Investigator Manual

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Contents

What is the purpose of this manual?

This Investigator Manual is designed to guide you through policies and procedures related to the conduct of Human Research at Spectrum Health. As a SH investigator or staff member working on a human subject's research project, you are expected to follow the federal, state, and local policies regarding the protection of human subjects.

What is Human Research?

The organization considers activities to be "Human Research" when they meet the Department of Health and Human Services (DHHS) regulations definition and/or the Food and Drug Administration (FDA) regulations definition.

The Department of Health and Humans Services defines a human subject as any ***"living-individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction with the individual, and"***

- uses, studies or analyzes the information or
- obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

The FDA regulations define a human subject as "***an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy human or a patient".***

The "IRB Guidance Document on Quality Improvement Activities vs. Research", located in the IRB Policies and Guidance section of the HRPP website is available to assist researchers in distinguishing human research activities.

Use these documents for guidance as to whether an activity meets either the **DHHS** or **FDA** definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

[45 CFR §46.102(e) and 45 CFR §46.102(i) and/or 21 CFR §56.102(c), 21 CFR §56.102(e), and 21 CFR §812.3(p)]

How do I determine if my project requires IRB approval?

You cannot conduct Human Research, as defined by the DHHS and FDA regulations, without prior IRB review and approval, or a formal exempt determination. If you have questions about whether an activity is Human Research, we encourage you to submit an intake application via IRB manager (the systems online tool for application processing) for a formal determination from the IRB office prior to starting any project-related activities. Guidance for getting started and for submitting your application can also be found on our internal research webpage.

What is the Human Research Protection Program?

A Human Research Protection Program (HRPP) is an organization's overall plan to protect subjects participating in Human Research. The primary mission of this Institution's HRPP is to protect the rights and welfare of participants involved in human research conducted at this Institution by providing support to the Institutional Review Boards and maintaining a program of compliance oversight.

What are the general responsibilities of investigators?

Through the act of, submitting a protocol to the IRB and agreeing to be the principal investigator (PI) of that study, a PI is agreeing to assume the overall responsibility for the study conduct.

PI responsibilities include, but are not limited to:

- Personally, conduct or supervise the research
- Ensure that each individual, to whom a task is delegated, is qualified by virtue of education, training, and experience (e.g., hospital certification, human subjects research training, state license) to perform each of their delegated tasks.
- Protect the rights, safety, and welfare of the participants who will be under their care. To do this they are agreeing that the research:
    - is conducted in accordance with all federal regulatory requirements, state law, and Spectrum Health policies (including IRB SOPs)
    - is conducted in accordance with the IRB approved plan
    - data is accurate and securely stored during analysis

Prior to initiating a study, the PI should establish that they have adequate ***time and resources***, including competently prepared personnel to conduct the research study. When applicable, the PI should update the delegation of authority log, and submit a modification to the IRB prior to adding new personnel, and/or changing study roles and responsibilities.

The IRB can conduct audits either for cause or via routine procedures of investigator consent documents, study conduct, and study documentation. If the IRB or IRB chair has information (i.e. a subject complaint) that the study is potentially not being conducted in accordance with IRB requirements for protecting research subjects, an inquiry or audit can be conducted by the Office of Research Integrity (ORI). If the ORI requests to audit your records or observe your consenting practices, you will receive a written notice with further instructions on how to prepare for the audit or observation. At the conclusion, of the audit or observation, you will receive a written documentation of any findings, requirements, or recommendations.

What training do my staff and I need to conduct Human Research?

All research study personnel must complete the online Collaborative Institutional Training Initiative (CITI) human subject protections training program ***prior*** to the submission of their research for IRB review and complete the Research COI (conflict of interest) questionnaire annually.

All research personnel are required to complete and pass CITI's Basic Biomedical Course.

