§46.111 Criteria for IRB Approval of Research

REFERENCES

- 45 CFR 46 HHS Common Rule
- 21 CFR 56 for FDA regulated research
- 21 CFR 50 informed consent requirements for FDA regulated research
- Policy 204 Levels of IRB Review and Criteria for IRB Approval of Research

Criteria for Approval

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) **Risks to subjects are minimized**: (i) By using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) **Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.** In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) **Selection of subjects is equitable**. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) **Informed consent will be sought** from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) **Informed consent will be appropriately documented** or appropriately waived in accordance with, and to the extent required by §46.117

(6) When appropriate, the research plan makes adequate provision for **monitoring the data collected to ensure the safety of subjects**.

(7) When appropriate, there are adequate provisions to **protect the privacy of subjects and to maintain the confidentiality of data**.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Basic Elements of Informed Consent

REFERENCES

- 45 CFR 46 HHS Common Rule
- 21 CFR 56 for FDA regulated research
- 21 CFR 50 informed consent requirements for FDA regulated research
- Policy 301 Informed Consent
- Consent FAQs – Look under "Everything you need to know about consent"
- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

DEFINITIONS

Clinical trial (as defined by the *NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information*) - **"**A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes" and is broader than the statutory definition of an "applicable clinical trial."

Coercion - An overt or implicit threat of harm that is intentionally presented by one person to another in order to obtain a certain outcome.

Legally Authorized Representative (LAR) (2018 Common Rule) – An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research. (45 CFR 46.102(i))

Legally effective – Informed consent is legally effective if it is both obtained from the subject (or the subject's legally authorized representative) and documented in a manner that is consistent with the US Department of Health and Human Services (HHS) protection of human subjects regulations, FDA regulations, and with applicable laws of the jurisdiction in which the research is conducted.

Undue Influence - An offer of an excessive or inappropriate reward or other overture in order to obtain a certain outcome.

General Requirements of Informed Consent

Unless waived or altered as approved by the IRB, informed consent must be legally effective and comply with Common Rule requirements as described in 46.116, 46.117, applicable subparts of 45 CFR 46 (B, C and D), and NIH policy for consenting adults lacking capacity to consent or for staff participating in NIH research. In addition, for FDA-regulated research informed consent

must comply with requirements as described at 21 CFR 50 Subparts B and D and in further detail below.

- Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative. (46.116(a)(1)/50.20)

- An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence. (46.116(a)(2)/50.20)

- The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative. (46.116(a)(3)/50.20)

- The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information. (46.116(a)(4) *2018 Common Rule only*)

- Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. (46.116(a)(5)(i) *2018 Common Rule only*)

- Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate. (46.116(a)(5)(ii) 2018 Common Rule only)

- No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. (46.116(a)(6)/50.20)

Basic Elements of Informed Consent

When seeking informed consent, the following information shall be provided to each subject or the legally authorized representative (LAR):

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental (46.116(b)(1)/50.25(a)(1))

- A description of any reasonably foreseeable risks or discomforts to the subject (46.116(b)(2)/50.25(a)(2))

- A description of any benefits to the subject or to others that may reasonably be expected from the research (46.116(b)(3)/50.25(a)(3))

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (46.116(b)(4)/50.25(a)(4))

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. (46.116(b)(a)(5)) *Additionally for FDA-regulated research*: "that notes the possibility that the Food and Drug Administration may inspect the records." (50.25(a)(5))

- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained (46.116(b)(6)/50.25(a)(6))

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject (46.116(b)(7)/50.25(a)(7))

- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (46.116(b)(8)/50.25(a)(8))

- One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: (46.116(b)(9) *2018 Common Rule only*)

    - A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

    - A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional Elements of Informed Consent

In addition to the basic elements of consent described above, one or more of the following elements of information, when appropriate, shall also be provided to each subject or the LAR:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable (46.116(c)(1)/ 50.25(b)(1))

- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent (46.116(c)(2)/ 50.25(b)(2))

- Any additional costs to the subject that may result from participation in the research (46.116(c)(3)/ 50.25(b)(3))

- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject (46.116(c)(4)/ 50.25(b)(4))

- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject (46.116(c)(5)/ 50.25(b)(5))

- The approximate number of subjects involved in the study (46.116(c)(6)/ 50.25(b)(6))

- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit (46.116(c)(7) *2018 Common Rule only*)

- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions (46.116(c)(8) *2018 Common Rule only*): and

- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen). (46.116(c)(9) *2018 Common Rule only*)

Additional FDA Requirements for Informed Consent

In addition to above, the FDA also requires the following:

- A description of procedures which are experimental.

