Marshfield Clinic

Informed Consent for Research

1. SCOPE

1.1. System Wide

2. DEFINITIONS & EXPLANATIONS OF TERMS

2.1. **Human Subject**: A living individual about whom an investigator conducting research obtains: 1) data through interaction with the individual or 2) identifiable , private information

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

2.3. Research :

- A systematic investigation including research development, testing and evaluation, designed to contribute to generalizable knowledge
- The FDA defines research as "[a]ny experiment that involves a test article and one or more human subjects that is either subject to requirements for prior submission to the Food and Drug Administration under section 505(i), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration as part of an application for a research or marketing permit."

2.4. **Consent Document:** A structured, written description in lay terms of relevant research project information. The written consent document is not "consent" itself; it is the "record" of what has been communicated to a prospective subject. It is the document that ensures all regulatory elements are present and communicated to a potential subject. When signed by the potential subject, the consent document is a record of the receipt of research-related information by the subject. It also serves as reference material for the subject as the research project progresses. It is not legally binding and the subject may choose to withdraw consent at any time.

2.5. **Informed Consent (IC):** An ongoing process of communication between the subject and the investigator or designee. Informed consent is a continual process by which a subject, after having been informed, voluntarily confirms his or her willingness to participate in a research project and can demonstrate understanding of all aspects of the research project that are relevant to the subject's decision to participate.

2.6. **Legally Effective Informed Consent:** A subject has been provided enough information to make a decision; the subject has the capacity to make a decision; the subject understands the consequences of his or his decision; and the subject can communicate the decision.

2.7. **Electronic Informed Consent (eIC or e-consent):** includes many varieties and combinations of systems and processes to be used to convey study information to participants and to obtain and document informed consent. eIC processes could include: websites, podcasts, video, audio, text and graphics, iPad, tablets etc.

Generally, the use of an electronic document which is printed and used in a hard-copy form is not considered eIC.

2.8. **Digital Signature Capture:** The process of collecting a signature to document informed consent for research in a digital form that is incorporated in and attached to or associated with an electronic document. This process utilizes an electronic device, such as a tablet, while the subject, and/or subject's representative, is in the physical presence of the person authorized to obtain consent.

2.9. **Personal Identification Number (PIN):** a number allocated to an individual to validate electronic transactions. PINs are usually used in conjunction with usernames or other passwords.

3. PROCEDURE BODY

This document outlines the requirements for obtaining informed consent from subjects to participate in human subjects research at institutions from whom Marshfield Clinic Research Foundation Institutional Review Board (MCRF IRB) serves as the IRB of record. It incorporates the informed consent requirements outlined in the Department of Health and Human Services (DHHS) regulations (45 CRF 46), DHHS Office for Human Research Protections (OHRP) guidance, Food and Drug Administration (FDA) regulations (21 CFR 50), and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

A fundamental ethical principal of the Belmont Report, respect for persons, requires that prospective subjects "be given the opportunity to choose what shall or shall not happen to them." Legally effective informed consent is a process that involves disclosing information that potential subjects need to make an informed decision, understanding and comprehension potential subjects need to make an informed decision, understanding and comprehension of what has been disclosed and voluntariness of the decision whether or not to participate.

3.1. Regulations and Guidance

a. DHHS

- 45 CFR 46.116 and 46.117 outline the informed consent requirements for human subject research
- 46 CFR 46 Subpart B, C, and D contain special consent provisions for research involving pregnant women, fetuses, children and prisoners
- Institutional Review Boards (IRBs) reviewing research have the authority to waive the requirement to obtain informed consent (45 CFR 46.116 (c,d), or to waive the requirement for written documentation of informed consent (45 CFR 46.117(c)) if certain requirements are met.
- DHHS Office for Human Research Protections (OHRP) has issued several guidance documents relevant to informed consent, including:
  - Exculpatory Language in Informed Consent Documents: Examples of Acceptable and Unacceptable Language (OPRR Letter, 1996) http://www.hhs.gov/ohrp/policy/exculp.html

