

HUMAN SUBJECTS RESEARCH GUIDANCE

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SPRINGFIELD COMMITTEE FOR RESEARCH INVOLVING HUMAN SUBJECTS
(SCRIHS)

This document represents GUIDANCE for Investigators and Study Staff conducting research sponsored by SIUSOM; taking place in SIUSOM facilities; or involving SIUSOM faculty, staff, residents, medical students, patients, and affiliates.

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IRB REVIEW, APPROVAL, AND COMMUNICATION

A. Communication from the IRB

Communication (e.g. notifications, outcome letters, e-mails) from the IRB to Investigators and study staff will come through the electronic IRB system also known as iRIS. These can be accessed by visiting the correspondence tab within the electronic IRB system. Additionally, copies of communications from the IRB may also be sent to the Investigators/study staff's e-mail address listed on file.

B. Guidance for Investigators working with the IRB and with SCRHS Staff

1. General Guidance

For a researcher to be clear on their responsibilities, it is advisable to be familiar with SCRHS Standard Operating Procedures and to review federal regulations that pertain to the type of research that is being proposed before preparing submissions to the IRB.

- When preparing submissions, investigators and study staff should approach this process with the same care they use in submitting grant applications to funding agencies.
- Utilize the most current forms and templates available within the electronic IRB system and the SCRHS website. Contact SCRHS staff for guidance.
- Answer all questions - if you do not know what the question means, call the SCRHS office for assistance.
- The SCRHS staff is responsible for communicating the regulations of the federal government, University policy and guidance, and the deliberations of the IRB Board.
- Timely communication helps speed the process along.
- Be sure to provide as much contact information as possible (e.g., e-mail address, phone numbers, fax numbers, and a pager number.) This will aid in processing your submission in a timely manner. This can be done within the electronic IRB system under the profile tab.

2. Who Can Help Me?

SCRIHS is happy to advise any investigator or new research staff member through the IRB process. Call SCRHS at 217-545-7602 and ask for assistance. A designated staff member will be glad to meet with you about the process.

3. Who Handles My Study Once it has Been Submitted?

Studies submitted to SCRHS are divided among staff for the pre-review process. Investigators are contacted if items are missing or if additional information about their submission is required.

Pre-review by SCRHS staff is not the same as the Board review. Pre-review by staff is only to point out readily obvious missing elements in the consent form, items that should have been submitted (e.g. questionnaires, data collection forms, recruitment materials), regulatory issues, and other information that may render your submission incomplete. IRB members have asked the SCRHS staff to conduct this pre-

review so that incomplete submissions are not forwarded to the IRB for review.

4. Deadlines

Deadlines for submission are posted within the electronic IRB system and on the SCRIHS website. Investigators are strongly encouraged to submit their studies prior to the deadline. This will provide additional time for corrections or to obtain submission elements that are missing before the materials are sent out to Board members.

It is especially important that continuing reviews be submitted in a timely fashion. If studies are not submitted on time they will expire. When this occurs, additional research cannot be carried out until the study is re-approved.

5. Guidance on IRB Submission Packet

- A complete packet must be submitted. Copies of all documents must be in each packet.
- All materials must be submitted via the electronic IRB system known as iRIS.
- The Principal Investigator, and other staff as applicable, must electronically sign-off on the Application for Approval.
- Recruitment materials should be enclosed if there are intentions of using them. Please note that some recruitment materials may require approval by SIUSOM's Office of Public Affairs. Approval by Public Affairs should be received prior to submission to SCRIHS.
- All appropriate attachments should be included, (e.g., survey instruments, questionnaires, or other research instruments). Missing items will only delay the review.
- Check for typos and spelling errors.

6. Where are the forms I need for submission?

All forms can be found within the SCRIHS electronic IRB system: <https://siu.imedris.net/> and on the SCRIHS website: <http://www.siumed.edu/adrfa/scrihs.html>

When preparing your submission, use only the most up-to-date version of the appropriate form and templates. Investigators should not download forms or templates to their computers for continual use. It's the responsibility of the investigator/study coordinator to visit the SCRIHS electronic IRB system to be sure a new version has not been posted. Under no circumstances will handwritten forms be accepted. All submission must come through the electronic IRB system.

7. Turnaround Time

- Turnaround time is related to the completeness of the submission.
- The electronic system dates all submissions provided to SCRIHS. The receipt date is used to triage how materials are processed and forwarded for review.
- Timely communication helps speed the process. To inquire about the status of your submission, please contact SCRIHS staff. Include the submission date, the investigator's name, and a SCRIHS protocol number.

- Review outcome letters are generally prepared in the week following an IRB meeting. Review outcome letters are sent as correspondence through the electronic IRB system with an additional copy sent to the e-mail address on file.
- After receiving a "pending" approval letter requiring changes to the consent form or other clarifications, prompt response by the investigator will undoubtedly speed up the approval process.

8. Responses to “Pending” Approval Letters

- Responses to letters should be sent to SCRIHS by responding within the electronic IRB system. They should include a complete response with all points addressed. If changes are requested that you do not agree with, you need to explain in writing why you do not agree. Ignoring a request slows down the review and approval process.
- If changes to documents were requested, please appropriately update the version date on the document to differentiate it from the original submission. Additionally, all documents should be uploaded as “revisions” within the electronic IRB system. Incorrectly uploaded documents will be returned to the Investigator. This is done to prevent regulatory issues for the Investigator once the study has been approved.
- Responses to "pending approval letters" are required within ninety (90) days of the receipt of the letter. SCRIHS can provide better service when revisions are submitted in a timely fashion.

C. IRB Decisions and the Appeal Process

1. Investigators Attending the IRB meeting

Investigators may request, or may be invited, to attend an IRB meeting to explain their study, to provide background, or offer additional information. The Board, on occasion, invites investigators to the IRB meeting when a study has complex ethical issues or if the investigator wishes to undertake a large-scale study.

2. What Does Disapproval of a Study or of an Amendment Mean? Can It Come Back as a New Study?

When a study is disapproved, it means that the study cannot be implemented as described in the submission. Sometimes disapproval is based on profound ethical objections or the investigator did not adequately address issues raised by the IRB.

Occasionally a study can be redesigned and resubmitted under a new protocol number. This requires that the previous issues be presented in a substantive and fundamentally different way. If the study is sponsored by industry, the company representatives may be unwilling to change the protocol.

Disapproval of a full-board amendment most often occurs when an investigator is proposing to add procedures to a study that radically alters the original proposal. Sometimes a sub-study may be approved as a completely new study.

3. Criteria for Appeal

If a study has been tabled, the Investigator is advised to fully answer all questions and concerns raised by

the Board. The investigator will be notified of these questions and concerns through iRIS after initial review of the study. Usually appeals are not necessary when a study has been tabled only once and the investigator has fully complied with the Board's request for changes or information.

Sometimes a study is rejected due to a misunderstanding or incomplete information about the study. When this occurs, the IRB will make every effort to review the study carefully and suggest changes that would make the study acceptable for implementation.

4. How the Appeal is Resolved

To resolve an appeal, it is helpful for the investigator to attend the IRB meeting to present additional information that the IRB may need in order to make a decision on whether a study can move forward. In some cases it will be clear that, despite additional information, the IRB agrees that the study simply cannot be approved.

MEETING DATES AND AGENDA DEADLINES

The deadline submission for materials to be reviewed at the upcoming month's SCRIHS meeting is typically the Monday before the LAST Wednesday of the current month. SCRIHS meetings are typically held on the SECOND Wednesday of the month. These dates are subject to change. Please visit the SCRIHS website ([CLICK HERE](#)) or contact the SCRIHS office (545-7602) for the most up-to-date information.

For example, Monday January 26, 2015 is the submission deadline for items to be placed on the February 11, 2015 meeting.

Investigators and Study staff are encouraged to attend a meeting to present their research and answer any questions SCRIHS members may have. Please contact the SCRIHS office if you wish to attend a meeting.

WHAT IS HUMAN SUBJECT RESEARCH?

Activities involving “Research” and “Human Subjects” as participants require SCRIHS review and approval prior to implementation. However, not every project involving human participants constitutes human subject research.

RESEARCH is a *systematic investigation*, including research development, testing and evaluation, designed to develop or contribute to *generalizable knowledge*.

A *systematic investigation* is an approach involving a predetermined system, method, or a plan for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory. A *systematic investigation* includes the collection of information and/or biospecimens, and analysis either quantitative or qualitative.

Activities designed to develop or contribute to *generalizable knowledge* are those activities designed to draw general conclusions, inform policy, or generalize outcomes beyond the specific group, entity, or institution (i.e., to elaborate, to be an importation factor in identifying or expanding truths, facts, information that are universally applicable).

To develop or contribute to generalizable knowledge requires that the results (or conclusions) of the activity are intended to be extended beyond a single individual or an internal program. Normally, research is reported at a professional meeting, or published and distributed in a journal or through other media. Some systematic investigations may not be research. For example, quality assurance studies for improving a service, if not disseminated outside the local institution, usually are not considered research. Classroom evaluations are also for "internal" purposes only and usually are not considered research.

Determining whether quality assurance, classroom evaluations, or demonstration studies become research cannot solely be based on the intent at the outset of the study. Does the investigator intend to disseminate results beyond the local institution or to "generalize" results to share with populations other than those studied? If so, then the Investigator should design the study to be generalizable. The design of the study will ultimately determine if it does or does not meet the definition of Human Subjects Research.

Medical practice is not designed to contribute to generalizable knowledge; however, medical treatment may generate information that is usable for research. Medical data from the treatment of several persons, when used for an investigational purpose is an activity designed to contribute to generalizable knowledge and therefore is considered research.

Social and behavioral science research covers many disciplines and methodologies. The field employs a variety of methodological approaches including: surveys and questionnaires, interviews, direct observation, physiological manipulations and recording, descriptive methods, laboratory and field experiments, standardized tests, economic analyses, statistical modeling, ethnography, and evaluation.

If the proposed activities involves a *systematic investigation* approach AND is designed to develop or contribute to *generalizable knowledge* the activity constitutes RESEARCH.

HUMAN SUBJECTS refers to *living individuals* about whom an investigator (whether professional or student) conducting research obtains: (1) data through *intervention* or *interaction* with the individual; or (2) *identifiable private information*.

Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private Information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place and information, which has been provided for specific purposes by an individual, which the individual can reasonably expect, will not be made public (e.g., a medical record). Private information must be individually *identifiable*.

Note: IRB approval is required not only during the period when patients are being entered into the study, but for the entire time that PRIVATE INFORMATION about study subjects is being collected/analyzed for investigational purposes.

Identifiable is where the identity of the subject is or may be ascertained by the research, or will be associated with the information. The research could involve the use of *coded* data/specimens.

To determine if data being collected is IDENTIFIABLE PRIVATE INFORMATION; ask the question "If I realize that I omitted a data point when I was reviewing a medical record (or interviewing a subject) for my research data, can I go back to that record (or that subject) to "fill-in" the omitted data point?" If the answer to that question is "Yes", then the information collected was IDENTIFIABLE.