- A statement which identifies the test article as "investigational" or "not approved by the FDA," if the test article under study is not FDA-approved for the proposed use. OR If the test article is approved, include a statement as whether it is being used according to its labeled indications. (21 CFR 50.25(a)(1))

- Make no claims which state or imply, directly or indirectly, that the test article is safe or effective for the purposes under investigation or that the product is in any way equivalent or superior to another product. (21 CFR 312.7(a)/ 21 CFR 812.7(d))

- NIH PIs must include the statement below word or word for either clinical trial (as defined above) informed consent documents as required by the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, or for "applicable clinical trials," as defined by statute at 42 U.S.C. 282(j)(1)(A):

  "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Waiver or Alteration of Informed Consent & Waiver of Documentation of Consent

REFERENCES

- 301 - Policy - Informed Consent
- 46.116 and 46.117/ 50.23, 50.24 and 56.109(c)
- Guidance for Sponsors, Investigators, and Institutional Review Boards - IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects
- Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research

The IRB only may waive or alter elements of informed consent or waive documentation of informed consent when the IRB determines and documents that the requirements for waiver or alteration are met, as specified in 45 CFR parts 46.116 and 46.117 or, for emergency research, as noted at 61 Federal Register 51531[1] .

HHS - Waiver or Alteration of Consent

When waiving or altering consent or waiving the requirements under 46.116, the IRB must find and document that:

(1) The research involves no more than minimal risk to the subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
(4) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format (*This clause only applies to the 2018 Common Rule (CR)*); and
(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA - Waiver or Alteration of Consent

When the research is regulated by the FDA, the IRB may only waive informed consent for emergency research as specified in 21 CFR parts 50.23 and 50.24 and waive documentation of

[1] Waiver of informed consent is not permitted for certain research with vulnerable populations. Per 61 FR 51531, because of special regulatory limitations relating to research involving prisoners (Subpart C of 45 CFR part 46) and research involving fetuses, pregnant women, and human *in vitro* fertilization (Subpart B of 45 CFR part 46), the waiver for emergency research is not applicable to these categories of research/

informed consent as specified in 56.109(c) or waive or alter elements of informed consent for non-emergency, minimal risk research in accordance with applicable FDA guidance.

NOTE: *The FDA is in the process of harmonization with the HHS 2018 Common Rule however this process is not yet complete. The FDA has not accepted the revised waiver criteria adopted by the 2018 CR.*

HHS - Waiver of Documentation of Consent

The informed consent document must be signed and dated by the subject[2], except when the IRB has approved a waiver of documentation of informed consent, consistent with 46.117(c) and when applicable 56.109(c) (see related requirements for FDA regulated research below).

(1) An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

(i) That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

(ii) That 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

(iii) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*This clause only applies to the 2018 CR)*

(2) In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

FDA – Waiver of Documentation of Consent

(c) An IRB shall require documentation of informed consent in accordance with §50.27, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the

[2] When minor subjects reach the age of majority, investigators must seek informed consent from the now-adult subject for their continued participation unless consent is not required (e.g., for certain exempt research) or if waived by the IRB (See Policy 402 Research Involving Children).

research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements for an exception from informed consent for emergency research are met as described in §50.24. (For more information about emergency research see Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research.)

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Subpart D - Children

REFERENCES

- Policy 402 Research Involving Children
- 45 CFR 46 Subpart D/ 21 CFR part 50, Subpart D
- IRB Tip Sheet - Research Involving Children
- OHRP Research with Children FAQs

Under Subpart D children are defined as follows: **Children** are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted[3] (45 CFR 46.402(a)).

