has been completed.



Prior to the scheduled SIV, the study coordinator will perform the following activities:

- Establish a suitable date/time/location for the SIV and ensure sponsor, PI and other key personnel availability.
- Request an agenda from the Monitor.
- Ensure that all study staff are familiar with sponsor-provided study materials (e.g., protocol, Investigator Brochure, CRFs, etc.) in advance of visit.
- Ensure that all study staff are certified for the study or, if not yet certified, understand the strategy and timeline to complete certification.
- If needed, schedule educational session(s) with involved clinical staff (e.g., technicians)
- Review the regulatory binder to ensure that it contains all of the necessary documents.
- Ensure the location of test article storage is ready for review and meets the sponsor's requirements.
- Identify any sponsor-provided supplies needed once enrollment begins (e.g., paper-based CRFs, lab kits, and shipping supplies).
- Ensure any study-specific initiation visit checklists are completed in advance of the visit.
- Review regulatory files for completeness.
  - If the study already has been submitted to the IRB and other committees, review approval documentation that has been received.
  - Follow up on any submissions with pending approvals.
  - Document the status of pending approvals and expected approval timeframe.
- Compile a list of questions and items that need clarification. (If possible, send the list to the monitor prior to the visit.)

During the SIV, the study coordinator will:

- Assure that the PI is present
- Review details of the protocol, including study operations with the Monitor.
- Discuss with the Monitor which key personnel are authorized to perform what study-related functions or procedures
- Document operational questions not covered in the protocol and the answers provided by the sponsor/Monitor.
- Discuss test article administration and accountability (if applicable)
- Review instructions on study-specific activities such as tests, lab kits or study-required software and any related recordkeeping requirements (e.g., temperature logs, calibration logs, etc.).
- Review directions for source documentation and/or CRF completion.




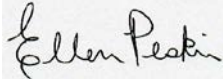

- Review required source documents and documentation to be provided at future monitoring visits.
- Provide the Monitor with an update on any study related issues.
- Inventory and document all study supplies, such as
  - CRFs
  - central lab supplies
  - supplies for subject use (i.e., diaries, self-assessment supplies, etc.)
  - sponsor-supplied equipment
- Review study procedures with assigned research staff.
- Notify sponsor of launch date for recruitment and screening activities.
- Review recruitment and retention plan with site staff.

Following the SIV:

- File all SIV training certificates in the regulatory binder. If the sponsor does not provide a record of training, record the timing and details of any training sessions and file in the regulatory binder.
- Document the SIV in Site Visit Log if not provided by sponsor and file in regulatory binder
- Ensure receipt of sponsor/CRO written documentation summarizing important agreements made during the visit.
- Assemble screening/enrollment materials.
- Activate recruitment plan once IRB approval is obtained.

References:

ICH E6 (R2) 1.53 Sponsor  
ICH E6 (R1) 4.2 Adequate Resources  
21CFR 312.50 General Responsibilities of Sponsors  
21CFR 312.52 Transfer of Obligations to a Contract Research Organization  
21 CFR 312.60 General Responsibilities of Investigators  
21CFR 312.62 Investigator Recordkeeping and Record Retention  
21 CFR 312.66 Assurance of IRB Review  
21CFR 312.68 Inspection of Investigator's Records and Reports

 <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b>  <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>		<b>SOP # SC03</b>	
		<b>Title: Study Close-Out Procedures</b>	
		<b>Effective Date: September 15, 2020</b>	
Revised Date: N/A	Next Review Date: Sept. 15, 2022	<b>Page 1 of 5</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: August 15, 2020	<b>Related SOPs:</b> #SD01: Essential Study Documents #SD04: Retention of Research Records #ST01: Responsibilities of the Study Team
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: August 15, 2020	

**PURPOSE:** To describe the procedures followed by key research personnel engaged in clinical research at Wills Eye Hospital during a close-out visit with a sponsor representative from the time the monitor schedules the visit until all associated follow-up activities have been completed.

**SCOPE:** This SOP applies to key research personnel involved in arranging, managing, participating in, and/or resolving outstanding items resulting from the study close-out visit.

**RESPONSIBILITY:** Principal Investigators, Clinical Research Coordinators, Key Personnel, other pertinent staff.

#### **DEFINITIONS:**

**Case Report Form (CRF):** A paper or electronic questionnaire specifically used in clinical research. The CRF is the tool used to collect data. All data on each patient participating in a study are held and/or documented in the CRF, including adverse events.