Coded means a living individual's identifiable information such as name or social security number has been replaced by a code, such as a number, letter, or combination there of AND there is a key to link the code to the identifiable information of that individual. Coded data are considered identifiable under the Common Rule.

Use of *coded* information does not involve a *human subject* if:

- The holder of the key and the investigator enter into an agreement prohibiting the release of the key to the investigator under any circumstances, until the individuals are deceased.
- The investigator has documentation of written policies and operating procedures from a repository or data management center that prohibits the release of the key to the investigators under any circumstances, until the individuals are deceased.
- There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

If the proposed activity includes obtaining information about living individuals through *intervention or interaction* with the individual, or by obtaining *identifiable* and *private information (and/or specimens)* from living individuals, the activity involves HUMAN SUBJECTS.

To be considered Human Subjects Research the proposed active must meet the above definitions of RESEARCH and HUMAN SUBJECTS.

If you are unsure if your project meets the definition of Human Subjects Research you may submit a research determination to SCRIHS or contact the SCRIHS office at 545-7602 for assistance.

The IRB strongly recommends that QI/QA (typically considered to be Non-Human Subject Research) be submitted for a research determination. Research journals have increasingly been requested proof of IRB review prior to publishing study results. Additionally, a determination can help protect subjects and prevent regulatory issues for the PI and Study Staff.

WHO IS CONSIDERED AUTHORIZED STUDY PERSONNEL?

Definitions

Authorized Study Personnel (ASP): Research personnel who are directly involved in conducting research with human subjects, or who are directly involved with the handling of identifiable private information related to those subjects, including protected health information, in the course of a research project.

NOTE: All ASP must complete the SCRIHS required CITI training prior to participation in human subjects research.

ASP who should be listed on the SCRIHS application

- Principal Investigator and Co-investigators
- Research Nurses and Coordinators
- Any individual engaged in the research meeting the definition of ASP

All ASP who engage in the informed consent process are included on the application AND the informed consent form. It is possible for ASP to be listed on the application but NOT the informed consent form because they are not involved in the consenting process.

Examples of persons who do not need to be listed as ASP

- Consultants
- Non-authoring Statisticians
- Individuals performing clinical trial-related medical services that are performed as part of their routine, daily activities (for example: phlebotomists, x-ray or CT technicians)

*Any changes to ASP (additions OR deletions) must be reported as an amendment to SCRIHS

WHEN DO STUDIES NEED TO BE REGISTERED ON CLINICALTRIALS.GOV?

HHS Final Rule and NIH Policy concerning ClinicalTrials.gov:

In an effort to make information about clinical trials widely available to the public, the U.S. Department of Health and Human Services has issued a [final rule \(link is external\)](#) that specifies requirements for registering certain clinical trials and submitting summary results information to ClinicalTrials.gov. The new rule expands the legal requirements for submitting registration and results information for clinical trials involving U.S. Food and Drug Administration-regulated drug, biological and device products. At the same time, the National Institutes of Health has issued a [complementary policy \(link is external\)](#) for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded trials, including those not subject to the final rule.

Which trials need to register with ClinicalTrials.gov?

FDA Final Rule: Applicable clinical trials are (1) clinical trials of drug and biological products that are controlled, clinical investigations, other than phase 1 investigations, of a product subject to FDA regulation; and (2) prospective clinical studies of health outcomes comparing an intervention with a device product against a control in humans (other than small feasibility studies) or any pediatric post-market surveillance studies required by FDA under the FD&C Act. Does not apply to phase 1 trials or small feasibility device studies.

NIH Policy: All clinical trials funded wholly or partially by NIH. Includes phase 1 clinical trials and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions.

Timeframe for registration?

Not later than 21 days after enrollment of the first participant.

Timeframe for results information submission?

Not later than 12 months after primary completion date.

Potential Consequences of Noncompliance?

For federally funded trials, grant funding can be withheld if required reporting cannot be verified. Civil monetary penalties of up to \$10,000/day

The Southern Illinois University School of Medicine ClinicalTrials.gov website is maintained by the Center for Clinical Research and the SCRIHS office. Please direct any questions to Amber Fifer, PharmD at afifer56@siu.edu or 217-545-4541.

Please note, studies registered with ClinicalTrials.gov should be disclosed on both the Initial Submission Packet and Informed Consent.

A checklist and an FAQ created by ClinicalTrials.gov is available in Appendix D of this document. [Click Here](#)

INFORMED CONSENT

A. Overview

1. Participation in Research is Voluntary

Truly effective, legally informed consent occurs when the information presented in the consent form is comprehended and when the subject decides voluntarily to participate in the study.

The consent form is the vehicle to provide the information for potential subjects and the consent process is the expansion of the information in a voluntary setting allowing for give and take in the exchange of information about what will happen in the research. In addition to what is written in the consent form, the “give and take” should provide the potential subject with adequate information to make an “informed” decision about whether or not to participate in the research study. The setting and the amount of time for the consent interview has an effect on whether the subject feels coerced and whether the consent given is truly voluntary.

2. Disclosure of Benefits and Risks

When people are ill and looking for a potential cure for their disease, they may not read or hear the disclosure of risks and benefits in the same way that a normal healthy subject might. It is important when writing consent forms that risks and benefits are described exactly. This is full disclosure. Since the nature of research is to find answers, it is often difficult to say that the benefits can really be known.

3. Federal Regulations and Guidelines

The federal regulations address consent in a complete and simple manner. Investigators and research staff should be familiar with the federal regulations regarding informed consent.

They can be found at: [45 CFR 46.116](#) and [21 CFR 50 subpart B](#).

B. Constructing the Consent Form

1. Informed Consent Form Template

Every informed consent form should include the basic elements of informed consent and any additional elements, as appropriate. The basic elements of informed consent are found in 45 CFR 46.116. Additionally, SCRIHS has created an Informed Consent Form Template that contains all of the basic elements of informed consent as well as, format, suggested language, and other requirements.

The IRB requires use of the consent form template. The IRB also has templates for specimen collection, LAR, tissue banking, and assent. . All of the templates are available at the SCRIHS website or in the electronic submission system. **It is recommended to download the consent template each time a study is started.** This ensures that the most up-to-date version is being used. If you have any questions on how to develop an informed consent form using the provided templates please contact the SCRIHS office at 545-7602 for assistance.

2. General Guidance for Developing an Informed Consent Form

- The SCRIHS consent template must be used. Do not submit sample consent forms provided by a study sponsor. The template includes the format, the section headings, and all required language.
- Use simple (lay) language - the form should be written at no higher than 8th grade level.
- Avoid scientific or technical terms. If they must be used, provide an explanation in lay terms.
- Use second person throughout, with the exception of the consent agreement to participate. (e.g. You will be asked...)
- Include only pertinent information. Avoid redundancies. Sometimes it helps to outline the consent and make sure you have covered everything once.
- Exculpatory language--Do not use qualifying phrases such as "you understand that", "you acknowledge that", etc., or references to understanding. Avoid language which may appear to waive any rights to which the subject is entitled.
- Check spelling and grammar.
- Section headings should be underlined or bolded.
- Use size 11 point, or larger, Arial font throughout the consent form.
- Number pages "page x of y" on each page. (e.g., page 2 of 4)
- Include header or footer (left side only) with current version date on each page of the consent form.
- Call the SCRIHS office for guidance when you have questions.

3. Consent Forms for Studies Involving Children or Others Unable to Give Informed Consent

- If children are involved and are 7 years of age or older, provide for permission of parent and assent of child.
- For younger children, add a sentence stating that the study has been discussed with them and they agree to participate.
- If other persons are involved in the procedures (caregiver, spouse, parent, teacher), consent must be obtained from each via an additional consent form.

4. Glossaries and Lay Language

The glossaries, dictionaries and writing aids listed below have been compiled by other IRBs and organizations to provide guidance and suggestions for using lay language in consent forms. In addition, a multilingual glossary is provided to help in preparing consent forms in languages other than English or to check the translation of an already prepared consent form.

"Alternative Lay Language for Medical Terms for Consent Forms" is copyrighted from the University of Kentucky and is provided here for your use. <http://hso.research.uiowa.edu/medical-terms-lay-language>

"MedTerms.com is the medical reference for MedicineNet.com, containing easy-to-understand explanations of over 10,000 medical terms. This online medical dictionary provides quick access to hard-to-spell medical definitions through an extensive alphabetical listing." Descriptions of terms, diseases, medical procedures that may assist in writing in lay language. www.medterms.com/Script/Main/hp.asp

"The Plain Language Action & Information Network is a government-wide group of volunteers working to improve communications from the federal government to the public."
<http://www.plainlanguage.gov/usingPL/government/index.cfm>

Multilingual Glossary of Technical and Popular Medical Terms in Nine European Languages:

<http://users.ugent.be/~rvdstich/eugloss/welcome.html>

C. The Consent Process

1. Who Should Obtain Consent—Authorized Study Personnel (ASP)

The Application for Approval requires all ASP to be listed and their roles defined. Those persons who will be assigned to obtain consent in the study must have this role indicated on the Application. In order to obtain consent the study personnel should be very familiar with the protocol, very familiar with the consent form, and trained in obtaining consent.

If there are changes in personnel, when the study is active, investigators should submit an Amendment Summary Form describing the changes in personnel.

***Investigators are reminded that new personnel must have fulfilled the SCRIHS human subjects protection educational requirements before being able to participate in the research study.**

2. PIs Role in Consent

The PI is responsible for either personally obtaining consent from prospective subjects, or designating an approved ASP to obtain informed consent. Ultimately, the PI is responsible for whoever is enrolled in the study.

Sign-off on the consent form by the person obtaining consent should occur at the same time the subjects is signing the consent. Since consent and the initial visit could take place at the same time, it is important that the eligibility for participation be reviewed by the PI in a prompt manner.

3. Training to Obtain Consent

Research staff, vested with this important task, must have training specific to obtaining informed consent because this is one of the critical elements of human subjects' protections - assuring that all elements of the consent process have been honored (voluntariness, comprehension, information, competency to understand).

Consent is a process and not merely the presentation of a form or a reading aloud of a form. Research staff and investigators should not assume they know how to obtain consent. Practice, reading, and discussion among staff are important elements in moving toward a more complete process.

Research staff may wish to practice obtaining consent by role-playing. When a new study is about to start, research staff may wish to review the consent form aloud and think of the questions that a potential subject might have about the study.

4. Taking the Consent Form Home Prior to Signing

Sometimes it is important that a subject be given the opportunity to take the consent form home to discuss it more fully with family members, their personal physician, or others. This should be encouraged as truly informed consent takes place when all questions have been asked by the subject and answered by the investigator or the research staff. If a subject requests to take the consent form home, this request must be honored.

An investigator should never be so eager to reach an enrollment goal that they do not allow the subject adequate time to consider enrollment in the study. Subjects are more inclined to stay enrolled if they fully understand everything that will be happening during the course of the study.

There are some low risk studies that probably do not require lengthy or measured consideration about whether to enroll or not. Sometimes the study itself takes as long as the consent process. This may be true when total participation is answering a single questionnaire or participating in a single blood draw. However, a subject, though, has the right to review the consent form in a manner that is appropriate to ensure understanding.