Approval Categories for Research Involving Children

Research involving children is only approvable under one of the following categories:

404/51: No greater than minimal risk

- Assent of child (as applicable);
- Permission of parents (may determine permission of 1 parent is sufficient[4])

405/52: Greater than minimal risk, but with the possibility of **direct benefit** to individual subjects

- Risk is justified by the anticipated benefit to the subjects;
- Relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternatives;
- Assent of child (as applicable); and
- Permission of parents (may determine permission of 1 parent is sufficient[5])

406/53: Greater than minimal risk and **no possibility of direct benefit** to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

- Risk represents a minor increase over minimal risk;

[3] For research conducted at an NIH site, an adult is anyone 18 years or older, unless the child is legally emancipated.
[4] For research taking place at an NIH site, and in cases where parents share joint legal custody for medical decision-making of a child (e.g., by a custody agreement or court order), both parents must give their permission regardless of the risk level of the research. Exceptions may include if one parent has since died, become incompetent, or is not reasonably available.
[5] Ibid. 4

- Intervention or procedure presents experiences to the children that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations;
- Intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition;
- Assent of child (as applicable); and
- Permission of both parents

407/**54**: Greater than minimal risk research **not otherwise approvable** which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children

- IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children, and
- The HHS Secretary or FDA Commissioner approval and publication in federal register.

Parental Permission

Parental signature requirements - If the research contains interventions that are only minimal risk, or greater than minimal risk with a prospect of direct benefit, the IRB can determine the signature from either 1 or 2 parents is sufficient.

For research taking place at an NIH site, and in cases where parents share joint legal custody for medical decision-making of a child (e.g., by a custody agreement or court order), both parents must give their permission regardless of the risk level of the research. Exceptions may include if one parent has since died, become incompetent, or is not reasonably available

However, if the research contains any procedures determined by the IRB to be greater than minimal risk without a prospect of direct benefit, the IRB must require 2 parent signatures. This is true even if the same study contains interventions that have a prospect of direct benefit.

Assent of Children

The IRB must determine that adequate provisions are made for soliciting the assent of children, when in the judgment of the IRB the children are capable of providing assent. When determining whether children are capable of assenting, the IRB must take into account:

- age
- maturity, and
- the psychological state of the children

This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.

Waiver of Assent

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the research intervention/procedure 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, then the assent of the children is not a necessary requirement. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent consistent with 46.116.

The regulations at 46.408(a) identify three types of circumstances where the IRB may determine that waiver of children's assent is appropriate, if the:

1. Capability of some or all of the children is so limited that they cannot reasonably be consulted;

2. Intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research.

3. Research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 46.116(c) or (d).

When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

Wards

For research involving wards of the state, in order to be approvable under 46.406 or 46.407 the requirements of 46.409 must be met.

Subpart B – Pregnant Persons, Fetuses and Neonates

REFERENCES

- Policy 400 Research Involving Pregnant Women, Human Fetuses, and Neonates
- 45 CFR 46 Subpart B
- IRB Tip Sheet - Research Involving Pregnant Subjects
- Guideline for Inclusion-Exclusion of Pregnant Persons and Information about Pregnancy Testing *(file will download from webpage)*

Under Subpart B pregnancy is defined as follows: *Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.*

Pregnant Persons and Fetuses

Pregnant women or fetuses may only be involved in research if **all** of the following conditions under 46.204 are met, as applicable:

Scientifically Appropriate:

a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

Risk/Benefit:

b) **The risk to the fetus** is caused solely by interventions or procedures that hold out the **prospect of direct benefit for the woman or the fetus**; or,
   - if there is no such prospect of benefit, the risk to the fetus is not greater than minimal, and
   - the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

c) Any risk is the **least possible** for achieving the objectives of the research.

d) If the research holds out the **prospect of direct benefit to the pregnant woman**, the **prospect of a direct benefit both to the pregnant woman and the fetus**, or
   - no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal, and
   - the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means,
   - her consent is obtained in accord with the informed consent provisions of subpart A.

e) If the research holds out the **prospect of direct benefit solely to the fetus**, then the **consent of the pregnant woman and the father** is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

Consent of Parents:

f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

Pregnant Children:

g) For children who are pregnant, assent and permission are obtained in accord with the provisions of subpart D. (See previous section on Children)

Prohibitions on researchers against termination:

h) **No inducements**, monetary or otherwise, will be offered to terminate a pregnancy.
i) Individuals engaged in the research will have **no part in any decisions** as to the timing, method, or procedures used to terminate a pregnancy.
j) Individuals engaged in the research will have **no part in determining the viability** of a neonate.