**Close Out:** The procedures undertaken to fulfill administrative, regulatory, and human subjects requirements after all participant follow-up in a study has been completed and the study results released.

**Investigational Product (IP):** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. (ICH GCP 1.33)

**Key Personnel:** An individual designated by the principal investigator who is knowledgeable about the research study. This may include investigators, coordinators, assistants, residents, fellows, students working on the research, administrators or managers who oversee the research, and external individuals associated by agreement or contract who are involved in conducting the research. Individuals providing services in the course of their position (e.g., pharmacist, biostatistician) are not considered key personnel unless involved in key aspects of the research such as protocol development, consenting, masking procedures etc.

**Monitoring:** The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).





**Regulatory Binder/File:** Contains essential documents required to conduct a clinical study and is often the first document reviewed during audits and inspections. Referred to synonymously as Study Files, Investigator Files or Investigator Binder, it includes a record of all data pertinent to the conduct of the investigation and includes evidence of required reviews and approvals.

**Investigator:** The Code of Federal Regulations defines an investigator as the individual who actually conducts a clinical investigation. When an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

## INTRODUCTION:

When operating under FDA regulations, study completion occurs when all study subjects have completed the study at the investigative site. Federally funded research is considered complete after all data have been analyzed. Sponsors may have additional criteria for when a study is complete at a site. Studies may also end because the PI decides to stop participating or the sponsor terminates the study. Most sponsors conduct a Study Close-Out Visit at the study site.

These procedures are designed to ensure that all study related activities and materials are appropriately reconciled, reported, and stored in accordance with GCP, contractual agreements, and the applicable regulatory requirement(s). Close-out is an integral part of the quality control of a study to ensure that all required documents are in place should it be necessary for the study information to be retrieved or inspected in the future. The study close-out should mean that the site is ready for an audit or inspection.

In general, close-out processes include:

- Data verification and collection of all remaining completed case report forms (CRFs)
- Inspecting files for completeness
- Reviewing the records of IP distribution, where relevant, including accountability records, inventory and reconciliation. This also includes the return or destruction of materials.
- Discussion of issues and next steps with the study sponsor. This may include the requirement for follow-up and data retention.

## PROCEDURE:

### 1. Preparing the Study Close-Out Visit:

- 1.1 After the last subject has completed all scheduled visits associated with the study, arrange a mutually convenient date and time for the study monitor to conduct the study close-out visit.



- 1.2 Request a visit agenda from the monitor describing what is expected, what needs to be accomplished before visit takes place and to ensure that key personnel will be available, if applicable.
- 1.3 Complete a study close-out checklist (Attached).
- 1.4 Ensure that all regulatory documentation and case report forms (CRFs) not previously monitored are completed and ready for review.
- 1.5 Ensure that all data queries received to date have been resolved.
- 1.6 Inventory investigational product (IP) supply and complete final accountability records. If previously instructed, return or dispose of any unused IP in accordance with the protocol and regulations. File copies of study packing slips and shipment receipts appropriately in regulatory binder for monitor review.
- 1.7 Arrange for the monitor to meet with the PI and/or Manager of Sponsored Projects to discuss any outstanding issues.

## 2. Managing the Study Close-Out Visit:

- 2.1 Ensure all documentation is filed appropriately and ready for the monitor to review during the close-out visit. Discuss all open study-related issues and what steps will be taken to resolve them.
- 2.2 Review with the monitor the list of outstanding issues related to regulatory documents, source data verification, IP reconciliation, and any requirements for data retention and storage.
- 2.3 Review with the monitor the responsibilities for reporting serious adverse events and IND safety reports after formal termination of the study.
- 2.4 The PI is responsible for ensuring the appropriate follow-up, per the protocol, for any participant experiencing an ongoing unanticipated problem (e.g., serious adverse event) at study end and providing this information to the sponsor, assuring all sponsor's requirements have been met.
- 2.5 Discuss the timelines and requirements for final payments (if applicable).

## 3. Follow-up after the Study Close-Out Visit:

- 3.1 The monitor will document the visit by submitting a study termination visit report outlining what was accomplished during the visit and noting any items that need additional attention. Ensure that a copy of the report and follow-up letters are placed in the regulatory file.
- 3.2 If not previously instructed, ensure that any remaining IP is either returned to the sponsor/CRO per their requirements or if the sponsor allows remaining investigational drug



to be disposed of at the site following the close-out visit in accordance with the study pharmacy protocol.