- Informed Consent Checklist (1998)
  http://www.hhs.gov/ohrp/policy/consentckls.html
- Informed Consent FAQ (OHRP website)
  http://www.hhs.gov/ohrp/policy/consentfaqsmar2011.pdf
- Informed Consent, Legally Effective and Prospective Obtained (OPRR Letter, 1993) http://www.hhs.gov/ohrp/policy/hsdc93-03.html
- Informed Consent: Obtaining and Documenting Informed Consent of Non-English Speakers (OPRR Memo, 1995)
  http://www.hhs.gov/ohrp/policy/ic-non-e.html
- Informed Consent Tips (1993)
  http://www.hhs.gov/ohrp/policy/ictips.html
- IRB Review of Protocol & Informed Consent Changes in Cooperative Group Protocols (OHRP Memo to NCI, 2008)
  http://www.hhs.gov/ohrp/policy/consent/nci200870929.html

b. FDA

- Regulations at 21 CFR 50 outline the informed consent requirements for research involving FDA-regulated products
- FDA has also released guidance documents pertaining to informed consent, including:
  - A Guide to Informed Consent – Information Sheet (1998), updated draft (July 2014)
    http://www.fda.gov/regulatoryinformation/guidances/ucm126431.htm
  - Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (2006)
    http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071265.pdf
  - Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c) (February 2012)
    http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm291085.pdf
  - Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers (draft 2015)
    http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm436811.pdf

- FDA regulations at 21 CFR 50.24 and confirming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814 provide a narrow exception to the informed requirements prior to enrollment in emergency research. Since such emergency research is not conducted locally, MCRF IRB is not in a position to waive informed consent under those provisions.

3.2. Informed Consent Requirements

a. General rule is that legally effective informed consent must be obtained from every subject, or from his or her legally authorized representative, before he or she can participate in human subjects research.

b. Legally effective informed consent involves a process that continues during the research, requiring ongoing communication between investigators and subjects.

c. MCRF IRB has the authority to waive the requirements to obtain informed consent and waive the requirement to document informed consent, but only if certain requirements are met (see sections 3.5 and 3.6 below).

d. Informed consent documents must contain all required elements unless waived by the IRB, or unless a short form is used pursuant to the document, "Informed Consent of Non-English Speaking Subjects":

- Required Informed Consent Elements are as follows whether a paper copy or an (eIC):
  - Statement that the study involves research
  - Explanation of the purpose of the research
  - Statement that the subject's participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject may otherwise be entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which subject may otherwise be entitled;
  - Expected duration of the subject's participation
  - Procedures to be followed
  - Procedures which are experimental/investigational
  - Any reasonably foreseeable risks or discomforts to the subject
  - Any benefits to the subject or to others, which may reasonably be expected from the research
  - Appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject. If no alternatives exist, the document should state that there are no alternatives except to not participate in the research
  - The extent, if any, to which confidentiality of records identifying the subject will be maintained, and if applicable, whether the research subject may be subject to audit or inspection, identifying the entities that will have access to the subject's record (e.g., FDA, National Institutes of Health (NIH), sponsors, or contract research organizations.
  - Whether any compensation will be offered and whether any medical treatment is available if the subject incurs a study-related injury
  - The person to contact with questions about the research and the subject's rights, and the person to contact should the subject incur a research related injury.

- If the study meets the FDA definition of "applicable clinical trial," and is initiated on or after March 7, 2012 the following statement: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at anytime."
- If the research is pharmaceutical industry-sponsored research aiming to comply with ICH GCP Guidelines, an explanation of the subject's responsibilities and rights (ICH E6 4.810(e)), and the risks and benefits of any procedures or courses of treatment that are alternatives to the research intervention (ICH E6 4.810(i))

☐ Informed Consent document must also include the following additional elements as applicable:

- Statement to treatment or procedure involved in the research may involve unforeseeable risks to the subject, or to an embryo or fetus if the subject is, or may become pregnant
- The circumstances under which a subject's participation may be unilaterally terminated by an investigator
- Any additional costs to the subject that may result from participation
- The consequences of a subject's decision to withdraw from the research, and procedures for orderly termination of the subject's participation
- Statement that the subject will be informed of any significant findings made in the course of the research that may influence his or her willingness to continue participation
- Approximate number of subjects involved in the research
- Study treatments, and the probability of random assignment to the placebo, or to each treatment
- Statement explaining Genetic information Non-Discrimination Act (GINA) protections, if the research involves a genetic component

e. Informed consent document cannot include exculpatory language that makes, or attempts to make, subjects or their legally authorized representatives waive any legal rights, or release the investigator, the sponsor, the institution or its agents from liability for negligence.

f. Electronic Informed Consent (eIC)

eIC includes many varieties and combinations of systems and processes to be used to convey study information to participants and to obtain and document informed consent. eIC may take place with the study personnel and participants at the same site, or participants may be located remotely.