Neonates (newborns)

For research involving neonates, review under 46.205

Placental/Fetal Material

For research involving use of the placenta, the dead fetus or fetal materials (after delivery), review under 46.206

Secretarial Review

For **research not otherwise approvable** but which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of pregnant persons, fetuses or neonates, review under 46.207.

Subpart C – Prisoners

REFERENCES

- Policy 401 Research Involving Prisoners
- 45 CFR 46 Subpart C
- Guideline for Enrolling Prisoners in Research (*file will download from webpage*)
- Epidemiological Research - 68 Fed. Reg. 36929 (Jun. 20, 2003)
- Emergency Research - 61 Fed. Reg. 51531 (Oct. 2, 1996)
- OHRP Prisoner Research FAQs

DEFINITIONS

- **Prisoner** means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

- **Minimal risk** is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons

Apply Subpart C whenever the research involves prisoners regardless of whether prisoners are the intended subject population, or for a protocol not previously approved under Subpart C, but a subject becomes a prisoner during the course of the research and the investigators wants the subject to remain on the research during the period of incarceration.

Prisoners - Composition of the IRB

In order to review research involving prisoners the IRB must be composed in accordance with 46.304.

Required Findings of the IRB	Permissible categories of approval
The Board will approve research involving prisoners only if it finds that: (1) The research under review represents one of the categories of research permissible under §46.306(a)(2) (See next column) (2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the	(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if: (1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and (2) In the judgment of the Secretary the proposed

prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Prisoners - Epidemiological Research

The Secretary granted a waiver of the applicability (68 Fed. Reg. 36929 (Jun. 20, 2003)) of 45 CFR 46.305(a)(1) and 46.306(a)(2) in order to allow for important and necessary epidemiologic research on prisoners that meets specific criteria (e.g., epidemiological research related to chronic diseases, injuries, and environmental health), provided that these studies meet the following criteria:

- Present no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
- Prisoners are not the particular focus of the research.
- The IRB must review the research subject to a waiver under Subpart C and document all other required findings under HHS regulations at 46.305(a)

Prisoners - Emergency Research

Prisoners cannot be involved in emergency research where the Secretary HHS has waived the requirement for informed consent (46.101(i) and 61 Fed. Reg. 51531 (Oct. 2, 1996))

Individuals Lacking Capacity to Consent To Research

REFERENCES

- Policy 403 Research Involving Subjects Lacking Capacity to Consent to Research Participation
- Research Involving Individuals Without Consent Capacity (*file will download from webpage*)
- SACHRP Recommendations Regarding Research Involving Individuals with Impaired Decision making (2009)
- IRB Review of Research Involving Potential Subjects Lacking Consent Capacity

The regulations do not include a separate subpart describing protections for those with impaired decision making as they do for pregnant women/human fetuses/neonates, prisoners, and children. However, the criteria for IRB approval of research at 46.111(b), notes that the IRB must determine "*When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.*"

At the NIH, adult individuals lacking capacity to consent to research participation may participate both in research studying disorders about their condition as well as studies of conditions unrelated to their cognitive impairment that have the prospect of direct benefit.

Risk Categories for Adults Lacking Capacity to Consent

The NIH IRB may only approve research that permits the participation of subjects without consent capacity if it determines and documents that the research meets one of the following risk/benefit categories:

Category A - The research is **minimal risk**

Category B - The research is greater than minimal risk, and offers a **prospect of direct benefit** to the participant

Category C - The research is no more than a **minor increase over minimal risk with no prospect of direct benefit**, and does not adversely affect the rights, safety, or welfare of the participants, or

Category D - The research **does not meet** the above conditions but **has undergone additional institutional review** and approval by the NIH Institutional Official

Safeguards Based on Level of Risk

In addition to assessing the level of risk, the IRB should determine if appropriate safeguards are in place:

- If the potential subject lacks the capacity to consent to research participation, consent must be obtained from their Legally Authorized Representative (LAR).
- For studies that pose greater than minimal risk, consider whether consent capacity assessments should be conducted by a qualified professional who is independent of the study team.
- Ensure the plan for assessing initial and ongoing consent is adequate, when applicable.
- Consider if consent monitoring or assent by the potential subject (verbal or written) should be required.
- The hierarchy for determining who may serve as the LAR at an NIH site[6] is specified in Policy 403 and in the table below.