- 3.3 Ensure all documentation is complete (i.e. sponsor drug accountability/ destruction logs).
- 3.4 Ensure all IP slips and shipment receipts are accounted for and properly filed in the regulatory binder.
- 3.5 Ensure return or destruction of all other study-related materials, such as unused lab kits and CRFs.
- 3.6 After all data queries have been resolved, check regulatory binders, subject files and other study files for completeness.
- 3.7 Arrange for transfer/storage of study documents to secured approved storage location.
- 3.8 Submit the Final Report to the Wills IRB. Provide the sponsor/CRO with a copy of the IRB closure letter.
- 3.9 Verify participant stipends have been distributed per the study budget, as outlined in the informed consent document.

**Prematurely Terminated or Suspended Studies:**

If the trial is prematurely terminated or suspended for any reason, the Investigator must promptly inform the subjects enrolled in the study, provide follow-up for the subjects and, where required, inform the regulatory authority(ies).

If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator must inform the Vickie and Jack Farber Vision Research Center and the Manager of Sponsored Projects at WEH. The investigator must promptly inform the sponsor and the IRB, with a detailed written explanation of the termination or suspension.

If the sponsor terminates or suspends a trial, the investigator must promptly inform the IRB and provide the IRB a written explanation of the termination or suspension. The Vickie and Jack Farber Vision Research Center and the Manager of Sponsored Projects at WEH must also be informed immediately.

If the IRB terminates or suspends its approval, the investigator shall notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

**Attachments:** Wills Study Close-Out Checklist

**References**

- 21 CFR 312.50 General Responsibilities of Sponsors
- 21 CFR 312.59 Disposition of Unused Supply of Investigational Drug



VICKIE AND JACK FARBER  
VISION RESEARCH CENTER

**STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH**

**SOP # SC03**

**Title: Study Close-Out Procedures**

**Effective Date: September 15, 2020**

Revised Date: N/A

Next Review Date: Sept. 15, 2022

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21 CFR 312.60 General Responsibilities of Investigators

21 CFR 312.62 Investigator Recordkeeping and Record Retention

21 CFR 312.64 Investigator Reports

21 CFR 312.66 Assurance of IRB Review

21 CFR 312.68 Inspection of Investigator's Records and Reports

FDA Sheet: January 1988 Guidelines for Monitoring of Clinical Investigations May 1997 International Conference on Harmonization (ICH) Good Clinical Practice

## Study Close-Out Checklist

**This form is adapted from:**

[https://www.nidcr.nih.gov/research/toolkit/Documents/Study\\_Close\\_Out\\_Checklist\\_approved\\_v20.docx](https://www.nidcr.nih.gov/research/toolkit/Documents/Study_Close_Out_Checklist_approved_v20.docx)

**Tool:** Study Close-Out Checklist

**Purpose:** This document provides a checklist for study personnel to ensure that all necessary aspects of study closure and archival have been addressed.

**Audience/User:** Investigators and Study Coordinators may use this template as a starting point for customizing a protocol/study specific checklist for site closure activities.

**Details:** Prior to considering a study closed or archived, necessary steps must be completed to ensure all aspects of study components have been addressed. This checklist provides a reference point for closure status.

**Best Practice Recommendations:** Review this template and customize it to the specific needs and requirements of the study. Close-Out activities may be updated as needed. Remove or mark as “not applicable” those elements that are not required.


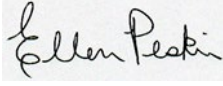

### Study Close-Out Checklist

No.	Task	Person Responsible	Date Completed	Comments
<b>Case Report Forms (CRFs)/Source Documents</b>				
1	Confirm that appropriate source documentation is present for all subjects			
2	Paper Studies: Confirm that all CRFs have been completed, collected, and the proper legible copies are present in study files  Electronic Data Capture (EDC) Studies: Confirm that all electronic CRFs have been completed and submitted to the Sponsor/CRO, as applicable			
3	Paper Studies: Confirm that all data clarification forms (DCFs) and queries issued to date have been submitted to the Sponsor/CRO, appropriately resolved, signed and dated by the investigator, and that signed and dated queries are filed with the corresponding CRF page or subject  Electronic Data Collection (EDC) Studies: Confirm that all electronic queries issued to date have been appropriately resolved, reviewed by the CRA/SC/DM as appropriate, and closed, where applicable			
4	EDC Studies: Ensure that all CRF pages requiring signature have been electronically signed and dated by the investigator			
<b>Data Management</b>				
<i>Note: If the site is using a Database managed by the Sponsor/CRO or Data Coordinating Center (DCC), skip tasks 5-8.</i>				
5	Confirm all data is entered into the database			
6	Ensure all queries have been issued, returned, and resolved			
7	Once all queries have been resolved, clean and QC the database			
8	Perform database lock			
<b>Adverse Event, Unanticipated Problem, and Serious Adverse Event Reporting/Reconciliation</b>				
9	Ensure that all AEs, UPs, and SAEs have been captured, followed, and resolved per protocol, and reported to the appropriate parties (Sponsor, IRB, and FDA, if applicable) according to protocol reporting requirements			
10	Confirm that all required follow-up documentation has been retrieved, communicated to appropriate parties, and is present in the study files			