- CITI training is valid for three years after which a refresher course must be completed to continue conducting Human Research at Spectrum Health.
- If you have completed the CITI course at another institution, you will need to affiliate your account with Spectrum Health. IRB approval will not be granted for protocols in which research team members have not completed training under the Spectrum Health affiliation.
- Upon completing the course, a certificate of completion will be sent electronically by CITI administration to the IRB office. It is your responsibility to retain a valid copy of the completion certificate for your records.
- Spectrum Health as an institution, the IRB, the Sponsor, and/or funding agency may also require additional training and /or credentials to conduct the research depending on the Sponsor and/or the type of research. Further information can be found at our training and education page.

How do I write a Research Protocol?

A protocol is a detailed plan of why the research is being done and how it will be conducted. A well written protocol will help to ensure a timely IRB review and serves as a recipe for the conduct of the research. Typically, the sponsor of the Human Research will provide the protocol, but if you are an investigator sponsoring or leading your own Human Research, you are expected to create and submit a protocol for the IRB to review.

You may use the appropriate template protocol available on our forms and polices page. These templates include the sections at a ***minimum*** that the IRB expects to see included.

Here are some key points to remember when developing a protocol:

- Keep an electronic copy of the final IRB approved protocol. You may need to modify this copy and submit it to the IRB with tracked changes, if future modifications are made.
- Be sure to update the version date with each modification to the protocol.
- Remove sections of the protocol template that do not apply to your project.
- Additional help with protocol development can be provided. Reach out to our colleagues in the scientific support research team via email for assistance.

How do I create an Informed Consent document?

The informed consent form (ICF) provides the potential subject important information to consider before deciding whether to participate in the Human Research.

Typically, the sponsor of the Human Research will provide a sample informed consent document. If the sponsor has not provided you with an ICF, you can find templates under Forms and Policies.

You are expected to ensure the informed consent document includes the required regulatory elements, local contact information, and includes any additional information which would be important in a subjects decision to participate.

When writing your informed consent form please keep these tips in mind:

- Please adhere, as closely as possible, to the exact informed consent template wording to ensure all required elements and statements are met for approval.
- Be sure to date your informed consent document so that you use the most recent version approved by the IRB when consenting subjects.
- Always keep an electronic copy of the final IRB approved consent document.
    - You may need to modify this copy and submit it to the IRB with tracked changes, if future amendments/changes need to be made.
- Update the version date with each modification to the consent.
- Once the IRB has approved your informed consent form, it will be stamped in the bottom right corner with the date of the IRB approval and the last date the document can be used (when applicable).
    - The most current stamped informed consent form must be the one used to obtain informed consent and must be signed by the research participant.

If you have questions on creating your informed consent document or other consent documents (assent, short forms, information sheets or telephone scripts), please email IRB Assist or call (616) 486-2031.

How do I determine if my research requires HIPAA authorization?

The federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) requires authorization (permission) from the subject to be obtained to access, use or share protected health information (PHI) for research purposes.

The DHHS Office for Civil Rights defines when health information is considered identifiable under regulation 45 CFR §164.514(b) and the criteria that must be met to permit a waiver of authorization can be found at 45 CFR §164.512.

A waiver from this requirement may be granted for the Human Research by the institution's Privacy Board if certain regulatory criteria are met. The Spectrum Health IRB serves as the Research Privacy Board.

To request a waiver of HIPAA authorization, select this option on the initial IRB application. If your Human Research will access, collect or share any of the listed identifiable items with the subject's PHI and you do not meet the criteria for a waiver of authorization, you will be expected to include a HIPAA authorization to participate in the Human Research.

The HIPAA authorization can be found in the Informed Consent Template. While it is not required, it is recommended that the informed consent and HIPAA authorization remain one document. If you wish to use a separate HIPAA Authorization, contact the IRB Office.

The are several types of HIPAA Authorization waivers that may be issued by the IRB assuming certain regulatory criteria are met:

- Waiver of HIPAA Authorization
- Waiver of Specified HIPAA Authorization Element(s)
- Partial Waiver of HIPAA Authorization

The IRB may approve a full waiver of the requirement to obtain HIPAA Authorization to use and disclose protected health information, provided the research meets the criteria enumerated in 45 CFR 164.512.(i)(2)(ii).