[6] For research conducted at non-NIH sites, who may serve as the LAR may vary due to state law or institutional policy

Risk Category	Risk/Benefit Level	Hierarchy for Determining the LAR (at an NIH site)
Category A	Minimal Risk	1. Court-appointed guardian of the person, who is authorized to consent to the research[7] 2. The individual(s) appointed in the patient's Durable Power of Attorney (DPA) for health care 3. If the prospective subject does not have a court appointed guardian or DPA for health care, and they are capable of understanding the DPA process, even if they lack capacity to consent to research, the prospective subject may execute a DPA for health care 4. If no court-appointed guardian or DPA for health care exists, and the prospective subject is unable to execute a DPA for health care, then the next of kin hierarchy listed below may be used to identify the LAR in the following descending order: a. Spouse or domestic partner b. Adult child c. Parent d. Adult sibling, or e. Other relative
Category B	Greater than Minimal Risk (GMTR) but offers prospect of direct benefit (DB)	Same as Category A
Category C	No more than a minor increase over minimal risk with no prospect of DB, and does not adversely affect the rights, safety or welfare of participants	Same as Category A
Category D	Research that does not fall into one of the above categories	• There must be a court-appointed guardian or DPA for healthcare who can provide consent on behalf of the participant, and • The next of kin hierarchy (as listed above) **may not** be used to identify an LAR In addition, institutional review and approval by the NIH Institutional Official is required followed by review by the convened Board

[7] A court-appointed guardian may only consent for a subject without capacity to participate in research if the guardian has authority to do so under the laws of the state that issued the guardianship order and the terms of the guardianship order

Investigational Devices

REFERENCES

- Policy 501 Research Involving FDA Regulated Devices
- FDA regulations - 21 CFR parts 50, 56, 809, 812, and 814
- Device Determinations (March 2022) (*file will download from webpage*)

DEFINITIONS

Clinical investigation of a device – A clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (21 CFR 812.3(h))

Investigational Device – A device, including a transitional device, that is the object of an investigation.

Non-significant Risk (NSR) Device – An investigational device that is not a significant risk device as defined at 21 CFR 812.3(m).

Significant Risk (SR) Device - An investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

Determinations Involving Investigational Devices

If the research will use a **legally marketed** device(s) in accordance with the FDA labeling, then no IDE is required. OR

The device investigation is **exempt** if it meets FDA criteria under 21 CFR 812.2(c):

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the labeling.

2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the labeling.

3. A diagnostic device if the sponsor complies with applicable requirements in §809.10(c) and if the testing:

    1. Is noninvasive,
    2. Does not require an invasive sampling procedure that presents significant risk,
    3. Does not by design or intention introduce energy into a subject, and
    4. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

5. A custom device as defined in §812.3(b) unless the device is being used to determine safety or effectiveness for commercial distribution.

Otherwise, if the research involves the **study of the safety or efficacy** of an investigational device, then an IDE is required. In that case, the IRB must determine if the device is a Significant Risk (SR) or a Non-significant Risk (NSR) device. When the IRB makes an NSR determination it is acting in lieu of the FDA and it is issuing an IDE under abbreviated requirements at 812.2(b). When the FDA has already provided the Sponsor a formal determination regarding the Investigational Device Exemption (IDE), the FDA's determination is final.

IRB Responsibilities When Reviewing Non-exempt Device Investigations

If the research involves the **study of the safety or efficacy** of an investigational device, then the Sponsor is responsible for making the initial assessment whether the device is an NSR or SR device. This will be provided to the IRB.

- If the FDA **has not** provided a determination regarding the IDE, then the IRB is responsible to determine if it agrees with the Sponsor's initial assessment.

- If the IRB **agrees** with the Sponsor's initial assessment, then the IRB should review the study, applying requisite criteria for review and approval. If the IRB **disagrees** with the Sponsor's initial assessment, then it should make its assessment based on the table below.

- If the FDA **has** provided a determination, the FDA's determination is final. However, in accordance with 812.42 the investigation may not commence until IRB has conducted its review, and documented this determination in the Minutes.