Investigator Site Files				
11	Confirm that signed consent forms are on file for all subjects			
12	Reconcile study files with Trial Master File (TMF) list. For studies where the TMF is maintained at the lead site or by another DCC, ensure all required documents are present, including collection of all required documents from all Investigator Site Files, where appropriate. These can include, but are not limited to: <ul style="list-style-type: none"> <li>• protocols and amendments</li> <li>• approved consent document templates</li> <li>• IRB approvals</li> <li>• study team licenses</li> <li>• study certification documentation and CVs</li> <li>• laboratory documentation</li> <li>• Manual of Procedures (MOP)</li> <li>• Standard Operating Procedures (SOPs)</li> </ul>			
13	Ensure reporting of study closure to the IRB and receipt/filing of study closure confirmation in the investigator site files			
14	If study was terminated early, confirm notification of study termination has been sent to all enrolled subjects as appropriate			
15	Confirm that all protocol deviations have been noted in source documentation and reported to the IRB as appropriate			
16	Consider appropriate storage of Quality Management (QM) reports / metrics			
17	Confirm sponsor and institutional requirements for record retention and notify sponsor when study files will be transferred to long term off-site storage			
<b>Ensure the completeness of the following logs:</b>				
18	Pre-Screening Log ( <i>if applicable</i> )			
19	Subject Screening and Enrollment Log			
20	Monitoring Visit Log ( <i>if applicable</i> )			
21	Delegation of Responsibilities Log			
22	Telephone Log			
23	Training Log			
24	Subject Code List			
25	Randomization Log ( <i>if applicable</i> )			
26	Investigational Product Accountability Log: Stock Record ( <i>if applicable</i> )			
27	Investigational Product Accountability Log: Subject Record ( <i>if applicable</i> )			
28	Specimen Tracking Log ( <i>if applicable</i> )			
29	Freezer/Refrigerator Temperature Logs ( <i>if applicable</i> )			

<b>Investigational Product</b>				
30	Confirm that investigational product disposition forms and accountability records are complete and present for all subjects receiving study drug			
31	Confirm final disposition of investigational product was completed per MOP, site pharmacy protocol, supplier, and sponsor requirements			
<b>Collected Laboratory Specimens (Samples)</b>				
32	Confirm that all specimens have either been analyzed or stored for future use			
33	Ensure that specimens collected for future use have been adequately processed, labeled/de-identified, and stored			
34	Confirm site process for identification and disposition of future use specimens connected to subjects who withdraw consent or do not consent for their specimens to be saved			
35	Confirm destruction, per institutional policies, of specimens not identified for future analysis			
<b>Analysis, Manuscripts, and Submissions/Publications</b>				
<i>Tasks 36-38 may be skipped if not applicable</i>				
36	Data analysis complete			
37	Primary manuscript finalized			
38	Results submitted to ClinicalTrials.gov			
	Confirm that the appropriate party has updated ClinicalTrials.gov with current study status (both internal and extramural studies)			
39	Confirm final disposition of study supplies and any equipment provided for the study: <insert study-specific items>			



 <b>WILLS EYE HOSPITAL</b> <b>VICKIE AND JACK FARBER</b> <b>VISION RESEARCH CENTER</b>  <b>STANDARD OPERATING PROCEDURES FOR</b> <b>CLINICAL RESEARCH</b>		<b>SOP # SC04</b>	
		<b>Title: Unanticipated Events with Risk to Participants and Others: Definitions and Reporting Requirements</b>	
		<b>Effective Date: June 10, 2021</b>	
Revised Date: N/A	Next Review Date: June 10, 2023	<b>Page 1 of 7</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: June 1, 2021	Related SOPs: #ST 01: Responsibilities of the Study Team  #SD 01: Essential Study Documents  #SD 02: Source Documents in Clinical Trials
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: June 1, 2021	

**PURPOSE:** to define and describe the reporting requirements of unanticipated problems, adverse events and serious adverse events that occur during the conduct of studies conducted at the Wills Eye Hospital to ensure compliance with the Wills IRB, ICH guidelines and sponsor requirements.