A partial waiver of HIPAA authorization can be sought for recruitment purposes per 45 CFR 164.512(i)(2). This waiver allows for the collection and use of specific Protected Health Information (PHI) that will be used in order to recruit participants with the expectation that a full HIPAA Authorization will be signed prior to starting study procedures. The full HIPAA Authorization must be included in the consent form that is submitted to the IRB along with this request. The intention of this partial waiver is to allow investigators access to names and contact information of potential participants when there is an absence of a treatment relationship with potential participants. For example, if an investigators wishes to gain access to the EMR in order to recruit a large number of participants across a number of departments/divisions within the Institution. Continued access to health-related PHI for use in the research study will be limited to those who later volunteer for the study and provide written HIPAA authorization.

The request for a partial HIPAA Authorization waiver must be requested in the initial IRB application when a study team plans to access the medical record for recruitment purposes. Reference our guidance document, HIPAA & Research FAQ, on the forms and polices page for further clarification around HIPAA For assistance with partial waiver requests, contact the IRB Office.

How do I submit the initial IRB application?

The SH IRB conducts all protocol reviews with the online research management system: IRBManager
You can log in to IRBManager with your username and password or copy and paste this link:
https://spectrumhealth.my.irbmanager.com

All new projects must be submitted utilizing the new Ideation xForm contained in IRBManager.

Contracting, budgeting, and regulatory review (IRB) per our Research Process will all follow once the complete Intake package has been received.

Please note that the Intake package will be first reviewed by the OSP Analyst. The OSP Analyst will inform the Principal Investigator (PI) and study team when the IRB application xForm can be completed and submitted within IRBManager.

If you have further questions, please call the IRB at 616-486-2031 or email IRB Assist.

How do I request a waiver from the informed consent requirement?

In the initial IRB Application there will be an option to request a waiver of consent. The IRB may approve a waiver or alternation of informed consent provided all the following are true:

- The research involves no more than minimal risk
- The waiver of informed consent will not adversely affect the rights and welfare of the subjects
- It is not practicable to conduct the research without the waiver or alteration
- Whenever appropriate, participants will be provided with additional pertinent information after their participation

How do I submit a Humanitarian Use Device application to the IRB for review?

If you are using a Humanitarian Use Device (HUD) consistently with FDA approved labeling for medical treatment

- Be sure to select “HUD” on the Ideation/IRB initial application form.
- You are NOT required to submit a research informed consent document with your application for IRB review
- You must include a copy of the patient information or brochure that will be provided to the patient describing the device and the potential risk and benefits.

*If you are using the HUD as part of a research study evaluating the safety and effectiveness of the device, this request will be reviewed by the convened IRB as a typical device study.

How do I submit a reliance request?

A reliance agreement is a document signed by two or more institutions engaged in human subject’s research that permits one or more institutions to cede review to another IRB. The signed agreement permits a single IRB to review human subject research activities for more than one site.

A reliance agreement avoids duplicate IRB initial review and continued oversight when multiple IRBs have jurisdiction for the same multi-site research protocol. When submitting a reliance request, utilize the reliance request section in the intake x-form of IRB Manager. If SH IRB review is to be ceded after initial approval, the modification x-form will need to be submitted with a reliance screening form included in the submission.

If SH has not already completed a reliance agreement with the other institution involved the proposed reliance agreement should also be included. Your information will be reviewed to determine if the SH IRB is willing to cede review based upon the details provided. SH may choose not to cede review for several reasons and those reason while be provided to you should you request. If a decision is made to cede review and a reliance agreement is established, oversight should be provided by the IRB of record. Additionally, if the Spectrum Health IRB has agreed to rely upon an external IRB for continuing oversight of this research, all study modifications, request for continued IRB approval, and study completion notices should be sent to the IRB of record. Please note that your research records must remain accessible to the Spectrum Health IRB and Research Integrity Office for quality and compliance monitoring activities.

In the event SH cedes IRB review, it still retains privacy board oversight, and therefore will review and approve all HIPAA language changes and requests for HIPAA waivers and/or alterations.