5. Debriefing

When a study has utilized deception in the conduct of the study, subjects must be debriefed after the procedures of the study have been completed to explain what actually happened in the study. The debriefing has the goal of disclosure; repairing the breach of the informed consent process, minimizing concerns or tension that the subject may have as a result of learning they have been deceived, and offering additional discussion if necessary.

Further it is important when deception has been used in a study that debriefing occur so that subjects involved in future studies don't make assumptions that perhaps the use of deception is common and occurs in many research studies.

A debriefing plan will include an oral discussion and some written materials including an expression of regret that the use of deception was necessary, explaining why it was necessary, and reviewing what really happened in the study. It is important to emphasize that the approval of the use of deception was granted by the IRB.

Subjects must be offered a chance to ask questions and discuss any confusion or concerns they have about the study. In addition, in the case of a potential significant reaction, information about additional support or counseling that subjects may need as a result of the deception must be offered.

6. Regulations About Which Consent Form to Use

The most recently approved consent form must be the one offered to the research subject for signing. Subjects must not be offered a consent form that has expired. Expiration dates are printed on the consent form to assist investigators in remaining in compliance.

If, for some reason, a study's approval has lapsed, investigators may not enroll subjects using an expired consent. If the subject shows up and the outdated consent is discovered, the consent interview will have to be postponed for a later time. Such delays cause problems in subject recruitment and retention. Investigators are urged to regularly monitor that their study is in compliance and fully approved. In preparing for a consent interview and signing, it is a good idea to check that the consent form has not expired prior to scheduling the subject visit.

7. Re-consenting Subjects When the Consent Form Has Changed

Subjects must be re-consented when the consent form has changed and the changes in the consent form directly affect the subject. Examples of changes that would affect the subject include changes in the contact information for the Principal Investigator, the addition of another blood draw, or other procedures, a change in existing procedures, the addition of a study visit, new risks as a result of adverse events, new side effects, the addition of a questionnaire, the addition or subtraction of drugs used in the study, and changes in confidentiality (who can see the data). Usually re-consenting can take place at the next study visit. The timing and methods need to be discussed with SCRIHS to advise how the new consent should be presented to the subjects.

There are some instances when all participants have completed a study but new risks are later discovered through data analysis or through reporting at other active sites that are still enrolling subjects. In the case where new risks are very serious or complicated or could be long-term effects of the drug or device, it may be necessary to bring the subjects back to the clinic to explain the risks in a face-to-face discussion and re-consent. A letter can be sent to participants explaining the information and then participants can be offered a return visit or a group session to further discuss new risks and re-consent.

If the change might impact the health or well-being of the active subject, re-consenting should occur immediately. This means that subjects must be contacted to come to the clinic before their next study visit to discuss the new risks and sign a new consent form. Contacting subjects should be done with care so as not to alarm participants.

If the changes are easily explained, it is possible to mail the consent form to the subjects to inform them of the change, yet have them discuss and sign the actual consent form when they come in for their next study visit. The changes could be outlined in a letter to study subjects that accompanies the consent form. It should indicate clearly in the letter that subjects should not sign and send the consent form back. A letter such as this and a description of this process needs to be approved by SCRIHS prior to implementation.

Changes that occur in the protocol, such as lab values or screening criteria, do not usually impact the consent form and therefore the consent form would not be changed. If there are changes, they must be submitted for IRB review as an amendment.

Sometimes when a finding is issued before the end of the study, an information letter may be sent to all study participants explaining what was discovered. This would not mean that persons would be re-consented but it does provide them with additional information to judge whether they wish to remain enrolled in the study.

In some cases, investigators should inform subjects by certified letter. Whether a certified letter is sent depends on the type of information communicated and its importance. Such a letter is not in place of a consent form. Sometimes a letter will be sent to participants and then the information incorporated into the consent form at a later time. Other options include creating an addendum consent. This option is not utilized more than once or twice during a study because the subjects may get confused with multiple additions to a consent form. Each study's unique situation is considered when additional information must be shared with subjects, but the standard procedure will be to change the consent form.

Study subjects do not have to be re-consented when a version date changes as a result of a continuing review. If no changes were made to the consent form, then it is not necessary to re-consent them because of the IRB review. If the only changes made are to comply with changes to the consent form template, the subject does not have to be re-consented. Additionally, changes such as the title, the addition of a co-investigator, and small corrections, do not require that subjects be re-consented.

Each sponsor may have different requirements regarding re-consenting. Investigators can discuss sponsor requirements with SCRIHS.

Note: The consent form cannot be altered by crossing out sentences if something is eliminated.

8. Regulations About Signing and Storing Consent Forms

Consent forms must be fully signed and dated before filing. The subject should have received a photocopy of the signed consent immediately upon completion of the consent interview. If consent is done in a location without a photocopier available, two copies of the consent should be signed and one labeled as the copy and given to the subject.

By maintaining a study log, investigators and research staff can easily track that consent forms are signed and dated as appropriate. This may be especially useful in a study with multiple consent forms or a study that has updated consent forms on a regular basis.

Original copies of the consent forms should be kept in the study binder, subject file, or with the research records. A copy of the signed consent form must be placed in the patient's medical record, if applicable, or according to affiliated hospital/SIU HealthCare policies.

9. Witnesses

A witness is required in the consent processes when consenting non-English speaking subjects and illiterate English-speaking subjects. Please contact the SCRIHS office for specific guidance and regulatory requirements if you have a new or existing study that may require the use a witness.

10. Consent by Someone Other than the Patient

When adults are enrolling in research studies and are not competent to understand consent and enroll themselves, the same rules that apply to regular patients apply to research subjects. If the subject is competent to consent and enroll themselves, then they may do so. If the subject cannot participate in that process then, under various laws in Illinois, a legal representative would need to consent on behalf the

subject. Please refer to the LAR guidance section of this document, the LAR SOP, or contact the SCRIHS office for detailed information.

D. Special Types of Consent and Additional Consent Templates

1. Oral Consent

In some instances, oral consent may be appropriate or even preferred.

In instances where the notation of a person's identity could compromise issues of privacy and confidentiality or could adversely harm their employability or insurability, oral consent might be appropriate. In other instances, the study may be of such low risk as to not warrant written consent.

Investigators wishing to waive written consent should review the Waiver of Consent Guidelines and Form to determine if they have adequate justification to submit a waiver of consent request.

A script is always required when written consent is waived. The elements of consent are included in the script but can be written in a more informational manner. An information sheet describing the study and giving contact information is also required.

2. Children and Assent

Special regulations apply to enrolling children in research studies. The description below indicates how investigators can prepare the appropriate form, script, or consent form for the appropriate age group.

Below Age 7

As appropriate and depending on the study, some explanation can be given to the child about what is involved in the study.

7-14 year olds

Verbal consent (directed to the child) should be given by the investigator. This verbal discussion should include the following:

- child-friendly language
- what the child will experience (risks)
- what will be done
- statement that results will be private
- if they get paid
- they have a choice to participate or not participate

Parent(s) will sign the consent form. On the assent form, parent(s) will sign verifying that a verbal consent was delivered and the child should sign their name if possible.

14 year olds up to 18 year olds:

During the consent process, the investigator should direct the discussion to the parent(s) and the child. The discussion should be based on the consent template and in age appropriate, child friendly language.

Parent(s) will sign the consent form. The assent form will have the following statement:

"I have read the consent form and/or the research study has been explained to me and I understand what is involved in my participation. I had the chance to ask questions. If I have more questions, I know whom to call. I will receive a copy of this signed assent form"

If the child agrees to participate, the child must sign the assent form. If the child does not or cannot sign for some reason, the investigator should provide an explanation for the lack of assent.

Please note: If the assenting child declines participation in the study, the parents or legally authorized representative cannot force the child to participate. Also, mere failure to object should not be construed as assent.

Consent Form for Parents:

- If the adult is also a participant, the consent should be in "you and your child" language. There should be an assent form but it does not have to say "you and your parent."
- If the adult is not a participant, the consent should be in "your child" language.

3. Pharmacokinetic/Pharmacogenetic Studies as Part of a Clinical Trial

Pharmacokinetic studies are often added to a clinical trial as an amendment or sub-study to evaluate drug metabolism.. Since pharmacokinetic studies often involve additional blood draws and other lab tests, it is important that the subject can easily differentiate between the main study and the sub-study. Often pharmacokinetic studies are a means of evaluating gender or age differences in drug efficacy and therefore are not open to all persons enrolled in a trial. In some circumstances, the IRB may approve the use of the sponsor's model consent for the pharmacokinetic studies.

E. Waiver of Consent

1. Regulations and Overview

Informed consent is mandated by Federal policy (45 CFR 46 Section 116 and 21 CFR 50.20). Informed consent is also one of the fundamental principles of ethical conduct in the use of human subjects. Occasionally there are reasons to waive written consent or to alter the requirements of consent. Only the IRB can make the determination to waive some (written) or all (written and verbal) consent requirements. Under some circumstances, described in the Federal Regulations, an investigator may feel that his/her study justifies a request to waive consent. The essential conditions of a waiver that must be justified are:

- That the research pose no more than minimal risk to subjects;
 - An individual is considered to be at more than minimal risk if exposed to the possibility of harm -physical, psychological, social, legal, or other - as a consequence of participation as a human subject in any research activity which departs from the performance of routine physical or psychological examinations and tests, or which departs from established and

accepted procedures necessary to meet the individual's needs, or which increases the probability or magnitude of risks ordinarily encountered in daily life.

- That no adverse effects will occur as a result of the waiver or alteration;
- That without the waiver or alteration the research in question could not be carried out; and
- That information will be provided after participation is completed, if appropriate.

Investigators may wish to consult the federal regulations: Federal Policy for the Protection of Human Subjects **§46.116 General requirements for informed consent; §46.117 Documentation of informed consent:** (Section 116(d) and 117)

2. Examples of Situations Where a Request for Waiver of Consent Would Not Be Approved by the IRB:

1. I do not have enough money in my research grant to print consent forms and distribute them and file them.
2. These are my patients so I see them anyway and they trust that I will not involve them in something that might harm them.
3. I already have access to the patient records.
4. There is not any risk even though it would be possible to get consent.
5. I do not have a staff member who can handle all the paperwork involved in obtaining informed consent.
6. If I consent people, they will not want to participate in the study.
7. The consent form will scare people. It seems so legalistic.
8. It is an inconvenience and a lot of added time to get all the consents signed.

3. Waiver or Alteration of Written Informed Consent

A waiver of alteration of written informed consent could be used in studies where participation does not require the potential subject to return a card, sign a consent form, or call to indicate a willingness to participate. Generally granting a waiver or alteration of written informed consent is not an acceptable practice. Federal regulations and state regulations require “legally effective informed consent” to participate in research. The IRB must approve waivers or alterations of written informed consent procedures.