**SCOPE:** This SOP applies to all unanticipated problems and potentially study-related adverse study events, serious and non-serious, that must be recorded in the Case Report Form (CRF) and reported to the sponsor and IRB.

**RESPONSIBILITY:** Principal Investigator, Sub-Investigators, Clinical Research Coordinators and other study staff in contact with research participants. The Principal Investigator is required to immediately submit to the IRB and to the sponsor any unanticipated problems involving risk to human subjects or others. The Principal Investigator (PI) is responsible for the accuracy, completeness and timeliness of records and reports. The PI will review all reports before signature or transmission.

**DEFINITIONS:**

**Adverse Drug Reaction (ADR):** The World Health Organization (WHO) defines an ADR as “any response to a drug that is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

**Adverse Event (AE):** Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the study participant’s participation in the research, whether or not considered related to the study participant’s participation in the research. For the purposes of this SOP, the term Adverse Event includes Adverse Device Effects.

**Case Report Form (CRF):** A paper or electronic questionnaire specifically used in clinical research. The CRF is the tool used to collect data. All data on each patient participating in a study are held and/or documented in the CRF, including adverse events.

**External (Off-Site) Adverse Events:** Adverse events experienced by participants enrolled by investigators engaged in the same clinical trial, or a different clinical trial involving the same intervention at a site NOT within the purview of the Wills IRB.



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STANDARD OPERATING PROCEDURES FOR  
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**Internal (On-Site) Adverse Events:** Adverse events experienced by participants enrolled by the investigator(s) at a site within the purview of the Wills IRB.

**Investigational Product (IP):** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. (ICH GCP 1.33). Sometimes referred to as Test Article, Investigational Agent, Study Material, or Study Product.

**Investigator:** The Code of Federal Regulations defines an investigator as the individual who actually conducts a clinical investigation. When an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

**Investigator's Brochure:** A collection of all relevant information known prior to the start-up of a clinical research study involving an investigational product (s). It includes the pre-clinical data such as chemical, pharmaceutical, toxicological, pharmacokinetic and pharmacodynamic data in animals and humans as well as the results of earlier trials.

**Life threatening:** The Code of Federal Regulations defines life threatening as (1) diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival.

**Relatedness:** Adverse and unexpected events may have a causal association or relationship with either a) the investigational drug or device (study intervention) or b) any procedures involved in the research. Assessing relatedness is an evaluation of the likelihood that an event is at least partially caused by participation in the research or by the study intervention. Relatedness is assessed using the following terms: *Definitely related*, *Probably related*, *Possibly related*, *Unlikely to be related* or *Unrelated*. Possibly related means there is a reasonable possibility that the adverse event may have been caused by the procedures or intervention involved in the research. **In this document, related to the research means at least possibly related.**

**Serious Adverse Event (SAE):** An adverse event occurring at any dose or level of intervention that results in any of the following outcomes:

- Death
- A life threatening event (places the participant at immediate risk of death from the event as it occurred)
- Requires or prolongs inpatient hospitalization (hospitalization for a protocol-specified activity or for an elective, pre-planned procedure is not considered an SAE.)
- Persistent or significant disability / incapacity
- A congenital anomaly or birth defect



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- Medically important events (may jeopardize the participant’s health and may require medical or surgical intervention to prevent one of the other outcomes listed above).

**Severity:** Refers to the intensity of an event and is used without regard to whether or not it meets the criteria for “serious”. For example, a headache may be severe but not serious.

**Sub-Investigator:** The Code of Federal Regulations (21 CFR 312.3(b)) states that when “an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. ‘Sub-investigator’ includes any other individual member of that team.” Although many people are involved in the performance of a clinical trial, a sub investigator is a person who makes a direct and significant contribution to the data. Sub-investigators may include but are not limited to physicians, residents, and research coordinators.

**Unanticipated/Unexpected Adverse Event:** An adverse event or suspected adverse reaction is considered unanticipated or unexpected if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required, is not consistent with the risk information described in the general investigational plan (21 CFR 312.32 (a)).

**Unanticipated Problems Involving Risks to Subjects or Others:** Any incident, experience, or outcome that occurs during a study that meets all of the criteria listed below. **Throughout this document, these will be referred to as “unanticipated problems involving risks”.**

- (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents and (b) the characteristics of the population being studied;
- (2) related or possibly related to an individual’s participation in the research; and
- (3) suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

**INTRODUCTION:**

All Unanticipated Problems Involving Risks and Adverse Events that occur during a study shall be managed in accordance with federal regulations, Wills Eye Hospital policy, the requirements of the study protocol and in a manner to ensure the protection of study participants and collection of high quality data.