☐ Process for obtaining electronic consent **can be considered if**:

- Subjects are 18-years of age or older

- Subjects under 18, who require assent are located at the same site as the study personnel and with their legally authorized representative (not remotely)
- Subjects are NOT pregnant women, fetuses, neonates, Illiterate, legally blind, unable to speak or write or are non-English speaking
- The electronic consent form contains all elements of informed consent required by FDA regulations (50.25) as listed above in section 3.2(d).
- The eIC programs allow the user to proceed forward or backward within the system or stop and continue at a later time.
- Informed consent process takes place at study site or remotely

  If at study site then study personnel must verify personally the subject's identification, present the eIC content, answer questions about the material, have follow-up discussions and witness the signing of the eIC, with the subject.

  If remote then all interactive responses by subjects, witnesses, or other parties involved should be documented electronically using software systems to ensure responses cannot be altered. In addition, if the consent process is not personally witnessed by study personnel, the computerized system should include a method to ensure that the person signing the informed consent is the subject who will be participating in the research or the subject's LAR.
- There is a mechanism for participants to ask questions and receive answers prior to signing the eIC to participate in the study

  May be accomplished via telephone, electronic messaging, videoconference, live chat, etc.

  Participants must be informed of how and when they will receive answers to their questions and how to contact an appropriate individual with questions and to report research-related injury.
- Investigator or designee is able to assess participant understanding of the provided information
- Investigator provides a way that participant receives amended eIC and is given adequate opportunity to ask questions about any amendments
- Subjects should be able to print a hard copy of the eIC form. If e-copy offered to subjects, they need to be informed of risk of storing or viewing on a personal electronic device (IED).
- The computerized system/technology that supports the eIC is secure with restricted access and should include methods to ensure confidentiality regarding the subject's identity, study participation and personal information after informed consent has been obtained
- The system securely maintains an archive of all signed versions of the eIC form for all subjects

- Investigators considering electronic consent may wish to obtain IRB review/approval of the consent document **text** prior to developing the electronic consent tool. Revisions based on IRB feedback are likely easier to implement before programming and animation has begun.
- If waiver of consent is requested by the PI, the PI must submit the "Waiver or alteration of Informed Consent form, which must be approved by the IRB. (This is part of the IRB Application - New Research.)

g. Verbal Presentation

- The PI, or an individual deemed qualified by the PI, must verbally present the content of the informed consent document and any supplementary information approved by the IRB to subjects or their legally authorized representatives. Verbal presentation is an active process of sharing information and giving the subjects or legally authorized representatives, opportunity to read the document(s), ask questions and seek clarification before agreeing to participate and signing the document or information sheet.

h. Signatures and Documentation

- The PI is responsible for obtaining the signatures of subjects or legally authorized representatives on the written informed consent document or short informed consent form, as well as that of the person who obtained informed consent
- When written informed consent is required (waiver of documentation is not being requested), the use of electronic (including digital) signature is permitted, provided the electronic signature is in compliance with applicable FDA regulations. In such cases, the electronic signature is considered by FDA to be trustworthy, reliable, and generally equivalent to handwritten signatures executed on paper (see 21 CFR part 11, subpart A (11.1)(a)).
- A Full electronic signature is an option as long as they are legally valid within the jurisdiction where the research is conducted, provided that the Investigator and IRB considers the following:
  - How the signature is created
  - If the signature can be shown to be legitimate
  - If the consent document can be produced in hard copy for review by the potential participant
- Consent other than full signature can take several forms. (i.e. participant checks a box to indicate consent or a "PIN" number is provided). DHHS and FDA regulations state that an IRB must require documentation of informed consent as required by 45 CFR 46.109(c) and 21 CFR 56.109(c)
- Remote eIC processes without any in-person interaction with the research team must include a method to ensure that the person signing the informed consent is the subject or subject's legally authorized representative who will be participating in the research study