The Spectrum Health IRB reserves the right to withdraw its acceptance of reliance agreement at any time for reasons such as subject safety concerns or noncompliance with the reviewing IRB policies and procedures.

Is there an application fee for IRB submissions?

There is a fee for all industry sponsored (research sponsored by for-profit organizations) study submissions, continuing review, and protocol modifications requiring expedited or convened IRB review. Please contact the Office of Research for specifics about our current fee's.

What are the types of IRB Review?

Submitted activities may fall under one of the following types of IRB review:

- **Review by the Convened IRB:**
  - Human research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.
- **Review Using the Expedited Procedure:**
  - Certain categories of human research may qualify for review using the expedited procedure. Reference the categories of research that may be reviewed using the CHECKLIST: Eligibility for Review Using the Expedited Procedure for reference.
- **Exempt:**
  - Certain categories of Human Research may be exempt from regulation but require IRB review.
  - It is the responsibility of the IRB, not the investigator, to determine whether Human Research is exempt from IRB review.
  - Review the CHECKLIST: Exemption Determination for reference.
- **Not Human Research:**
  - Activities must meet the DHHS or FDA definition of research involving human subjects for the activity to fall under IRB oversight.
  - Activities that meet neither definition of research involving human subjects are not subject to IRB oversight or review.
  - Review the CHECKLIST: Human Research Determination for reference.
  - Contact the IRB Office in cases where it is unclear whether an activity meets the regulatory definition of Human Research.
- **Not Engaged:**

- Office of Human Research Protections defines an institution as *engaged* in human research when its employees or agents for the purposes of the research obtain:
  - Data about the subjects of the research through intervention or interaction with them or
  - Identifiable private information about the subjects of the research or
  - The informed consent of human subjects for the research.
  - Contact the IRB Office in cases where it is unclear whether you are *engaged* in Human Research.

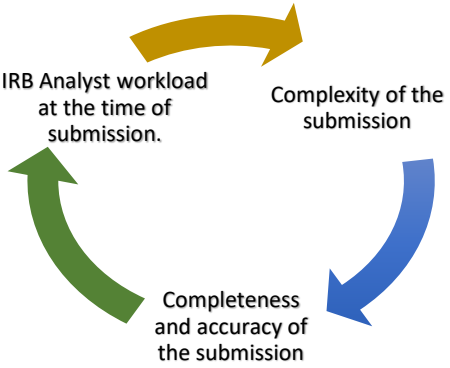
What is the typical turnaround time on IRB review?

Turnaround time on a submission varies depending on a few factors and fluctuates due to number of projects submitted. While the IRB would like to process every submission, we receive within 1-2 weeks, we must prioritize based on a variety of factors. Below is an outline of how the IRB prioritizes submissions.

- **Impact to patient treatment/welfare/safety submissions. For example,**
  - Emergency Use
  - Single patient IND
  - Safety related RNIs
  - Planned protocol deviations

- **First-come-first-serve, however:**
  - Continuing Reviews are prioritized based on expiration date to ensure approval does not lapse.
  - Protocols that must be reviewed due to impending funding (e.g., Just-in-Time) will be considered over other submissions in the review queue.
  - Treatment protocols (initial submissions) are often considered over other non-treatment submissions such as retrospective chart reviews.

The IRB generally convenes for meetings two times a month. The IRB meets the 1st and 3rd Tuesday of each month for regular meetings.



Expedited review occurs on an ongoing basis. The goal is to process submissions in a timely manner.