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## WILLS IRB POLICY ON REPORTING INTERNAL EVENTS

The Wills IRB requires reporting of internal events if they meet one of the following three criteria:

- Serious
- Related to research
- Unexpected/unanticipated (occurring at a rate/severity greater than previously known)

### I. PROCEDURES FOR INTERNAL EVENTS

#### A. Assessment of Potentially Unanticipated Problems Involving Risks

If the investigator determines that an event, incident, experience, or outcome represents an unanticipated problem involving risk, the investigator must report it promptly to the IRB and to the sponsor.

#### B. Potentially Unanticipated Problems Involving Risk: Adverse Events & Serious Adverse Events

AEs and SAEs are reportable from the time the patient consents to 30 days after the last study intervention, or as specified in the protocol. At every study visit, study participants are prompted to determine if any adverse events/serious adverse events occurred. Reports of any concomitant medication changes should also be discussed, as they may be indicative of an adverse event/serious adverse event. Additionally, any significant changes in ophthalmic examination may warrant an adverse event report. At each contact with the study participant, the Investigator or Coordinator should seek information on potential AEs/SAEs by open questioning and, as appropriate, by examination.

AE/SAE information may be reported between visits through spontaneous reports by participants, observations by clinical research staff and reports by family or medical care providers. The Investigator or Coordinator should question the participant or family member to determine if or when the study participant should be seen in the clinic.

An adverse event or serious adverse event meets the definition of an unanticipated problem involving risk when all of the following conditions are met:

- Unexpected
- Related to the research (see section C)
- Suggests that participants are at greater risk than was previously known.



C. Ascertaining Relatedness to the Research

All reported events are presented to the principal investigator/delegated sub-investigator to determine relationship to investigational product or study procedures. **The investigator** determines the potential relationship based on current medical history, concomitant medications, potential risks of the investigational product, and drug pathway.

Adverse events that are determined to be at least partially caused by one or more procedures involved in the research activity are considered related to participation in the research, whereas adverse events determined to be solely caused by a subject's underlying disease or other circumstances unrelated to the research are considered unrelated to participation in the research.

D. Assessing Seriousness of the Event:

**The Investigator** is also responsible for evaluating the seriousness of the event. The criteria for a SAE are listed in the definitions section, above. If possible, the coordinator should discuss the event with the Investigator while the study participant is still on site. All unanticipated and related serious adverse events must be reported to the Wills IRB within 5 days, and to the study sponsor within the reporting requirements specified in the protocol.

E. Unanticipated Events that are not Adverse Events and Require Reporting

Events that expose research participants or others to a risk of physical, social or psychological harm greater than the risk that was previously known must be reported to the IRB. Examples of unanticipated problems that are not adverse events that require reporting to the IRB due to their serious nature and relatedness to the research include:

1. Breach of privacy or confidentiality, including lost or stolen confidential information that might involve risk to that individual or others;
2. Receipt of the wrong dose of a study medication without evidence of harm;
3. Contaminated study drug (put participants at risk of harm);
4. Publication in the literature, safety monitoring report, including a Data and Safety Monitoring Report, interim result, or other finding that indicates an unexpected change to the risk-benefit assessment;
5. Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
6. Complaint from a participant or family member that indicates an unanticipated problem;
7. Laboratory or medication errors that may involve risk to that individual or other;



8. Change in FDA labeling due to adverse consequences or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
9. Disqualification or suspension of an investigator;
10. Sponsor imposed suspension of the study or study enrollment due to risk;
11. Change in the status of a participant that might affect their eligibility to remain in the study, require their withdrawal from the study or require the IRB to re-review the research to make determinations that adequate protections are in place to protect vulnerable populations.
12. Other events that are unanticipated and indicate the potential for increased risk of harm to subjects or others.

F. Timeframe for Reporting SAEs Unanticipated Problems Involving Risks to the Sponsor and IRB

All internal AEs and Unanticipated Problems Involving Risk must be reported to the sponsor and IRB as required by the protocol and in accordance with this SOP. The timeframe within which an SAE must be reported by depends on whether or not it is drug/device related, expected or unexpected, and degree of severity. Note that some sponsors might require reporting within a shorter period than listed below. Whenever there is a conflict, the shorter time frame applies.