Determinations for Investigational Devices that are not Exempt or Will be used as FDA-approved

Determination:	**Significant Risk (SR) Investigational Device** - An investigational device that: 1. Is intended as an implant; or 2. Is purported or represented to be for a use in supporting or sustaining human life; or 3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; or 4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))	**Non-significant Risk (NSR) Device** - Does not meet definition of an SR device study
Required Approval:	IDE from FDA **and** IRB approval	IRB approval only
Applicable FDA regulations:	Subject to full IDE regulations at 21 CFR 812	Subject to abbreviated IDE regulations at (21 CFR 812.2(b))

Evaluating Events – Unanticipated Problems

REFERENCES

- Policy 801 Reporting Research Events
- Guidance - Reporting Research Events and Non-compliance (*file will download from webpage*)
- IRB Member Review of Reported Events as Possible Unanticipated Problems
- OHRP Guidance - Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (2007)

DEFINITIONS

Unanticipated Problems Involving Risks to Subjects or Others – Any incident, experience, or outcome that meets **all** the following criteria:

1. **Unexpected** (in terms of nature, severity, or frequency) given

   (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
   (b) the characteristics of the subject population being studied.

2. **Related or possibly related to** participation in **the research** (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. **Suggests that the research places subjects, or others** (which may include research staff, family members or other individuals not directly participating in the research) **at a greater risk of harm** (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

Unanticipated (Unexpected) – An experience that was not expected or previously observed, or is not consistent in nature, severity, or frequency with existing risk information, such as in the investigator's brochure, device manual, research protocol, consent form, or other available information (e.g., Investigation New Drug (IND) application for an investigational drug or Investigational Device Exemption (IDE) application for an investigational device). Interchangeable with "unexpected". This includes an event or problem occurring in one or more subjects in a research study that is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the event/problem.

IRB Considerations for Unanticipated Problems (UPs)

When the IRB determines an event is a UP, IRB members should consider:

- Are corrective actions that are planned or already taken by the investigator appropriate and sufficient?
- Are risks to participants or others still minimized and reasonable in relation to anticipated benefits?
- Are modifications to the protocol and/or consent needed? For example,
    - Should safety monitoring frequency be increased?
    - Does the consent need to be updated to notify subjects of the new risk?
    - Should existing subjects be reconsented?
- Are risks to participants such that IRB should consider suspending enrollment? Suspend/terminate entire study?

IRB Authorities when the Event is a UP

In response to a reportable event, the IRB has the authority to:

- Request additional information
- Require modification of the protocol or consent(s)
- Require notification of subjects
- Require reconsent of subjects
- Require the investigator to suspend new enrollment to the protocol
- Increase the type and/or frequency of safety monitoring
- Change the period of review, or
- Other measures to protect the rights, safety and welfare of subjects