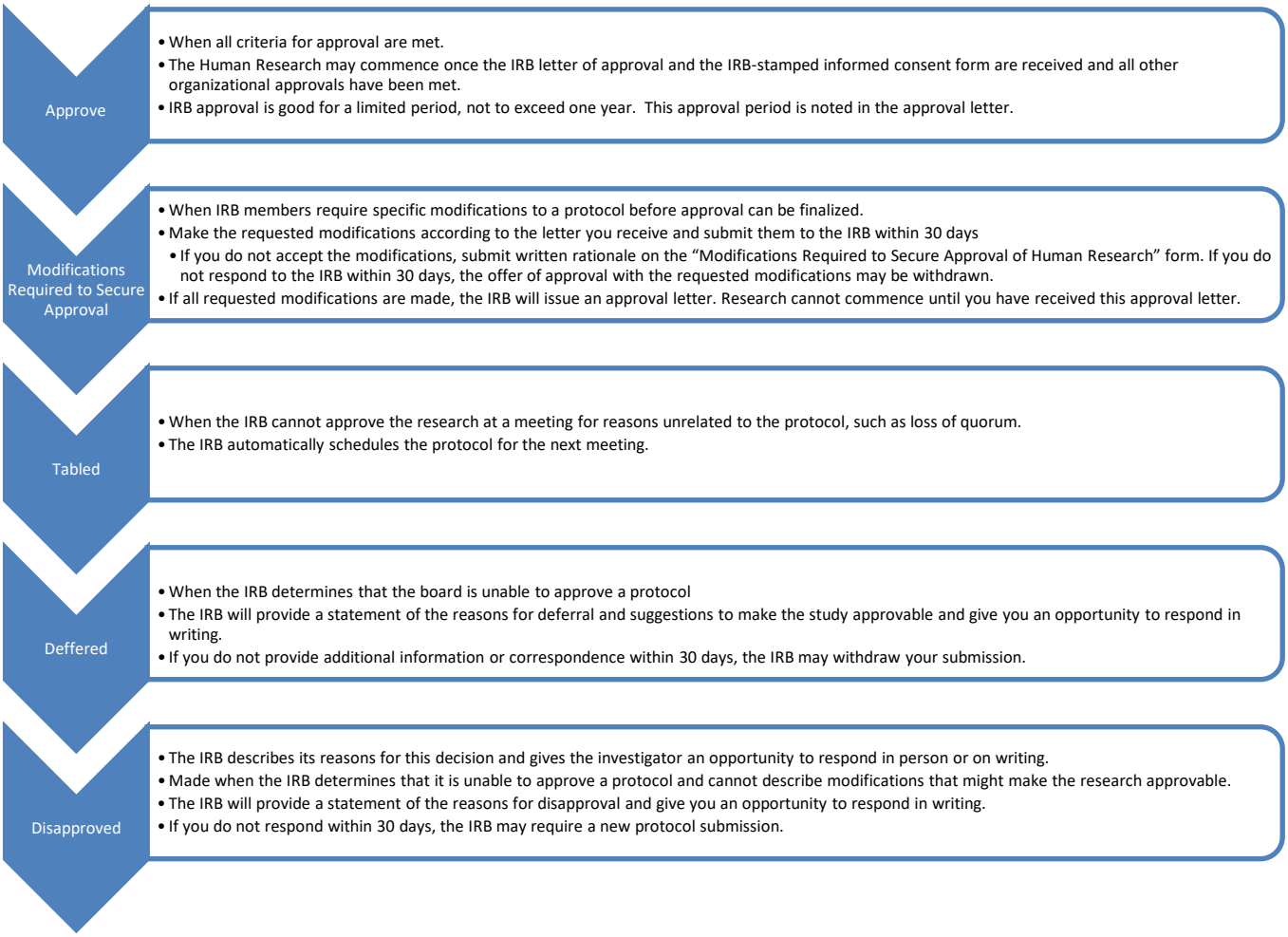
If it has been **more than four weeks** since your submission and you have not received correspondence from the IRB, please feel free to:

- Contact the assigned analyst directly
- Email IRB Assist
- Call the IRB main phone line at (616) 486-2031.

Please include the IRB number (example: 1900-500) in all communication with the IRB.

What are the decisions the IRB can make when reviewing a protocol?

The IRB follows the federal regulations that define approval criteria published by DHHS 45 CFR 46.111 and the FDA 21 CFR 56.111. The IRB may decide the following:



In all cases, you have the right to address your concerns (appeal) to the IRB directly.