1. All internal AEs and Unanticipated Problems involving risks and that are both serious and at least possibly related to the research procedures must be reported promptly to the Wills IRB. Investigators must report these events in accordance with the following timeline:
  - (a) Related events that are either life threatening or that result in death must be reported to the IRB **within 24 hours of discovery**.
  - (b) Related events that are not life threatening and do not result in death must be reported to the IRB **within 5 business days of discovery**.
2. All internal unanticipated events that are fatal and NOT related to the research must be reported **within 5 business days**.
3. In addition to their reporting responsibilities to the Wills IRB, investigators must meet the reporting requirements of the study sponsor, the monitoring entity, coordinating center, applicable regulatory agencies (NIH, FDA, etc.).

II. **External Unanticipated Events Involving Risks**

After review by the investigator, sponsor, and FDA if applicable, any serious and unexpected event that is probably or definitely related to the research (as determined by the sponsor, FDA or investigator) must be reported by the PI to the IRB **within 5 days of receipt of the report**. External reports that do not meet the criteria for an unanticipated problem involving risk do not need to be forwarded to the IRB.



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VISION RESEARCH CENTER

STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH

SOP # SC04

Title: Unanticipated Events with Risk to  
Participants and Others: Definitions and  
Reporting Requirements

Effective Date: June 10, 2021

Revised Date: N/A

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If an off-site safety report results in changes to the protocol, informed consent form or investigational brochures, the Principal Investigator or her/his designee ensures all coordinators and co-investigators are trained on the updated documents.

**References**

21 C.F.R. 50.3(j): Test Article

21 CFR 56 Institutional Review Boards Preamble

21 CFR 56.108(b) IND Safety Reporting IRB Functions and Operations

21 CFR 312.32 Adverse Event

21 CFR 312.81(a)


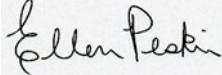

21 CFR 812.50: Labelling of Investigative Devices

ICH GCP 1.33: Investigational Product

FDA Guidance Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs- Improving Human Subject Protection (January 2009); [http://www.fda.gov/downloads/Regulatory Information/Guidances/UCM126572.pdf](http://www.fda.gov/downloads/Regulatory%20Information/Guidances/UCM126572.pdf)

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 15, 2007)



 <b>VICKIE AND JACK FARBER VISION RESEARCH CENTER</b>  <b>STANDARD OPERATING PROCEDURES FOR CLINICAL RESEARCH</b>		<b>SOP # SC 05</b>	
		<b>Title: Protocol Training</b>	
		<b>Effective Date: June 10, 2021</b>	
Revised Date: N/A	Next Review Date: June 10, 2023	<b>Page 1 of 3</b>	
<b>Author:</b> Ellen Peskin Manager of Clinical Research	Signature: 	Signature Date: June 1, 2021	Related SOPs: #ST 01: Responsibilities of the Study Team #ST 02: Required Training for Research Personnel #SC 02 Study Start-Up Processes
<b>Approved by:</b> Leslie Hyman, PhD. Vice Chair for Research	Signature: 	Signature Date: June 1, 2021	

**PURPOSE:** This standard operating procedure (SOP) outlines the procedures required for initial and continuing study protocol training of the research study team. Protocol training ensures all study team members are proficient in their roles and responsibilities in the protocol. Training should include information needed to conduct research properly, in addition to background information on structure, expectation, and goals.

**SCOPE:** This SOP applies to all members of a new or amended clinical study conducted within the Wills Eye Hospital (WEH) and to all research staff who join on-going studies at WEH.

**RESPONSIBILITY:** The Principal Investigator (PI), Study Coordinator, and Manager of Clinical Research

**DEFINITIONS:**

**Delegation of Responsibility Log:** also known as a Delegation and Signature Log, is a log that documents who is responsible for various activities in a research study. Every person involved with the study must be listed and their signature provided.

**Principal Investigator (PI) –** A Principal Investigator is the lead researcher on a study. She/he is the primary individual responsible for the preparation, conduct, and administration of a research study in compliance with applicable laws and regulations and institutional policy governing the conduct of sponsored research.

**Protocol:** A document that describes the rationale, objectives(s), design methodology, statistical considerations, and organization of a trial.

**Site Initiation Visit (SIV):** A visit performed by the sponsor to ensure that the investigators and study staff understand the study protocol, all the operational steps are in place, and everyone is clear and well trained in their specific roles and responsibilities. A trial initiation visit is conducted prior to the first patient being recruited into a study. The visit is usually conducted by the trial coordinator or monitor on behalf of the sponsor.