Is the event is a UP Flowchart

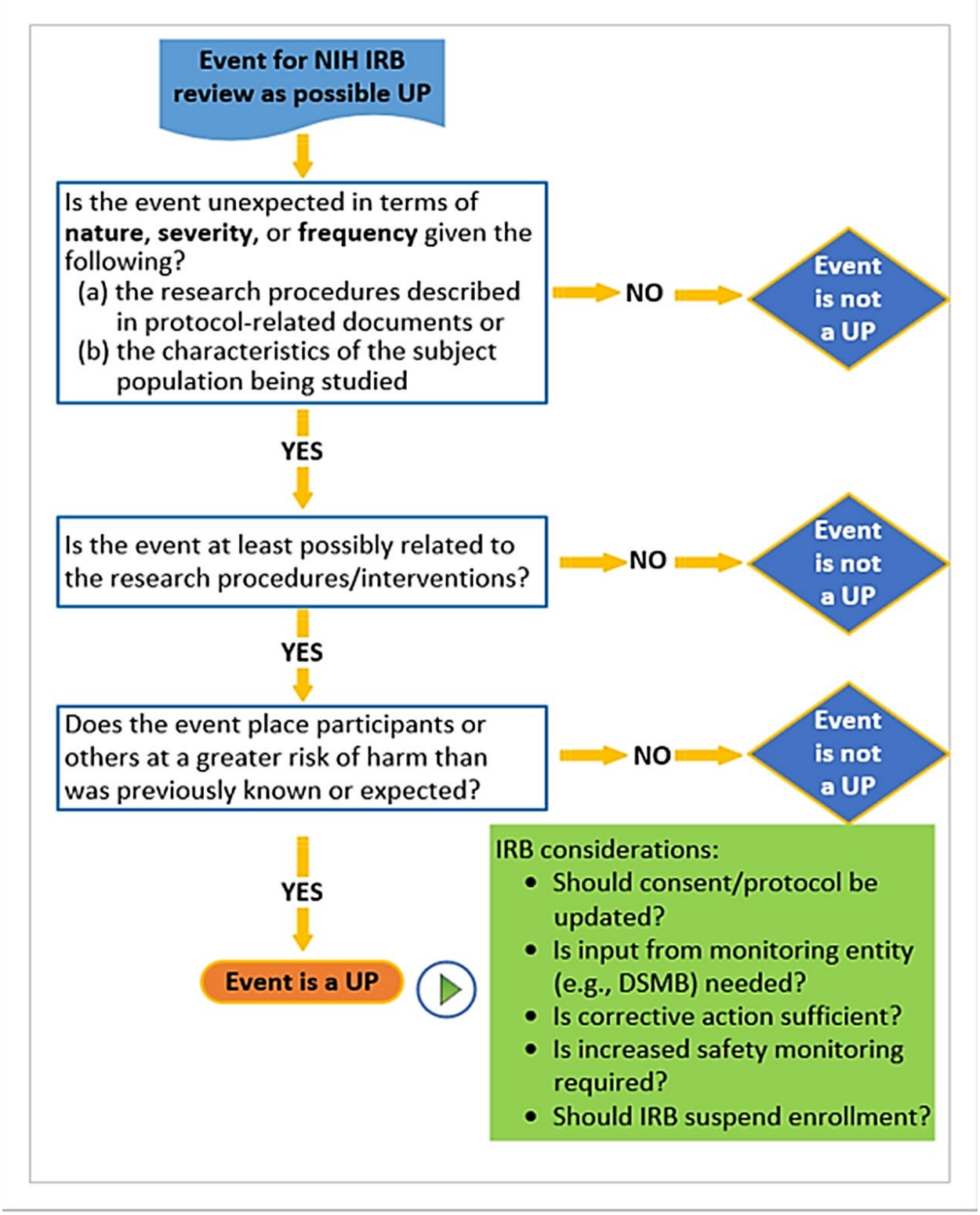

Figure 1 Flowchart to determine if the event is an Unanticipated Problem

RCRC IRB – Review of Potential Non-Compliance

REFERENCES

- Policy 802 Non-compliance in Human Subjects Research
- Guidance - Reporting Research Events and Non-compliance (*file will download from webpage*)

DEFINITIONS

Non-Compliance – Failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.

1. **Continuing non-compliance** - A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different non-compliant events. Such non-compliance may be unintentional (e.g., due to lack of understanding, knowledge, or commitment), or intentional (e.g., due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

2. **Serious non-compliance** - Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

RCRC Responsibilities When Reviewing Non-compliance

The Research Compliance Review Committee (RCRC) is a duly constituted IRB registered with OHRP. In accordance with Policy 802, for all protocols in which the research was conducted under the jurisdiction of the NIH IRB, the RCRC has the final authority to determine whether there is non-compliance.

When the RCRC reviews non-compliance, it:

- Will determine whether it is serious and/or continuing

- Will determine the adequacy of any corrective actions that are planned or already taken by the investigator or what corrective actions are needed to assure compliance moving forward

- Has all the authorities of the IRB including, requiring modifications to any proposed corrective action as a condition for continued approval of research. For example,

    - Continued monitoring,
    - Notification to past research subjects,
    - Reconsent of current subjects when the investigation results in information that might impact the subjects' willingness to continue participation in the research, or
    - Mandated training of the study team.

Expanded Access to Investigational Drugs & Devices

REFERENCES

- Policy 502 Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices (Test Articles)
- FDA regulations - 21 CFR parts 50, 56, and for treatment use of investigational:
    - Drugs - 21 CFR 312 subpart I
    - Devices - 21 CFR 812.36
- Emergency Use of an Investigational Drug or Biologic (January 1998, Content current as of 07/12/2018)
- Expanded Access to Experimental Biologics (Content current as of 09/16/2019)
- Expanded Access Categories for Drugs (Including Biologics) (Content current as of 01/04/2018)
- Expanded Access for Medical Devices (Content current as of 6/21/2019)

DEFINITIONS

Expanded access (Sometimes referred to as "compassionate use") – A potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. (See Expanded Access Keywords, Definitions and Resources.)

