1. PURPOSE

To define the special conditions for treating a patient under an expanded access IND, which includes the informed consent, serious adverse event reporting, and changes to the treatment plan.

2. INFORMED CONSENT PROCESS

Once the manufacturer, FDA, and IRB have signed off on the treatment, the patient must still provide consent for the use of an investigational agent. The process of discussing the investigational treatment and obtaining patient consent is referred to as "informed consent," and has requirements above and beyond those of a standard procedure consent. These requirements are defined in 21 CFR Part 50 Subpart B, Informed Consent of Human Subjects. Although expanded access treatment is not research, the research standards are used to ensure patient protection.

2.1 General Process

2.1.1 For non-emergency treatment, an IRB-approved consent form should be used. This will ensure that the consent document contains all necessary elements.

2.1.2 The physician should review the consent document with the patient. Care should be taken to explain the treatment in detail, including the expectation for use of an investigational agent and its risks and uncertainty of the effectiveness of the product.

2.1.2.1 If the patient cannot participate in the discussion, a legally authorized representative (LAR) can participate and sign the consent on behalf of the patient.

2.1.2.2 If the patient does not read or speak English, additional procedures may be required. You should consult your institution for specific guidance.

2.1.3 The physician should answer any and all questions that the patient has.

2.1.4 The patient should be given as much time as desired to think about their participation in the treatment.

2.1.5 Once all questions have been answered and the patient has agreed to treatment, the patient (or LAR if applicable) and the physician should both sign the informed consent form in order to document their conversation.

2.1.5.1 A copy of the signed form should be provided to the patient.

2.1.5.2 A note should be added to the patient's record that the conversation took place and that an informed consent document was signed.

2.1.5.3 The original paper copy of the informed consent form should be kept by the physician per institutional guidelines.

2.2 Emergency Treatment

2.2.1 Even in emergency cases, it is important to follow as much of the informed consent process as possible. However, it is understood that some steps (such as the use of an IRB-approved consent form) may not be feasible.

2.2.1.1 An informed consent form that includes all the required elements (See Reference Document 6.1) should be used if at all possible, even if it is not approved by the IRB.

2.2.1.2 If there is not time to create an appropriate informed consent form (e.g. patient is coding and needs the product immediately), the physician and patient should still have a discussion of the treatment, risks and benefits. This discussion should be documented in such a way that both parties are able to sign to acknowledge the discussion.

2.2.1.3 If it is not possible to have this discussion, because the patient is not awake/competent and a legally authorized representative is not available, a second opinion from an independent physician should be documented before treatment can proceed. This should be provided as a letter to the FDA and IRB.

3. SERIOUS ADVERSE EVENTS

Physicians are required to monitor patients who receive treatment through expanded access for adverse events. An "adverse event" is any negative health outcome that the patient experiences. In particular, physicians may have reporting requirements related to adverse events that are:

- Suspected to be related to the treatment
- Serious in nature, which means they result in:
  - Death
  - A life threatening experience
  - In patient hospitalization, or prolongation of existing hospitalization
  - Persistent or significant disability or permanent damage
  - Congenital abnormality or birth defect
  - Other important medical events
- Unexpected given the known (or expected) risks of the drug or device, as listed in the informed consent, Investigator's Brochure, or label

The most critical type of adverse events are those that are suspected, unexpected, and serious. These are referred to as SUSARs (Serious, Unexpected, Suspected Adverse Events).

The most common type of adverse event that requires reporting are those that are serious, whether or not they are related. These are referred to as SAEs (Serious Adverse Events).

3.1 Reporting Timelines

3.1.1 Most drug manufacturers require reporting of SAEs within 24 hours of becoming aware of the SAE, whether or not they are related to the treatment.

3.1.2 Consult the manufacturer directly for specific reporting requirements.

3.1.3 Most institutions require reporting of SAEs that are related to treatment to the IRB in a certain timeframe, usually 14 days.

3.1.4 SUSARs are required to be reported to the FDA as part of the IND within 15 calendar days (7 days if fatal). These should also be reported to the IRB per the appropriate institutional timeframe.

3.1.4.1 MedWatch 3500A form should be used to report these events.

3.1.5 Non-serious adverse events typically do not require individual reporting, but they should be tracked and recorded in the patient's medical record.

3.1.6 Any related adverse events that have not been individually reported should be included in the FDA annual report and/or IRB continuing review.

4. CHANGES TO THE TREATMENT PLAN

As Expanded Access is considered to be clinical care and not a research protocol, physicians are expected to use their clinical judgement in determining treatment for the patient. However, if significant changes to the patient's treatment are planned from those that were originally submitted, the physician is required to submit those changes to the FDA as part of the IND. Submission to the FDA can be done by submitting an amendment with a changed protocol (if available), a letter detailing the changes, and a FDA Form 3926 with "Change in Treatment Plan" selected under Item #9.

For IRB submission, follow the local institutional process.

5. END OF TREATMENT

Stopping the patient's treatment is also a change that requires reporting. The physician is required to submit a summary of treatment, which can take the form of a letter, to the FDA along with an FDA Form 3926 (Item #9 should have "Summary of Expanded Access Use (treatment completed)" selected). In this letter, the physician should also ask the FDA to "withdraw" (close) the IND, which will end their reporting responsibilities.

IRB submission is also typically required. Follow the instructions for the local institutional process.

6. REFERENCE DOCUMENTS

6.1 Example Text for Health Record Note for Informed Consent

@NAME@ has signed the informed consent form for the following research study on {date:} at [TIME].
Study Title: The ---- Study
Study Sponsor: -----
Sponsor-assigned protocol number: -----
Institution-assigned protocol number: Pro00-----
The study was explained in detail and all elements of the informed consent form were discussed with {mr ms dr:----} @LNAME@. {he/she/they:-----} was given adequate time to review the informed consent form and consider participation in this study. {mr ms dr:-----} @LNAME@ was given the opportunity to ask questions and all questions were answered to {his/her:-----1} satisfaction.
No study procedures were performed prior to written informed consent. {mr ms dr:-----} @LNAME@ will be given a copy of the signed and dated document and the original will be placed in the study file. A signed copy will be included in the electronic medical record.
The informed consent form this participant signed is the current IRB-approved consent form with a reference date of {date:----}.

6.2 Withdrawal Letter Template