The requirement for a written, signed consent form may be waived or altered by the IRB if the criteria below are met:

- The signed consent form itself might compromise the confidentiality of the data describing the subject and the subject prefers that no signed consent form be used; or
- The research presents no more than minimal risk and involves no procedures for which written consent is normally required outside the research context.

a. Verbal Consent and Script Still Required

Though waiver or alteration of written informed consent may be appropriate, this does not mean that verbal consent cannot be utilized in situations where the investigator or study staff will be meeting with the subject. A script for verbal consent should be submitted to the IRB for review. A verbal consent

script provides all of the elements of consent in a more informal style. In addition, each subject should be provided with an information sheet that describes the study and gives contact names and numbers.

Normally, investigators will be asked to keep a log of those who were approached about the study, and offered verbal consent. A simple chart can indicate the subjects as subject 1, subject 2, and subject 3. A column can indicate that verbal consent was given and a date. Since a specific number of study subjects have been requested in the IRB application, it is important that investigators keep some record to indicate that they are not enrolling more subjects than they originally requested.

b. Examples of when a waiver or alteration of written informed consent might be allowed:

A waiver or alteration of written informed consent may be allowed in a study, where for example, a sample population is mailed a survey and a letter (see sample letter below) describing the study, and they are asked to complete the survey and mail it back. No identifiable information is collected. The subjects are not signing a consent form prior to answering the survey. They can, on the other hand, not answer the survey and simply throw it away. This raises questions as to whether another round of surveys can be mailed to non-respondents. Investigators need to plan ahead and carefully describe in the study description what means will be used if there are not enough respondents to the first survey. Investigators should discuss their plans with the SCRIHS staff to get a reading on whether the proposed consent process is reasonable. Ultimately, the IRB decides if the consent process is acceptable.

A letter accompanying a questionnaire or survey should include the following elements:

- Introduction and identification of Researcher
- Purpose of the research
- Where the person's name was obtained
- What will subject be asked to do and how long will it take
- Privacy and Confidentiality
- Risks if there are any
- Agreement to participate voluntarily
- Participation is considered consent
- Contact Persons and information

a. Template 1 with Sample Language

Date

Dear *(Give name of respondent)*:

I am a graduate student working under the direction of Professor (Give the full name of the Faculty Member who is serving as the Faculty Advisor on this study), in the (give Department's name) Department at Southern Illinois University) or a professor in the Department of (give Department's name) at SIU School of Medicine)

I am conducting a research study to (state purpose of study - e.g., how young people obtain summer jobs in Springfield and what the experience of interviewing for a job is like or your opinion about whether the restaurants in Springfield contribute to the litter problem and what

business owners should do about litter.

I obtained your name and address from (describe the source of the name - e.g., the local YMCA teen chapter, or the community directory of recycling club presidents).

I am asking you to participate by (describe what is being asked of the participant. Describe length of time it will take to do the task).

It will take about 20 minutes to answer the questionnaire that is enclosed. When you are done with the questionnaire, please mail it back in the enclosed self-addressed, stamped envelope.

Your participation in this study is voluntary. If you choose not to participate or to withdraw from the study at any time, there will be no penalty.

The results of the research study may be published, but your name will not be used. [If anonymous questionnaires are completed, include statement that "The questionnaire is anonymous. The results of the study may be published but your name will not be known."].

If you have any questions concerning the research study, please call me [or Professor ____] at (____) ____-____.

Return of the questionnaire will be considered your consent to participate.

Sincerely,

Signature

Researcher's name

Address

Phone and E-mail

Signature

Faculty Advisor's Name

Address

b. Template 2 with Sample Language

You are invited to participate in this research project approved by the Institutional Review Board at the Southern Illinois University School of Medicine. This study is intended to assess _____. This study will help us better understand _____. You have been invited to participate because you are a _____. If you choose to participate you will be asked to _____. This should take approximately _____ to complete. Participation in the _____ implies that you have read the information on this form and consent to take part in the research. Your participation in this study is voluntary. If you choose not to participate or to withdraw from the study at any time, there will be no penalty. During this study no identifiable information will be recorded. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared because your name cannot be linked to your responses. If you have any questions, please contact _____ at (217) 545-_____ or _____@siu.edu. Thank you for your time and response.

4. Waiver or Alteration of All Elements of Consent (no verbal and no written consent)

A request to waive written and verbal informed consent must be accompanied by a complete explanation in response to the four statements below. All of the criteria must be met to qualify for a waiver of both written and verbal consent.

- a. The proposed research presents no more than minimal risk of harm to subjects.
- b. The waiver or alteration of consent will not adversely affect the rights and welfare of the subjects.
- c. The research could not practicably be carried out without the waiver or alteration.
- d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

F. Documentation of the Informed Consent Process

The process of informed consent must be documented. To do this, a chart note will need to be placed in the participant's medical records. If you are not accessing a participant's medical records, a memo can be created of the consent process. This document can be stored with the original informed consent form.

The documentation will need to be created by the individual who consented the participant and should include the following:

- The participant had the opportunity to review the consent form on their own
- The participant understood what was required of them to participate in the study
- The participant was able to have questions addressed
- The participant received a copy of the signed informed consent form
- The hospitals require the consent to be scanned into the participant's hospital medical record.

Example of a documentation note:

"I spoke with the patient today to discuss possible participation in the Dr. Smith's HEART study. We reviewed the informed consent together, then I gave her time to review it on her own. The patient had some questions regarding the follow up schedule, and blood draws. I addressed her questions. She understood what was required of her to be in the study, she agreed to participate and we signed the consent form. A copy of the signed informed consent form was given to the patient to take home. A copy will also be placed in the patient's records."

AGE OF CHILD ASSENT

Age of Assent

In all cases, regardless of whether SCRIHS requires assent, investigators are expected to provide children with developmentally appropriate information about their diagnosis, treatment, and proposed research participation. In particular, investigators should explain the purpose as well as the incremental procedures, risks and benefits of the clinical trial, and offer an opportunity to ask questions.

For children under 7 years of age, the formal assent of the child is not a necessary condition for participating in a research protocol.

For children 14 years of age or older, the formal assent of the child is a necessary condition for participating in the research. Investigators, however, may decide that assent is not required *for an individual child*, because the capability of that child is so limited that they cannot reasonably be consulted [45 CFR 46.408(a)]. The reason for not obtaining assent of the individual child must be documented on the Assent Form for Minors.

Children age 7 through 13 vary considerably in their development and cognitive capacity. Many of these children have limited ability to participate in decision making, and a formal request for assent may not be appropriate. Nonetheless, for all protocols, SCRIHS expects investigators to provide children in this age range developmentally appropriate information about their diagnosis, treatment, and proposed research participation. In particular, investigators should explain the purpose as well as the incremental procedures, risks and benefits of the clinical trial, and offer an opportunity to ask questions. The reason for not obtaining assent of the individual child in this age group must be documented on the Assent Form for Minors. The reason should also be documented in the medical record along with the documentation of consent.

- a. For research not involving greater than minimal risk to the children (45 CFR 46.404 and 21 CFR 50.51), or for research involving greater than minimal risk and no prospect of direct benefit to the individual child subject, but likely to yield generalizable knowledge about the child's disorder or condition for which there is no expected direct therapeutic benefit (45 CFR 46.406 and 21 CFR 50.53), the assent of children ages 7 and older is a necessary condition for participating in the research. Investigators may decide that assent is not required *for an individual child*, because the capability of that child is so limited that they cannot reasonably be consulted.
- b. For protocols involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subject (45 CFR 46.405 and 21 CFR 50.52), the formal assent of children below age 14 is not a necessary condition to proceeding with enrollment. Investigators may decide that assent is appropriate for an individual child, based on an individual assessment of capacity.

In limited and specific circumstances, assent can be waived under 46.408 and 50.55(c)(2) if "the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research." These waivers are only appropriate when the study intervention is likely to be more effective than other treatments available outside the trial and should only apply to those components that are judged more beneficial (thus assent may be sought for non-therapeutic components).

In limited and specific circumstances, assent can be waived under 46.116(d) and 50.55(d)(1-4) if “The research involves no more than minimal risk; and the waiver or alteration will not adversely affect the rights and welfare of the subjects; and the research could not be practicably carried out without the waiver or alteration, and whenever appropriate the subjects will be provided with additional pertinent information after participation.”

SCRIHS requires the permission of a child’s parent(s) or legal guardian(s) based on the risk level of the research [46.408(b) and 50.55(e)]. Please contact the SCRIHS office for additional guidance or assistance with a determination.

PARTICIPANTS WHO LACK DECISIONAL CAPACITY

The predominant ethical concern in research involving individuals with psychiatric, cognitive, developmental disorders, or who are substance abusers, is that their disorders may compromise their capacity to understand the information presented and their ability to make a reasoned decision about participation. In addition, for individuals with disabilities affecting their reasoning powers who are residents of institutions responsible for their total care and treatment, the impact of institutionalization may further compromise their ability to exercise free choice.

Definitions

Lack of Decisional Capacity: Having either a psychiatric disorder (e.g., psychosis or mood, anxiety, personality or behavior disorder), an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also lack the capacity to make decisions in their best interests.

Decisional Capacity: Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Decisional Capacity may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. (See also: Lack of Decisional Capacity.)

Guardianship: A designation of legal status, determined by a court that an individual is not capable of making decision on their own behalf. By court order, a guardian is appointed to make decisions for an individual. Courts can appoint a Guardian of the Person or a Guardian of the Estate or both. A court order appointing a Guardian of the Person should state that the Guardian is appointed a Guardian of the Person with the power to make healthcare decisions. If the order does not state the Guardian has the power to make healthcare decisions, the Guardian could only act as a surrogate decision maker in health care matters. A Guardian of the Estate is appointed when an individual is unable to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations. A Guardian of the Estate has no special authority to make healthcare decisions.

Institution: A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent; residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

Problems of Consent and Competence

As a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent unless there is evidence of a serious lack of decisional capacity that would impair reasoning or

judgment. Even those who do have a diagnosed mental disorder may be perfectly able to understand the matter of being a research volunteer, and quite capable of consenting to or refusing participation. A mental disability alone should not disqualify a person from consenting to participate in research; rather, there should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.

Persons formally adjudged incompetent have a court-appointed guardian who must be consulted and consent on their behalf. For incompetent persons who are institutionalized, consent by officials of the institution in which the person resides (even if they are the person's legal guardians) is not generally considered appropriate, since the supervisory duties may give rise to conflicting interests and loyalties. Family members or others financially responsible for the patient may also be subject to conflicting interests because of financial pressures, emotional distancing, or other ambivalent feelings common in such circumstances.

Some individuals may be incompetent and have no legal guardian, for example, geriatric patients with progressive cognitive disorders. Typically a spouse or adult child of such persons consents to their medical care, but no one is their legally authorized representative. The extent to which family members may legally consent to the involvement of such persons in research (especially if no benefit to the subject is anticipated) is not discussed in any known case law and thus, is unclear. It is generally accepted that the Illinois Health Care Surrogate Act may apply in these situations.

If the participant lacks decisional capacity due to a medical condition or mental capacity, consent must be obtained through a Legally Authorized Representative (as set forth in the LAR policy) In this case assent must also be sought from the participant. The LAR signature page and Assent Form for Participants who lack decisional capacity participants must be utilized in conjunction with the Informed Consent Form. Both the LAR signature page and Assent Form for Participants who lack decisional capacity is located on the SCRIHS website.