What are my obligations after IRB approval?

Once you have the final IRB approval letter and the IRB-stamped informed consent form (if applicable) in your possession, research activities may begin so long as all other institutional requirements have been met.

All Human Research must be conducted in accordance with the IRB approved protocol, institutional policies, and applicable federal, state, and local regulations regarding human subject protection.

Please reference the section titled "What are the general responsibilities of investigators?" within this document.

Further guidance and information can be found in:

- A detailed list of the investigator's responsibilities is outlined in the Investigator Responsibilities policy.
- Conduct Human Research in accordance with International Conference on Harmonization (ICH) E6 Good Clinical Practice Consolidated Guidance.
- When required by the IRB, ensure that consent or permission is obtained in accordance with the relevant current protocol, as approved by the IRB.

What are the types of submissions?

Submissions	Process	Important Notes
Modifications	• Choose the modification of approved Human Research application in IRB Manager • You will receive an official approval letter once your submission has been processed	Research must continue as is until IRB approval of the modification is received or unless the modification is to eliminate an apparent immediate hazard to the subject.
Continuing Review	• A continuing review application, per the approval or exemption letter, can be submitted through IRB Manager • You will receive an official approval letter once your submission has been processed. As a courtesy, the IRB office will issue a reminder email of your upcoming expiration beginning 90 days prior to expiration. However, you are ultimately responsible for ensuring your IRB approval does not expire ***** If you are submitting a continuing review for a HUD be sure to select ***"yes "***on the application to the question; "*Are you seeking continuing approval for a Humanitarian Use Device (HUD) used for medical treatment*"	Continuing human research procedures with an expired IRB approval is a violation of federal regulations. Continuing reviews cannot include modifications to previously approved research. Please submit all modifications as a separate x-form.
Study Expiration	**In the event of study expiration:** • All Human Research procedures related to the protocol ***must cease***, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information • If current subjects will be harmed by stopping Human Research procedures that are ***available*** outside the context of Human Research, provide these procedures on a	If your study IRB approval expires, you will be ***restricted*** from submitting any new Human Research for IRB review until a completed application for continuing review or a study completion notice has been received for the study.

	clinical basis, as needed, to protect current subjects from harm • If current subjects will be harmed by stopping Human Research related procedures that are ***not available*** outside the Human Research context, immediately contact the IRB chair at (616) 486-2031 and provide a written list of the currently enrolled subjects and explain why they will be harmed by stopping Human Research procedures	
Study Completion	A study completion notice should be submitted when the Human Research is closed. Following closure, ***you should maintain***: • Study documentation and signed and dated consent documents in accordance with SH policies for documentation retention.	**Please remember to:** • Reference requirements in your approval or exemption letter. • You will receive a formal letter acknowledging completion of your study
Reportable New Information	Report any new information items on the Reportable New Information form, which provides guidance on which items and events are reportable to the IRB. Unanticipated problems are to be reported to the IRB **no later than 5 business days** from when you become aware of the information. • If the new information requires a modification to the protocol, informed consent or other documents, a "Modification of Approved Human Research" form should be submitted • Depending on the severity of the unanticipated problem, further actions may be required by the IRB chair or IRB. You will receive a formal letter if further actions are required.	

What is required during the informed consent process?

Guidance on Informed Consent and Legally Authorized Representatives for Research can be found in in Policy Tech (reference # 2053) and in SH standard Operating Procedures for Subject Management (SOP 401). Additional consenting guidance can also be found on the:

- Forms and Policies page
- Research Department SharePoint page,
- Belmont Report

- Required CITI human subject protections training program module. This module outlines three main steps for obtaining informed consent.