Immediately life-threatening disease or condition – A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. (21 CFR 312.300(b))

Serious disease or condition – A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. (21 CFR 312.300(b))

Expanded Access to Investigational Drugs, Biologics or Devices for Treatment

Expanded access refers to the use of an investigational drug, biologic, or device product (test article) when the primary purpose is to **diagnose, monitor or treat** a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. The regulations are intended to facilitate access to investigational drugs for **treatment use** for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives. At the NIH:

- Only persons enrolled in an NIH research protocol may be treated using an expanded access protocol, and
- NIH Investigators may not perform research interventions or collect or analyze data for research purposes under an expanded access protocol.

Emergency use for an individual patient:

- For drugs under an existing IND emergency use can be requested and authorized by a rapid means of communication (e.g., telephone) and may start immediately upon FDA authorization
- For devices, if all of the criteria are met as described below, an unapproved device may be used in an emergency situation without prior approval by the FDA so long as other requirements are fulfilled.

For non-emergency expanded access applications of a:

- Drug - the expanded access IND will take effect at the end of the 30-day waiting period unless notified by the FDA earlier
- Device - the expanded access IDE will take effect at the end of the 30-day waiting period unless notified by the FDA earlier

Criteria for a Patient to be eligible for Expanded Access use of a Test Article

- In order for a patient to be eligible for expanded use, the following criteria must be met:
    - Patient(s) must have a serious or immediately life-threatening disease or condition, and
    - There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, and
    - The potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context of the disease or condition to be treated, and
    - The expanded use of the investigational test article for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product, and

  - At the NIH, the patient must be a subject enrolled on an NIH research study

- For a patient to be eligible for emergency use of a test article the following criteria **also** must be met:
  - The condition requires immediate intervention before review at a convened IRB meeting is possible, or to avoid major irreversible morbidity

IRB Review Expanded Access INDs/IDEs

For expanded access protocols, prospective IRB review and approval must be obtained, except in certain cases of individual patient use as described below. Even though expanded access is for treatment use, informed consent must still be obtained for treatment with the investigational drug or device, and if the treatment extends beyond 12 months then CR is required.

SINGLE-PATIENT EXPANDED ACCESS INDS/IDES

There are 2 types of single-patient expanded access protocols the first involves emergency access and the second non-emergency access. It is unlikely that the IRB will see these since Chair concurrence can be obtained by the physician. It is helpful to see the criteria for emergency access as described in the informed consent clause to distinguish this type of expanded access protocol from non-emergency access:

Informed Consent for treatment will be obtained from the patient or LAR, unless the PI and a physician who is not part of the investigation has concurred within 5 days after the use of the test article that:

- The patient was confronted by a life-threatening situation necessitating the use of the test article;

- Informed consent could not be obtained from the patient because of an inability to communicate with, or legally effective consent could not be obtained from the patient, and time was not sufficient to obtain consent from the LAR; and

- There is available no alternative method of approved or generally recognized therapy that provided an equal or greater likelihood of saving the life of the patient. (21 CFR 50.23(a))

In the case of emergency use of a test article, any subsequent use of the test article at the institution is subject to IRB review. (21 CFR 56.104(c))

OTHER EXPANDED ACCESS INDS/IDES

Other expanded access protocols including, "Intermediate-size population" and "Treatment IND/ Protocol" or rarely, a Humanitarian Use Device (HUD) involve more than one patient. The convened Board will review these expanded access protocols similar to research protocols unless a waiver for full IRB review has been granted by the FDA under 21 CFR 56.104. In its review the IRB will evaluate the submission to determine whether

the use complies with regulatory requirements for expanded access use described above. Other considerations include:

- Informed Consent **for treatment** will be obtained from the patient or LAR
- Continuing review and approval for expanded access protocols that will exceed a 12-month period
- For expanded access use involving devices, the investigator has established an appropriate schedule for monitoring the patient(s), taking into consideration nature of the test article and specific needs of the patient(s).
- The Submission of reportable events to the NIH IRB consistent with Policy 3014-801 Reporting Research Events.