POLICY: Investigators must submit the following with the Application for Approval for new studies: procedures for evaluating the mental status of prospective subjects to determine whether they are capable of consenting; procedures for obtaining the consent or assent of prospective subjects, if appropriate; procedures for determining the conditions under which consent may be provided by legally authorized representatives of prospective subjects.

Also, in studies where cognition may change during the course of the study, for example with persons who have Alzheimer's disease, a procedure must be set up to evaluate the person each time they come to the study clinic to assure continuing comprehension about study participation. In some cases, a caregiver may be a part of the study in which case such evaluation may not be necessary. In other cases, where the subject comes on their own, it is important that the investigator is sure they remember their involvement and what the study is about. Sometimes Mini-Mental Status Exams are employed; other times, specific tests that pertain to the study may be used.

The investigator must certify there is a process for reassessment if there is concern that the cognition status of the subject may change

Because no generally accepted criteria for determining competence to consent to research (for persons whose mental status is uncertain or fluctuating) exist, the role of the IRB in assessing the criteria proposed by the investigator is of major importance.

Criteria for determining decisional capacity might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gain can be anticipated. Investigators should recognize that the setting in which consent is sought as well as the person seeking the consent can influence a prospective subject's ability to comprehend or appreciate what is being asked. In certain cases SCRIHS may (i) require a competency assessment by someone independent from the investigator at the time of enrollment and during a subject's participation in the research, if mental capacity is likely to diminish, and (ii) appoint a consent monitor to supervise the informed consent process.

The selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without definitive answers from statutes, case law, or regulations; however, within the boundaries of existing precedents, SCRIHS will seek to help investigators formulate appropriate procedures for these uncertain areas as set forth in the LAR policy. Among other things, SCRIHS may consider whether to require investigators to solicit prospective subjects' assent (i.e., the willing and, to the extent possible, knowledgeable participation of those unable to give legally valid consent), and SCRIHS may consider whether an incompetent person's refusal to participate in research should override consent given by a legal guardian. Such decisions may be based on the amount of risk involved in the research and the likelihood that subjects will derive health benefits from their participation.

Selection of Subjects

It is now generally accepted that research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Persons who are **institutionalized**, particularly if disabled, should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researcher. Institutional settings can create circumstances that may compromise the voluntary nature of participation in research. For example, institutionalized individuals may have become emotionally dependent on their caretakers and may acquiesce too readily to requests for their "cooperation." Persons who are totally dependent on an institution may be vulnerable to perceived or actual pressures to conform to institutional wishes for fear of being denied services or privileges. If medical care, staff attention, or living conditions are inadequate, an invitation to move into a special unit or research ward may be appealing. Finally, with little or no opportunity to make decisions regarding their daily living, the ability of institutionalized subjects to make choices may be further diminished.

Investigators must provide SCRIHS with sufficient justification for using an institutionalized population.

The "Risk and Benefit Evaluation for Participants who Lack Decisional Capacity"

Although DHHS regulations charge the IRB with ensuring that adequate safeguards are in place to protect the rights and welfare of vulnerable subjects, including those with mental disabilities, no additional DHHS regulations specifically govern research involving subjects who lack decisional capacity. The National Commission for the Protection of Human Subjects has, however, issued recommendations for protection of participants who lack decisional capacity similar to the recommendations made with respect to children. In light

of these recommendations, SCRIHS shall determine the level of risk and benefit the study poses to participants who lack decisional capacity.

The assigned primary and secondary reviewers of the study protocol undergoing full board review must evaluate the level of risk and benefit the study poses and report their recommendations to the board on the Reviewer's Checklist. These recommendations will be discussed during full board review and the discussion and conclusion of the board will be documented in the minutes.

Criteria for Assessing Risk and Benefit

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

Research that presents more than minimal risk should involve participants who lack decisional capacity only if there is a prospect of direct benefit from participation.

If research does not involve beneficial interventions and presents more than minimal risk to participants who lack decisional capacity, the anticipated knowledge must be of vital importance for understanding or eventually alleviating the subjects' disorder or condition. Research proposals of this nature may require SCRIHS to obtain assistance from expert consultants.

HIPAA

HIPAA is the acronym for the Health Insurance Portability and Accountability Act that was enacted in 1996. Part of this act requires that protected health information (PHI) is handled in a confidential manner and remains secure.

Protected Health Information is defined as:

1. Names;
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Phone numbers;
5. Fax numbers;
6. Electronic mail addresses;
7. Social Security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web Universal Resource Locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including finger and voice prints;
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)

HIPAA does allow for an investigator or study staff to access, collect and use PHI in human subjects research. Provided, appropriate steps within the research design and submission process have been taken. For example, any PHI that will be collected must be listed on the consent form. Furthermore, the design of the study should have listed provisions for the responsible collection of PHI and the prevention of undue disclosure.

How can PHI be accessed or recorded?

PHI may be accessed or recorded if the subject provides written authorization or a waiver and/or a partial waiver of authorization is granted by the IRB.

How does a subject provide written authorization?

A subject can provide written authorization by signing the Informed Consent Form. The SCRIHS consent template has the appropriate HIPAA information integrated into the document. When consent is obtained so is written HIPAA authorization.

How is a waiver and/or partial waiver of authorization granted?

Investigators must make a request for a waiver and/or partial waiver of authorization. The SCRIHS application provides sections for the investigator/study staff to make these types of requests.

Depending on the submission type, the SCRIHS application will ask if a waiver or partial waiver of authorization is needed to conduct the research. The study design, as well as regulations/SOPs, will dictate if a waiver and/or partial waiver of authorization can be granted. If you are requesting a waiver and/or partial waiver of authorization select YES for those sections of the application. You will then be prompted to provide a justification for the request and how you will keep the data secure.

Which one do I need for my study?

If you plan on accessing or collecting PHI for research purposes AND subjects will not provide written authorization (due to study design) then you will need a Waiver of Authorization for Use and Disclosure of Protected Health Information (PHI). This type of waiver is most often used when conducting retrospective chart reviews. Be advised, for exemption submissions, the waiver of authorization only grants access to PHI, it does not grant permission to record PHI.

If you plan on accessing another institutions records for the purpose of screening and/or recruiting subjects then you will need a Partial Waiver of Authorization for Recruitment Purposes. For example, this type of waiver is needed if a SIUSOM physician is conducting a study and wanted to review Memorial Medical Center's records. However, if a SIUSOM physician is conducting a study and wanted to review only SIUSOM's records then a partial waiver of authorization would not be required. When accessing records that are not your own (or a member of your study team), it is recommended that a letter of support is provided by the physician and/or department who's records you will access.

Both types of waivers may be requested if it is appropriate for the study.

How will I know if a waiver and/or partial waiver of authorization has been granted?

The requests for either type of waiver will be granted when the IRB provides approval for the study. If the request for either type of waiver is denied or the justification is found to be insufficient, you will be notified of this during the review process.

DE-IDENTIFIED, LIMITED DATA SETS, AND CODED DATA

When conducting a study, investigators should use the least amount of subject identifiers as possible to minimize the risk to subjects as a result of accidental disclosures.

De-identified data: refers to data that has been stripped of *all* subject identifiers, including all 18 HIPAA identifiers (see below). If the data set contains any limited identifiers, it is considered a limited data set under HIPAA. If the data includes an indirect link to subject identifiers (e.g. via coded ID numbers), then the data is considered by the IRB to be coded, not de-identified.

Limited Data Sets: a limited data set is a set of data in which most of the Protected Health Information has been removed. The following identifiers are allowed in a Limited Data Set

- Geographic information – a limited data set can include full five digit zip code and any other geographic subdivision such as county, city, precinct, and equivalent, however, street address cannot be included.
- Dates – a limited data set can include dates related to an individual (e.g., birth date, admission and discharge date, any age over 89).
- Other unique identifiers – a limited data set can include any unique identifying number, characteristic or code other than those specified in the remaining 16 HIPAA identifiers.

Studies involving de-identified data or limited data sets may qualify for approval using exempt criteria.

Coded data: this refers to data that has been stripped of all direct subject identifiers (including all 18 HIPAA identifiers – see page 29), but in this case each record has its own study ID or code, which is linked to identifiable information such as name or medical record number. The linking file must be separate from the coded data set. This linking file may be held by someone on the study team (e.g. the PI) or it could be held by someone outside of the study team (e.g. researcher at another institution). Of note, the code itself may not contain identifiers such as subject initials or medical record number.

Studies involving coded data may qualify for approval using expedited criteria.

Please note that in some instances a Data Use Agreement, or other agreement, may need to be in place prior to transferring data from one entity to another entity. This will be dependent on the type of data and where it is coming from and/or going to. Some entities may require an agreement even though it is not required by the federal regulations. Please contact the SCRIHS office for additional information.

CASE REPORTS

A **case study** is a report of **treatment** (including innovative treatment, e.g., surgery) and, as such, does not meet the Common Rule definition of research (a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge).

If any of the following is present, the activity is considered research rather than a case study.

- Reporting on more than three patients
- There is a plan to perform the treatment on some individuals but not on others.
- Investigational drug(s) or device(s) are involved (off-label use of an approved drug or device is permissible).
- There is a clear intent before treating the patient to use systematically collected data that wouldn't ordinarily be collected in the course of clinical practice in reporting and publishing the case study.
- There is intent to manipulate medications (even approved ones) to determine maximum effectiveness, or to test if they work consistently well.
- Extra tests are conducted for the sake of reportability.
- There is a protocol/study plan.
- Separate sets of records or data sheets are maintained (particularly with identifiers).
- The primary purpose is to answer a research question, not to provide care.
- There is consideration that the treatment might yield a case series if it is effective in others (e.g., testing a hypothesis).

Case studies may be published; the published report must be descriptive, not analytical.

- **Case studies** that contain no PHI with identifiers do not need to be reviewed by either the Privacy Board or SCRIHS (note: a unique condition itself might be considered identifiable).
- **Case studies** that contain identifiers will be reviewed by the Privacy Board, which will determine the need for authorization.

Research activities with or without identifiers will be reviewed by SCRIHS. For questions contact the SCRIHS office at 545-7602.

CONTINUING REVIEW SUBMISSION FORM

Local Subject Accrual

The Local Subject Accrual section of the Continuing Review Submission Form contains eight text boxes to input information (labeled A-H for the purpose of this guidance). Please note that this section pertains to enrollment at the local site only.

For example, if the study is taking place at SIUSOM, MMC, and SJH. All of those institutions would be considered part of the local site because a member of the study team (listed on the ASP form) is consenting/reviewing charts/etc. Although the study is taking place at three different locations, SCRHS would *not* consider this study to be a “multisite” study. In this type of scenario, in the Local Subject Accrual section you would enter information of subjects from all three locations. However, if the study was taking place at SIUSOM and Washington University in St. Louis, SCRHS would consider that study to be a multisite study because different study teams are involved in conducting the study. In this type of scenario, in the Local Subject Accrual section of the Continuing Review Form, you would enter information about the subjects enrolled at SIUSOM only. Subjects enrolled at Washington University would be entered into another section of the form.