The following are the documentation requirements for consent documents:

- Complete all items in the IRB approved signature block, including dates and applicable checkboxes.
  - ***Signature-*** The subject, legally authorized representative in the case of adults with diminished decision-making capacity, or parent/guardian in the case of a minor
  - ***Witness-*** Must be present for the entire oral presentation to a subject, legally authorized representative, or parent/guardian unable to read the consent due to visual impairments, limited English proficiency and/or whenever required by the IRB or the sponsor
    - Must print, sign and date the consent document attesting to witnessing the entire consent process.
    - Will be provided a copy of the informed consent document to follow during the consent process to ensure accuracy, as well as a copy of the signed and dated consent document.
- Maintain the ICF
  - A copy of the signed consent document is added to the subject's medical record.
  - The original signed and dated consent document is maintained with other study/regulatory documents.

The following are the documentation requirements for short form consent documents

*(typically used for non-English speaking subjects when a fully-translated consent is not available):

- ***You must obtain IRB approval to use the short form consent for your proposed research.***
- The subject, legally authorized representative, or parent/guardian in the case of minors, prints their name signs and dates the short form consent.
- The individual obtaining consent signs and dates the IRB approved written summary (English version long form consent).
- The witness to the oral presentation (and interpretation), prints their name and signs and dates the short form consent document **AND** the IRB approved written summary (English version long form consent). The witness should be provided a copy of the IRB approved written summary (English version long form consent) AND short form to follow along during the process to ensure what was verbally relayed is accurate.
- A copy of the signed and dated short form consent **AND** signed and dated IRB approved written summary (English version long form consent) is to be provided to the subject, legally authorized representative or parent/guardian in the case in minors, and for Spectrum Health patients a copy is placed in the medical record. The original signed and dated short form consent **AND** signed and dated IRB approved written summary (English version long form consent) is maintained with the other study/regulatory documents.

Spectrum Health requires only certified interpreters be used to facilitate the informed consent process and serve as the witness to the oral presentation (and interpretation) when using a short form consent document. Please also reference the SH Guidance Document for "Consenting Limited English Proficiency Subjects" on our forms and policies page.

Payments and /or reimbursements of any form accepted and provided must be disclosed in the IRB approved Informed Consent Form and to Research Integrity suspending new enrollment).

Please email questions or requests for additional training on obtaining informed consent to Research Education or IRB Assist.

What if I need to use an unapproved drug or device in a life-threatening situation?

- Contact the IRB office or IRB chair immediately at (616) 486-2031 to discuss the situation.
- Reference the FDA Guidance for the regulatory criteria allowing such a use and make sure the regulations and SH policies are followed.
- You will need to submit a report of the use to the IRB within five days of the use
- You will need to submit an IRB application for initial review within 30 days if there is the possibility of subsequent use of the investigational product.
- Failure to submit the report within five days and/or the IRB application for initial review within 30 days if there is the possibility of subsequent use of the investigational product, will restrict you from conducting Human Research.
- Emergency use of an unapproved drug or device in a life-threatening situation without prior IRB review is "research" as defined by FDA, the individual getting the test article is a "subject" as defined by FDA, and therefore the use is governed by FDA regulations for IRB review and informed consent.
- Individuals getting an unapproved drug or device in a life-threatening situation without prior IRB review cannot be considered a "subject" as defined by DHHS and their results cannot be included in prospective "research" as that term is defined by DHHS.

Do I need to submit case reports for review?

Case reports involving ***three or more patients*** must be submitted for review. Please reference the IRB Guidance Document on Case Reports.

- **Do submit** for IRB review case reports that may constitute research involving human subjects. Case reports testing a hypothesis should be submitted (e.g. treatment A is better than treatment B for this rare condition).

- **Do not submit** case reports involving under three individuals and the collection and presentation of detailed information about a patient to highlight an interesting condition, treatment, presentation or outcome.

How do I get additional information and answers to questions?

If you have any questions or concerns about the HRPP, contact the IRB office at:

- Phone: (616) 486-2031
- Email IRB Assist
- Or reference the forms and policies page for specific guidance

If you have questions, concerns, complaints, allegations of coercion or undue influence, allegations or findings of non-compliance, or input regarding the HRPP that cannot be addressed by contacting the IRB office, please contact the Spectrum Health compliance hotline at 1-877-319-0266. The hotline is staffed by an independent organization.