- The PI must retain signed informed consent documents for six years past the study's termination date

3.3. IRB Review of Informed Consent Documents and Process

a. For each study reviewed by MCRF IRB, the IRB has the authority to review, require modifications to, and approve the process proposed by investigators for obtaining informed consent, as well as the documents to be used.

b. When a study is submitted for IRB review, the Principal Investigator (PI) must submit a description of a proposed informed consent procedure, along with a proposed written informed consent document (subject to section 3.5 and 3.6).

c. MCRF IRB shall give final approval of any written informed consent document prior to study activation.

d. Short Form Informed Consent Process

- For certain research, MCRF IRB may approve the use of a short form informed consent process whereby the required informed consent elements listed at 3.2.d are presented orally to subjects or their legally authorized representatives. See the document, "Informed Consent of Non-English Speaking Subjects" for information on the short form process.

e. Revisions Require IRB Approval

- Any proposed changes or revisions to an informed consent document, summary document, short form or to the process for obtaining informed consent as described to, and approved by the IRB must be submitted for IRB approval before any revised documents or processes can be used.

3.4. Additional Requirements Related to Consent from Vulnerable Subjects

a. Pregnant Women, Fetuses and Neonates

- For DHHS-funded research involving pregnant women, fetuses and neonates, there are special consent provisions in 45 CFR 46 Subpart B that must be met. Requirements set forth in the document "Vulnerable Populations" also must be followed.

b. Minor Children

- MCRF IRB in accordance with 45 CFR 46 Subpart D and 21 CFR 50 Subpart D, shall determine whether assent or any minor subjects is required. The PI must follow the procedures outlined in "Assent of Children" and adhere to the assent and permission requirements for enrolling children in the study as determined by the IRB

c. Minor Children who Reach Age of Adulthood During Research

- Written informed consent shall be obtained from any subject who was a minor when he or she was enrolled in research, but who subsequently reaches the legal age of consent (18) while still participating.
  - If the research involves ongoing interactions or repeated interventions requiring the subject to regularly visit, written informed consent must be obtained at the study visit following the date on which he or she

reaches the legal age of consent, unless the IRB approves an alternative process.

- A copy of the consent must be given to the subject, along with the IRB-approved document, "IRB Consent Addendum-Subjects Turning 18". The subject must sign the addendum in order to continue participation.
- When subject no longer attends study visits, or when the research does not include study visits, written informed consent may be obtained by mailing the subject a copy of the consent document signed by the subject's parent or guardian, along with the IRB-approved "IRB Consent Addendum-Subjects Turning 18" and an IRB approved cover letter. The subject must return the signed addendum to continue participation.
- Consent must be obtained within one year of the subject reaching the legal age of consent in order to continue involvement. If the subject chooses not to continue participation, data collected to that point may be retained and used for IRB-approved research purposes (see document, "Withdrawal of Subjects from Research", for additional guidance).

d. Illiterate or Legally Blind Subjects

- Investigators must follow the procedures set forth in "Informed Consent of Illiterate or Legally Blind Research Subject" to obtain informed consent for potential subjects who are illiterate or legally blind.
- When such potential subjects are less than 18, PIs must also follow the process in "Assent of Children". The assent form must be read to the minor subject, who must make his or her mark on the form in a witness' presence.
- At the time of continuing review, MCRF IRB will ask for the number enrolled who could not read, a summary of communication problems encountered during the consent process as the research progressed, and the manner in which problems were resolved. Based on the percentage of such subjects enrolled and on the research risks and complexity, the IRB may determine that further protections are necessary for future subjects.

e. Subjects Physically Unable to Speak or Write

- If a potential subject can understand spoken English, but is unable to speak or write, the PI must consult the Office of Research Integrity & Protections to determine how legally effective informed consent will be best obtained and documented.

f. Non-English Speaking Subjects

- The procedures outlined in the document "Informed Consent of Non-English Speaking Subjects," must be followed to obtain informed consent from potential subjects who speak language other than English.
- Investigators may not enroll any subject if they feel a language barrier is so significant that legally effective informed consent cannot be obtained.
- For such potential subjects who are less than 18, PIs must also follow the requirements in "Assent of Children." The assent form must make his or her mark on the form in a witness' presence.