How to Complete the Form

Local Subject Accrual	
<i>Please note that the following questions pertain to enrollment at <u>this site</u> only.</i>	
<p>Since last continuing review, how many subjects have been enrolled/ consented (please include screen fails)? <small>(If this study includes data or specimen collection only, please indicate the number of records reviewed and/or samples collected.)</small></p> <p>(A) <input style="width: 90%;" type="text"/></p> <p>(B) <input style="width: 90%;" type="text"/></p> <p>Provide a summary for each withdrawal since last continuing review:</p> <p>(C) <input style="width: 90%;" type="text"/></p> <p>1. Total number of subjects currently enrolled in study:</p> <p>(D) <input style="width: 90%;" type="text"/></p> <p>2. Total number of subjects that have completed the study:</p> <p>(E) <input style="width: 90%;" type="text"/></p> <p>3. Total number of screen fails since initial approval of study:</p> <p>(F) <input style="width: 90%;" type="text"/></p> <p>4. Total number of withdrawals since initial approval of study:</p> <p>(G) <input style="width: 90%;" type="text"/></p> <p>Total number of subjects consented (including screen fails) since initial approval of study (This should equal the sum of 1, 2, 3 and 4)?</p> <p>(H) <input style="width: 90%;" type="text"/></p>	<p>(I) </p>

In box (A) input the number of subjects that have been enrolled/consented since the last continuing review. This number should also include those who screen failed. If this is the **first continuing** review then enter the number enrolled/consented since the initial review in box (A). If your project is a **data or specimen collection study** then enter the number of records reviewed and/or samples collected. This guidance can also be accessed by clicking the question mark icon (I).

Screen Failure: Generally, a screen failure is someone who does not get enrolled into the study for various reasons, documented during the screening process. Screen failures signed the consent form and may have had screening procedures but did not undergo any other study procedure. Reasons for the participant to fail screening may include, but are not limited to, the participant not meeting inclusion

criteria or meeting exclusion criteria (ineligibility). Your sponsor or protocol may define a screen failure differently.

In box (B) enter the number of withdrawals since the last continuing review. If this is the first continuing review then enter the number of withdrawals since the initial review.

Withdrawn: Generally, a “participant who withdrew” is a participant who stopped the study before completing the full schedule of study visits (including follow-up).

Some protocols may have a variable number of visits and consider participants as completing, rather than withdrawing, in the case of disease progression or similar clinical outcome. In such cases, the protocol definition should be followed, with the withdrawal category reserved for participants who withdrew for other reasons.

There should always be a number in boxes (A) and (B). If no subjects have been enrolled/charts reviewed/specimens collected then enter “0” into the box. Please do not enter N/A.

In box (C) include a summary of each withdrawal since the last continuing review. For example, “Subject 012 was withdrawn because _”. If no subjects withdrew from the study since the last continuing review then you may enter N/A. Please do not leave this box blank.

Boxes (D)-(H) pertain to the total enrollment numbers for the study. These numbers will include **all** subjects and/or data or specimens collected since the study was opened. As instructed in the submission form, the number entered into box (H) will be the sum of boxes (D)-(G).

Example: Study with subject consent

100 people have consented to participate in a study. 10 subjects were enrolled since the last continuing review. Since the last continuing review, 3 subjects withdrew from the study. Out of 100 subjects, 15 screen failed, 10 were withdrawn, 25 complete all intervention and follow-up, 50 are still receiving intervention. The Continuing Review form would be completed as follows:

- A. 10
- B. 3
- C. Subject 3 was lost to follow-up. Subject 74 was withdrawn due to safety concerns as previously reported on Adverse Event submission ref number 004485. Subject 97 stated they no longer wished to participate as the time commitment was too great.
- D. 50
- E. 25
- F. 15
- G. 10
- H. 100

Example: Study with consent - 1st continuing review

10 subjects have been enrolled into a research study which is undergoing its first continuing review. No subjects have been withdrawn. 3 subjects were screen fails. All subjects are still undergoing intervention. The Continuing Review form would be completed as follows:

- A. 10
- B. 0
- C. N/A
- D. 7
- E. 0
- F. 3
- G. 0
- H. 10

Example: Data Collection Study

A retrospective chart review is being conducted. A total of 2000 charts have been reviewed. 100 have been reviewed since the last continuing review. Of the 2000 charts, 1500 did not contain the information needed for the study. The Continuing Review form would be completed as follows:

- A. 100
- B. 0
- C. N/A
- D. 0
- E. 500
- F. 1500
- G. 0
- H. 2000

USE OF ACKNOWLEDGMENTS AND MISCELLANEOUS SUBMISSION FORMS

This submission mechanism provides research personnel an ability to sign-off and submit miscellaneous, study-related items that do not warrant an Amendment Summary. It should be used to submit study-related items that represent no alteration to study conduct/design, patient safety and/or patient willingness to participate. Examples of items that could be submitted using the Acknowledgement/Miscellaneous submission mechanism include:

- Doctor to doctor letters
- Sponsor Correspondence
- General Non-Patient related study information

Additionally, this mechanism can be used, at the direction of SCRIHS Staff, to correctly upload previously reviewed and approved materials into iRIS. For an example, a document was not *stacked* within iRIS or an item was labeled as “Document 1.1” instead of “Document 1.2”.

Please consult with SCRIHS Staff prior to using this mechanism to submit study materials.

PAYMENT FOR IRB REVIEW

SCRIHS requires payment for review of Initial Review Submissions, Continuing Review Submissions, and Sponsor-required Amendments. There is no fee for Federally-funded, state supported, or non-profit funded clinical research. Additionally, there is no fee for SIU Investigator Initiated research or Exempt research.

Please visit the SCRIHS website or contact the SCRIHS office (545-7602) for the most up-to-date information regarding payment.

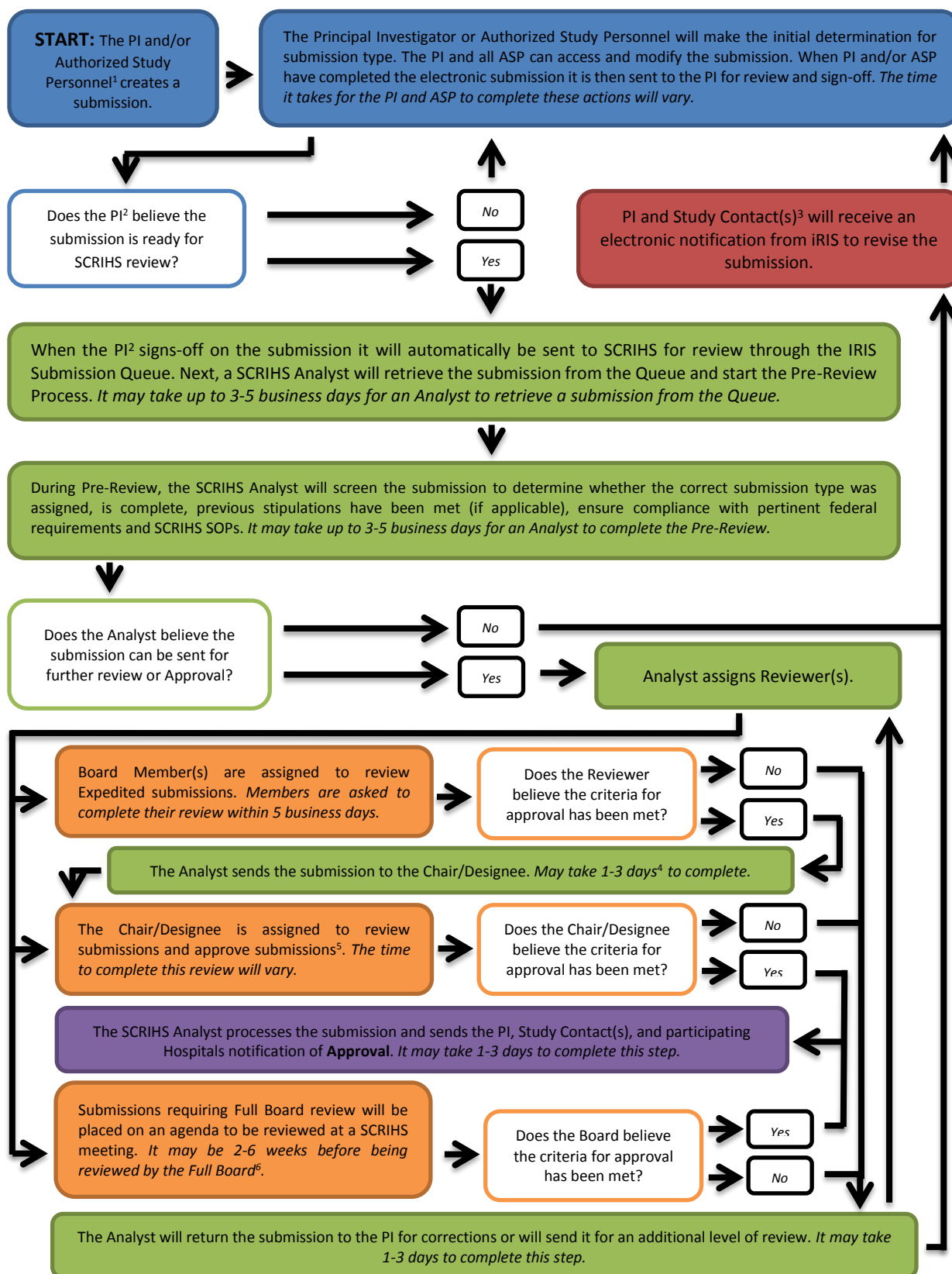
If you are submitting a protocol for IRB review to the SCRIHS, and the Clinical Trial Agreement (CTA) is not executed at the time of submission, SCRIHS requires documentation from the Sponsor stating that the Sponsor agrees to pay the IRB review fee regardless of the CTA negotiation outcome. Without this documentation, the protocol cannot be placed on a SCRIHS meeting agenda for review until the CTA is executed. A letter to the sponsor stating the above is available in Appendix C if needed.

It is highly recommended to submit for IRB review once the CTA has been executed or is very near execution. Submitting too far in advance of an executed CTA can create unnecessary issues for investigators and study staff.