**Sponsor:** An individual, company, institution, or organization that takes responsibility for and initiates a clinical research trial.





**Study Coordinator:** A Study Coordinator is a person responsible for conducting clinical trials using good clinical practice under the auspices of a Principal Investigator.

**Sub-Investigator:** The Code of Federal Regulations (21 CFR 312.3(b)) states that when “an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. ‘Sub-investigator’ includes any other individual member of that team.” Although many people are involved in the performance of a clinical trial, a sub investigator is a person who makes a direct and significant contribution to the data. Sub-investigators may include but are not limited to physicians, residents, and research coordinators.

## INTRODUCTION

Prior to participating in any trial, all members of the study research team must be trained on the study protocol and in their specific research role.

Protocol training for study team members may occur

- During the Site Initiation Visit (SIV)
- During Study Investigators Meetings
- After IRB approval for major amendments to the study protocol
- After significant adverse events/violations where the IRB approves consent or practice changes
- When a new study member joins the team

If possible, all people listed on the delegation of authority log should obtain protocol training during the SIV. The Principal Investigator and Study Coordinator(s) are required to be present at study’s site initiation visit. Other members of the research team are encouraged to participate in the SIV, especially when the discussion focusses on activities that the team member will perform. During the SIV, the PI and study team will be trained by sponsor-approved personnel on the currently approved protocol.

The Principal Investigator is responsible for ensuring that study team members not in attendance at the SIV are trained in the protocol. The PI may delegate a person to train study staff on protocol training, but the PI still retains overall responsibility.

If training is provided via email, the internet or face-to-face, a copy of any training materials must be available to each person trained. Completed protocol training should be documented in the study regulatory binder. If a sponsor requires web-based training, the protocol training documents should be provided as electronic documents.

All training must be documented on a training form retained by the study coordinator and filed in the study regulatory binder (see below).



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**STANDARD OPERATING PROCEDURES FOR  
CLINICAL RESEARCH**

**SOP # SC 05**

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As amendments to the protocol are distributed by the study sponsor, delegated study staff are provided the updated documents and summary of changes to self-review. After review, staff will document training on a site training log.

### **Documentation of Training Log**

The training log should note the type of training completed (e.g., SIV, Investigator meeting, reading of protocol, training slides) and the date it was completed. This log need not include training that is documented by a completion certificate or other written documentation, such as CITI trainings or sponsor provided documentation that the individual has completed the required role-specific study certification.

A sample log is appended to this SOP.

### **For best practices, please adhere to the following recommendations:**

- Record training on the log as it is completed, to ensure completeness and accuracy of the data.
- The study staff member listed on each line must sign to verify that the training has been completed.
- Number each page and maintain this log in the study Regulatory Binder
- Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the footer.

### **References:**

21CFR 312.50 General Responsibilities of Sponsors

21 CFR 312.60 General Responsibilities of Investigators

ICH GCP Consolidated Guideline-Part 4.5.2 Compliance with Protocol



**VICKIE & JACK FARBER VISION RESEARCH CENTER (VJF-VRC)  
RESEARCH STANDARD OPERATING PROCEDURES (SOPs)**

**SOP ACKNOWLEDGEMENT FORM**

I have read, understood and agree to comply with the following VRC SOPs, all dated 9/15/2020 (check all read SOPs).

- VRC SOP #SP 01: Policy on Standard Operating Procedures (SOPs)
- VRC SOP #HS 01: Required Elements of Informed Consent Documents for Research Participation (Rev 1)
- VRC SOP #HS 02: Obtaining Informed Consent for Study Participation (Rev 1)
- VRC SOP #HS 03: Obtaining Assent/Consent from Minor Research Participants and Parents/LAR/ Guardians
- VRC SOP #SD 01: Essential Study Documents(Rev 1)
- VRC SOP #SD 03: Retention of Research Records
- VRC SOP #ST 01: Responsibilities of the Study Team
- VRC SOP #ST 02 Required Training for Clinical Research Staff (Rev 1)
- VRC SOP #ST 03 (Ver. 2) Policy on Form FDA 1572
- VRC SOP #SC 01 (Ver. 2): Study Feasibility Assessment
- VRC SOP #SC 02: Study Start-up Processes
- VRC SOP #SC 03: Study Close-Out Processes
- VRC SOP #SC 04: Unanticipated Events: Definitions and Reporting Requirements
- VRC SOP #SC 05: Protocol Training

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Name (Please print clearly)

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Date

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Signature