3.5. Waiver or Alteration of the Informed Consent Requirement

a. For certain research, MCRF IRB can approve an informed consent process that does not include informed consent (waiver), or which alters some or all of the elements of informed consent (alteration) (see 45 CFR 46.116 and .117 and 21 CFR 50.24).

b. For research involving drugs, devices or biologics regulated by FDA, the IRB will not waive or alter the informed consent requirement, including parental permission for FDA regulated research involving minor subjects, except as allowed by FDA guidance, "Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are not individually identifiable."

c. For research not regulated by FDA, MCRF IRB can approve a waiver or alteration of the informed consent requirement if either:

- The research involves no more than minimal risk to the subjects; the waiver or alteration will not adversely affect the rights and welfare of the subjects; the research could not practicably be carried out without the waiver or alteration; and whenever appropriate, the subjects will be provided with additional pertinent information after participation; or
- The research is to be conducted by, or subject to, the approval of state or local government officials, and is designed to study, evaluate or otherwise examine:
  - Public benefit or service programs;
  - Procedures for obtaining benefits or services under those programs
  - Possible changes in or alternatives to those programs or procedures, or
  - Possible changes in methods of levels of payment for benefits or services under those programs, and the research could not practicably be carried out without the waiver or alteration.
- MCRF IRB al can allow for deviation from the informed consent requirement if it determines that the research is exempt from IRB review (see document, "Exempt Projects Review of")
- In order for MCRF IRB to consider a request for a waiver or alteration of the informed consent requirement, the PI must submit one of the following:
  - A completed "IRB Waiver of Consent/Authorization" form; or
  - A request for the waiver by completing the appropriate sections of an IRB Application form

3.6. Waiver of Documentation of Informed Consent

a. For certain research, MCRF IRB can approve a request to waive the requirement to document informed consent with signatures of the subjects or their legally authorized representatives on informed consent documents. In this scenario, informed consent is still provided verbally.

b. For research not regulated by FDA, MCRF IRB can waive documentation of informed consent if it finds, either:

- The research presents no more than minimal risk of harm to subjects, and involves no procedures for which written consent is normally required outside of the research context; or
- The only record linking the subject and the research would be the consent document, and the principal risk to the subjects is potential harm resulting from a breach of confidentiality. Under such circumstances, investigators shall ask each subject whether he or she would like to avoid documentation linking them with the research, and the subject's wishes will govern.

c. For research regulated by FDA, MCRF IRB can waive documentation of informed consent if the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is generally required outside of the research context (21 CFR 56.109 © (1)).

d. In order for MCRF IRB to consider a request for waiver of documentation of informed consent, the PI must submit one of the following:

- A completed "IRB Waiver-Documentation of Consent and Authorization" form; or
- A request for waiver by completing the appropriate sections of an IRB Application- New Research form

e. Even if MCRF IRB waives the documentation requirement, it may still require subjects to be provided with a written statement summarizing the research, or be read script over the telephone.

4. ADDITIONAL RESOURCES

4.1. IRB Forms for submission: (located in Policy Handbook Library [FORMS])

- IRB Consent Template
- IRB Assent Non-therapeutic Research Minor subject Age 7 and Above
- IRB Assent Therapeutic Research Minor subject Age 12 and Above
- IRB Addendum for Reconsenting Subjects Who Turn 18
- IRB Waiver of Consent/Authorization Form
- IRB Waiver – Documentation of Consent and Authorization

4.2. References:

- Assent of Children
- Exempt Projects, Review of
- Expanded Access to Investigational Drugs, Biologics or Devices
- Informed Consent of Illiterate or Legally Blind Research Subjects
- Informed Consent of Non-English Speaking Subjects
- Vulnerable Populations
- Withdrawal of Subjects from Research

5. DOCUMENT HISTORY

Version No.	Revision Description
1.0	New Document in Document Control System transferred from Policy & Handbook Library - #1781.2. Added definitions, DHHS & FDA guidance documents updated and their website links, electronic informed consent process and signature requirements, DHHS and FDA guidance documents updated. Formatting and administrative changes also.
2.0	Add hyperlinks to IRB Forms for submission and other applicable policies referenced in this document.

6. DOCUMENT PROPERTIES

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