APPENDIX A: ACRONYMS, ABBREVIATIONS, AND INITIALS

AE:	Adverse Event
ASP:	Authorized Study Personnel
CCR:	Center for Clinical Research
CFR:	Code of Federal Regulations
CIP:	Certified IRB Professional
CITI:	Collaborative Institutional Training Initiative
Co-I:	Co-Investigator
CR:	Continuing Review
CRF:	Case Report Form
DSMB:	Data Safety Monitoring Board
DSMP:	Data Safety Monitoring Plan
FB:	Full Board
FDA:	Food and Drug Administration
FWA:	Federal Wide Assurance
HDE:	Humanitarian Device Exemption
HIPAA:	Health Insurance Portability and Accountability Act of 1996
HSBS:	Hospital Sisters Health System
HUD:	Humanitarian Use Device
IB:	Investigator's Brochure
ICF:	Informed Consent Form
IDE:	Investigational New Device Exemption
IND:	Investigational New Drug
IRB:	Institutional Review Board
iRIS:	Integrated Research Information Systems
LAR:	Legally Authorized Representative
MMC:	Memorial Medical Center
OHRP:	Office of Human Research Protections
PHI:	Protected Health Information
PI:	Principal Investigator
QA:	Quality Assurance
QI:	Quality Improvement
SAE:	Serious Adverse Event
SCRIHS:	Springfield Committee for Research Involving Human Subjects
SIUSOM:	Southern Illinois University School of Medicine
SJH:	Saint John's Hospital
SOP:	Standard Operating Procedures
UP:	Unanticipated Problem

APPENDIX B: SUBMISSION FLOW CHART



Key:

- The submission is awaiting an action from the Principal Investigator and/or Authorized Study Personnel.
 - The submission is awaiting an action from the SCRIHS Analyst.
 - The submission is awaiting an action from the SCRIHS Reviewer, Chair, Vice-Chair(s), or Designee
 - The submission has received an outcome of Pre-Review changes requested, Approved with Contingencies, or Table. The PI and/or ASP will need to revise the submission and return it to SCRIHS for review.
 - The submission has been approved by SCRIHS.
1. Authorized Study Personnel are research personnel who are directly involved in conducting research with human subjects. Any ASP can create a submission for a study.
 2. All initial submissions will require the Principal Investigator to review and sign-off on the submission before it is sent to SCRIHS for review. However, submissions that have been returned for corrections do not require the PI to sign-off before it can be returned to SCRIHS for review. It is up to the PI to communicate to ASP if the PI wants to review all submissions, both initial and corrected, prior to submission to SCRIHS.
 3. Study Contacts are ASP that has been designated by the PI to also receive iRIS notifications.
 4. “Days” represents business days. Additionally, these times are approximate and may change based on the submission type and the number of submissions currently under review by SCRIHS.
 5. This review path includes submissions requiring Administrative Sign-Off, Final Approval after being Approved with Contingencies at the Full Board or Expedited level, Approval at the Expedited Level, and Non-Human Subject Research Determinations.
 6. SCRIHS Full Board meetings are held approximately 2-3 weeks following the agenda deadline for the meeting. The gap between agenda deadline and the meeting is to allow SCRIHS staff to screen submissions and allow Board Members adequate time to review submissions prior to the meeting date. Submissions requiring Full Board review must be submitted to SCRIHS on or prior to the agenda deadline and must be ready to be reviewed by the Board. If a study was initially submitted or resubmitted after agenda deadline it will be included on the agenda for the following month’s Full Board meeting.

For example, the agenda deadline for the February Full Board meeting is January 26th. A submission received by January 26th would be considered for the February meeting agenda. If the submission was received after January 26th it would be considered for the March meeting agenda.

Additionally, submissions received by the January 26th agenda deadline, but require corrections will be returned to the PI. The submission would need to be corrected and returned to SCRIHS by the deadline to be included on the February agenda. SCRIHS staff, in some instances, may extend the deadline. The PI will be responsible for the corrected submission being received by the new deadline for the submission

to be included on the February agenda. If the new deadline is missed or if the requested corrections were not made the submission would be considered for the March agenda.

It is highly advisable to submit well in advance of the agenda deadline. This allows the PI and Study Staff time to make any needed corrections that could delay its review at a Full Board meeting.

A list of agenda deadlines and Full Board meeting dates is posted on the SCRIHS website and within IRIS.

APPENDIX C: PAYMENT OF IRB REVIEW FEE LETTER



Effective date: May 22, 2015

Re: Payment of IRB Review Fee

If you are submitting a protocol for IRB review to the Springfield Committee for Research Involving Human Subjects (SCRIHS) at Southern Illinois University School of Medicine, and the Clinical Trial Agreement (CTA) is not executed at the time of submission, SCRIHS requires documentation from the Sponsor stating that the Sponsor agrees to pay the IRB review fee regardless of the CTA negotiation outcome. Without this documentation, the protocol cannot be placed on a SCRIHS meeting agenda for review until the CTA is executed.

Furthermore, if a protocol is reviewed by SCRIHS prior to CTA execution and any language to the protocol or informed consent is adjusted during the CTA negotiation process, an amendment must be submitted to SCRIHS for approval of those language adjustments. An amendment review fee will be charged for any resulting adjustments.

Sincerely,

A handwritten signature in black ink, appearing to read "Krishna Rao".

Krishna Rao, M.D., Ph.D.
IRB Chair
SCRIHS

CLINICALTRIALS.GOV CHECKLIST FOR EVALUATING WHETHER A CLINICAL TRIAL IS AN A.C.T.

Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) Under 42 CFR 11.22(b) for Clinical Trials Initiated on or After January 18, 2017¹

(NOT FOR SUBMISSION²)

Instructions: Answer the following questions to evaluate whether the study is an applicable clinical trial (ACT). Use the accompanying "Elaboration" for additional information to help answer the questions.

Question	Yes	No
1) Is the study interventional (a clinical trial)? <i>Study Type</i> data element is "Interventional"	<input type="checkbox"/>	<input type="checkbox"/>
2) Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)? <i>Studies a U.S. FDA-regulated Device Product</i> data element is "Yes" and/or <i>Studies a U.S. FDA-regulated Drug Product</i> data element is "Yes."	<input type="checkbox"/>	<input type="checkbox"/>
3) Is the study <u>other than</u> a Phase 1 trial of a drug and/or biological product or is the study <u>other than</u> a device feasibility study? For drug product trials, <i>Study Phase</i> data element is NOT "Phase 1" and for device product trials, <i>Primary Purpose</i> is NOT "Device Feasibility."	<input type="checkbox"/>	<input type="checkbox"/>
4) Do ANY of the following apply (is the answer "Yes" to <u>at least one</u> of the following sub-questions: 4a, 4b, OR 4c)?	<input type="checkbox"/>	<input type="checkbox"/>
a) Is at least one study facility located in the United States or a U.S. territory? <i>Facility Location – Country</i> data element is "United States," "American Samoa," "Guam," "Northern Mariana Islands," "Puerto Rico," "U.S. Virgin Islands," or other U.S. territory.		
b) Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)? <i>U.S. Food and Drug Administration IND or IDE Number</i> data element is "Yes."		
c) Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country? <i>Product Manufactured in and Exported from the U.S.</i> data element is "Yes."		

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT that is required to be registered under 42 CFR 11.22.

¹ All pediatric postmarket surveillance studies of a device product as required by U.S. FDA under section 522 of the FD&C Act and for which FDA approved the plan on or after January 18, 2017 meet the definition of an ACT in 42 CFR Part 11.22(b) and are subject to the final rule requirements.

² The outcome generated by the checklist tool will not be retained by the Agency and will not be binding on either the user or any Government agency in any future actions.

Elaboration: Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) Under 42 CFR 11.22(b) for Clinical Trials Initiated on or After January 18, 2017

The final rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) specifies requirements for submitting clinical trial information to ClinicalTrials.gov. The “Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT)” (or “ACT Checklist”) and this elaboration is intended to assist users in evaluating whether a clinical trial or study is considered to meet the definition of an ACT, as specified in 42 CFR 11.22(b), and is subject to “expanded” registration requirements under the final rule.

General Considerations

1. Definition of ACT.

Under the Final Rule, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), two types of ACTs are defined:

- *Applicable device clinical trial:* (1) a prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes); (2) a pediatric postmarket surveillance of a device product as required under section 522 of the FD&C Act (21 U.S.C. 3601); or (3) a clinical trial of a combination product with a device primary mode of action under 21 CFR Part 3, provided that it meets all other criteria of the definition under this part. [Source: 42 CFR 11.10(a); 81 FR 65139]
- *Applicable drug clinical trial:* a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the FD&C Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), where “clinical investigation” has the meaning given in 21 CFR 312.3 and “phase 1” has the meaning given in 21 CFR 312.21. A clinical trial of a combination product with a drug primary mode of action under 21 CFR Part 3 is also an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. [Source: 42 CFR 11.10(a); 81 FR 65139]

2. Determination of ACT.

42 CFR 11.22(b) sets forth an approach for determining whether or not a clinical trial initiated on or after January 18, 2017, meets the regulatory definitions of an applicable device clinical trial and an applicable drug clinical trial by identifying a series of specific criteria and the corresponding ClinicalTrials.gov registration data elements. [Source: 81 FR 65029]

Please note the following caveats:

- **Pediatric Postmarket Surveillance Studies of a Device Product.** While the ACT Checklist is intended to be used to evaluate clinical trials only, all pediatric postmarket surveillance studies involving a device product as required by U.S. FDA under section 522 of the FD&C Act and initiated on or after January 18,

2017, meet the definition of an ACT in 42 CFR Part 11.22(b) and are subject to “expanded” registration requirements under the final rule. *Pediatric postmarket surveillance of a device product* means the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the FD&C Act (21 U.S.C. 360l) about a marketed device product that is expected to have significant use in patients who are 21 years of age or younger at the time of diagnosis or treatment. A pediatric postmarket surveillance of a device product may be, but is not always, a clinical trial. [Source: 42 CFR 11.10(a); 81 FR 65140]

- **Study Start Date on or After January 18, 2017.** The ACT Checklist is intended to be used to evaluate clinical trials initiated on or after January 18, 2017. An ACT is considered to be initiated on the date on which the first human subject is enrolled according to 42 CFR 11.22(a)(3) and is based on the *Study Start Date* data element, defined in part at 42 CFR 11.10(b)(16) as the actual date on which the first human subject was enrolled. As specified in 42 CFR 11.10(a), *enroll or enrolled* means a human subject’s, or their legally authorized representative’s, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR Part 50 and/or 45 CFR Part 46, as applicable. For the purposes of this regulation, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol. [Source: 81 FR 65140]

Specific Considerations

1. Is the study interventional (a clinical trial)?

Study Type data element is “Interventional.” [Sources: 42 CFR 11.22(b)(1)(ii)(A) & (b)(2)(i)]

Study Type is defined in the final rule as the nature of the investigation or investigational use for which clinical trial information is being submitted, e.g., interventional, observational. [Source: 42 CFR 11.10(b)(7); 81 FR 65140-41]

Interventional is defined in the final rule to mean, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes. [Source: 42 CFR 11.10(a); 81 FR 65140-41]

Clinical Trial is defined in the final rule as a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes. [Source: 42 CFR 11.10(a); 81 FR 65139]

2. Does the study evaluate at least one U.S. FDA-regulated drug, biological, or device product?

Studies a U.S. FDA-regulated Device Product data element is “Yes” and/or *Studies a U.S. FDA-regulated Drug Product* data element is “Yes.” [Sources: 42 CFR 11.22(b)(1)(ii)(C) & (b)(2)(iii)]

These data elements are defined as follows:

Studies a U.S. FDA-regulated Device Product means that a clinical trial studies a device product subject

to section 510(k), 515, or 520(m) of the FD&C Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)). [Source: 42 CFR 11.10(b)(38); 81 FR 65143]

A device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act if any of the following is required before it may be legally marketed in the United States: (1) a finding of substantial equivalence under section 510(k) of the FD&C Act, (2) an order under section 515 of the FD&C Act approving a premarket approval application (PMA) for the device product, or (3) an HDE under section 520(m) of the FD&C Act. Device products that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of an IDE is required under section 520(g) of the FD&C Act, non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b), or device products that are exempt from the submission requirements of 21 CFR part 812. [Source: 81 FR 65012]

Regarding combination products, FDA regulations in 21 CFR part 3 specify that the primary mode of action of a combination product is the single mode of action that provides the most important therapeutic action of the intended therapeutic effects of the combination product. A study of a combination product with a device primary mode of action under 21 CFR part 3 would be considered an applicable device clinical trial, provided that it meets all other criteria of the definition under 42 CFR 11.10(a). We note that for such trials, the responsible party must indicate that the trial Studies a U.S. FDA-regulated Device Product. [Source: 81 FR 65014 and 65040]

Points to Consider:

- Device products may be used in clinical trials even though they are not the intervention studied in the clinical trial or the experimental variable of interest in the study. For example, clinical trials of procedures involving surgical device products may not be designed to study the effect of those device products. Therefore, when considering whether a clinical trial Studies a U.S. FDA-regulated Device Product a responsible party should consider whether (a) the study is designed to examine the effect or performance of an FDA-regulated device product or differences in the intended use, for example, variations in frequency of use, method of administration, design specifications, and other characteristics (e.g., used in one or more, but not all, arms in a multi-arm study); and/or (b) at least one pre-specified primary or secondary outcome measure reflects a characteristic, effect, or performance of an FDA-regulated device product (e.g., need for replacement or maintenance of the device). [Source: 81 FR 65040]

Studies a U.S. FDA-regulated Drug Product means a clinical trial studies a drug product (including a biological product) subject to section 505 of the FD&C Act (21 U.S.C. 355) or section 351 of the PHS Act (42 U.S.C. 262). [Source: 42 CFR 11.10(b)(38); 81 FR 65143]

This definition is interpreted to mean that the clinical trial studies a drug that is the subject of an approved NDA [new drug application] or BLA [biologic license application] or that would require an approved NDA or BLA to be legally marketed in the United States. A non-prescription drug product that is or could be marketed under an existing over-the-counter drug monograph (see 21 CFR 330–358) is not considered “subject to section 505 of the [FD&C Act].” [Source: 81 FR 65041]

Regarding combination products, FDA regulations in 21 CFR part 3 specify that the primary mode of action of a combination product is the single mode of action that provides the most important therapeutic action of the intended therapeutic effects of the combination product. A study of a combination product with a drug primary mode of action under 21 CFR part 3 would be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under 42 CFR 11.10(a). We note that for such trials, the responsible party must indicate that the trial Studies a U.S. FDA-regulated Drug Product. [Source: 81 FR 65014 and 65041]

Points to Consider:

- A clinical trial for which the responsible party indicates the Intervention Type to be “dietary supplement” or “genetic” or “procedure” could in fact be an applicable drug clinical trial studying a drug product subject to section 505 of the FD&C Act or a biological product subject to section 351 of the PHS Act. For example, a product otherwise marketed as a dietary supplement could be studied for the treatment of cancer, or a genetic trial could study a gene therapy. [Source: 81 FR 65041]
- A clinical trial may include an FDA-regulated drug product even though the drug product is not a variable of interest. For example, a clinical trial of a device product may involve the surgical insertion of the device product under anesthesia, but the anesthesia drug product is not studied in the clinical trial. In determining whether a clinical trial studies a U.S. FDA-regulated drug product, a responsible party should consider whether (a) the clinical trial is designed to examine the effect of the FDA-regulated drug product(s) or of differences in the intended use, including differences in dosing, frequency of use, or route of administration; and/or (b) at least one of the pre-specified primary or secondary outcome measures reflects a characteristic or effect of the FDA-regulated drug product(s). [Source: 81 FR 65041]

3. Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study?

For drug trials, *Study Phase* data element is NOT “Phase 1” and for device trials, *Primary Purpose* is NOT “Device Feasibility.” [Sources: 42 CFR 11.22(b)(1)(ii)(B) & (b)(2)(ii)]

These data elements are defined as follows:

Study Phase means, for a clinical trial of a drug product (including a biological product), the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, such as phase 2 or phase 3, and in 21 CFR 312.85 for phase 4 studies. [Source: 42 CFR 11.10(b)(6); 81 FR 65141]

Under 21 CFR 312.21(a)(1), a phase 1 study “includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During phase 1, sufficient information about the drug’s pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, phase 2 studies. The total number of subjects and patients included in phase 1 studies varies with the drug, but is generally in the range of 20 to 80.” Under 21 CFR 312.21(a)(2), “[p]hase 1 studies also include studies of drug metabolism, structure-activity relationships,

and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.” Clinical trials that are phase 1 studies under 21 CFR 312.21 are not applicable drug clinical trials. [Source: 81 FR 65015-16]

Points to Consider:

- Although we are aware that the term “phase 0” is used in practice (e.g., to refer to clinical trials that are exploratory in nature and are not designed to evaluate therapeutic or diagnostic intent), any trial that would be referred to as “phase 0” meets the definition of a phase 1 trial under FDA regulations (21 CFR 312.21). [Source: 81 FR 65036]
- Clinical trials that are identified as phase 1/phase 2 trials (i.e., trials with characteristics of both phase 1 and phase 2 studies) are not considered phase 1 studies and may be applicable drug clinical trials if they meet the other specified criteria. [Source: 81 FR 65016]
- A bioequivalence or comparative bioavailability study that falls within the scope of 21 CFR 320.24(b)(1), (2), or (3) shares many of the characteristics of a phase 1 study and is considered to be a phase 1 trial (and, therefore, not an applicable clinical trial) in this rule. [Source: 81 FR 65016]

Primary Purpose means the main objective of the intervention(s) being evaluated by the clinical trial. [Source: 42 CFR 11.10(b)(4); 81 FR 65141]

Regarding the options available under Primary Purpose, “device feasibility” should *only* be selected when a device product is being evaluated for the feasibility of the product or of a test prototype device and not health outcomes. Other options include “treatment,” “prevention,” “diagnostic,” and “screening.” [Source: 81 FR 65035]

Our explanation of this exemption [for “device feasibility” from the definition of applicable device clinical trial] is consistent with FDA’s regulation of devices. FDA published the guidance [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies](#) (October 2013) to address the development and review of IDE applications for early feasibility studies of significant risk devices. For the purposes of the guidance, the guidance defines an “early feasibility study” as a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication. The guidance further defines a “traditional feasibility study” as a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. Section 402(j)(1)(A)(ii)(I) of the PHS Act excludes “small clinical trial[s] to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes” from the definition of “applicable device clinical trial.” The excluded clinical trials described in this statutory definition appear to be consistent with the early feasibility study definition in the guidance, but not with that of the traditional feasibility study, which evaluates preliminary safety and effectiveness information (i.e., for “health outcomes”). Therefore, it is likely that only early feasibility studies would fall within this exclusion under the § 11.10 definition of an “applicable device clinical trial.” [Source: 81 FR 65011]

4. Do ANY of the following apply?

A. Is at least one study facility located in the United States or a U.S. territory?

Facility Location – Country data element is “United States,” “American Samoa,” “Guam,” “Northern Mariana Islands,” “Puerto Rico,” “U.S. Virgin Islands,” or other U.S. territory. [Sources: 42 CFR 11.22(b)(1)(ii)(D)(1) and (b)(2)(iv)(A)]

The *Facility Location* data element is required for each participating facility in a clinical trial and includes information about the country in which participating facilities are located. [Source: 42 CFR 11.10(b)(31)(ii)]

Points to Consider:

- If a clinical study of a device product includes sites both within the United States (including any U.S. territory) and outside of the United States, and if any of those sites is using (for the purposes of the clinical study) a device product that is subject to section 510(k), 515, or 520(m) of the FD&C Act, we would consider the entire clinical study to be an applicable device clinical trial, provided that it meets all of the other criteria of the definition under this regulation. [Source: 81 FR 65013]
- If a clinical investigation of a drug product (including a biological product) includes sites both within the United States (including any U.S. territory) and outside of the United States, and any of those sites is using (for the purposes of the clinical investigation) a drug product or biological product that is subject to section 505 of the FD&C Act or section 351 of the PHS Act, we would consider the entire clinical investigation to be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this regulation. [Source: 81 FR 65015]

B. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)?

U.S. Food and Drug Administration IND or IDE Number data element is “Yes” [Sources: 42 CFR 11.22(b)(1)(ii)(D)(3) and (b)(2)(iv)(C)]

The *U.S. Food and Drug Administration IND or IDE Number* data element provides an indication of whether there is an IND or IDE for the clinical trial. [Source: 42 CFR 11.10(b)(34)]

Points to Consider:

- Device products that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of an IDE is required under section 520(g) of the FD&C Act or non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b). [Source: 81 FR 65012]
- Drug products (including biological products) that are being studied under an IND are considered “subject to section 505 of the FD&C Act” both because (in most situations) the drug product being studied would need an approved NDA or licensed BLA to be marketed legally, and because INDs are issued by FDA pursuant to the authority in section 505(i) of the FD&C Act. [Source: 81 FR 65014]

- Furthermore, if a sponsor chooses to obtain an IND (issued under section 505 of the FD&C Act) for a clinical investigation of a drug product (including a biological product) that is not otherwise subject to section 505 of the FD&C Act or section 351 of the PHS Act, the sponsor, in so doing, agrees to regulation under section 505 of the FD&C Act, and that clinical investigation thus will be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. [Source: 81 FR 65015]

C. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?

Product Manufactured in and Exported from the U.S. data element is “Yes” [Sources: 42 CFR 11.22(b)(1)(ii)(D)(2) and (b)(2)(iv)(B)]

Product Manufactured in and Exported from the U.S. element means that any drug product (including a biological product) or device product studied in the clinical trial is manufactured in the United States or one of its territories and exported for study in a clinical trial in another country. [Source: 42 CFR 11.10(b)(15)]

Points to Consider:

- If the device product is manufactured in the United States or any U.S. territory, and is exported for study in another country (whether it is exported under section 801(e) or section 802 of the FD&C Act), the device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. If the device product is manufactured outside of the United States or its territories, and the clinical study sites are all outside of the United States and/or its territories, the device product would not be considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. A device product that is packaged and/or labeled in the United States would be considered “manufactured” in the United States subject to section 510(k), 515, or 520(m) of the FD&C Act. [Source: 81 FR 65013]
- If the drug product (including a biological product) is manufactured in the United States or any U.S. territory, and is exported for study in another country under an IND (whether pursuant to 21 CFR 312.110 or section 802 of the FD&C Act), the drug product or biological product is considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act (as applicable), and the clinical investigation may be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. A drug product that is packaged and/or labeled in the United States would be considered “manufactured” in the United States subject to section 505 of the FD&C Act or section 351 of the PHS Act. [Source: 81 FR 65015]