The Health and Human Services (HHS) waiver, just as the Food and Drug Administration (FDA) regulatory change (21 CFR 50.24), provides a narrow exception to the requirement for obtaining and documenting informed consent from each human participant or his or her legally authorized representative prior to initiation of research if the waiver of informed consent is approved by an IRB. The waiver authorization applies to a limited class of research activities involving human participants who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have available a legally authorized representative.

The intent of these regulations is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies. Note: Planned Emergency Research is not the same as Emergency Use of a Test Article. See http://researchaffairs.llu.edu/responsible-research/primers-tips/primer-emergencyuse-of-an-investigational-drug-or-device.

Emergency medicine research supported by the Department of Defense (DoD)

For emergency medicine research supported by DoD an exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense. See also Additional Requirements for Department of Defense Research.

International Conference on Harmonization-Good Clinical Practice (ICH-GCP) requirements

To fulfill ICH-GCP (E6) requirements, the participant or the participant's legally authorized representative must be informed about the clinical trial as soon as possible and provide consent if the participant wishes to continue.

Research Subject to FDA Regulation

The LLUH IRB reviews and may approve planned emergency research without requiring that informed consent of all participants be obtained if the LLUH IRB (with the concurrence of a licensed physician who is a member of the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

1. The research activity is subject to regulations codified by the Food and Drug Administration (FDA) 21 CFR 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE).
2. The application clearly identifies the protocols that will include participants who are unable to consent.
3. The research participants are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

4. Obtaining informed consent is not feasible because:
    (i) The participants will not be able to give their informed consent as a result of their medical condition;
    (ii) The intervention under investigation must be administered before consent from the participants' legally authorized representatives (LARs) is feasible; and
    (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
5. Participation in the research holds out the prospect of direct benefit to the participants because:
    (i) Participants are facing a life-threatening situation that necessitates intervention;
    (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual participants; and
    (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
6. The clinical investigation could not practicably be carried out without the waiver.
7. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence; the Investigator has committed to attempting to contact a LAR for each participant within that window of time and, if feasible, to asking the contacted LAR for consent within that window rather than proceeding without consent; the Investigator will summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review.
8. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25, which are to be used with participants or their LARs in situations when feasible. The IRB has also reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a participant's participation in the clinical investigation.
9. Additional protections of the rights and welfare of the participants will be provided, including, at least:
    (i) Consultation, including that carried out by the IRB where appropriate, with representatives of the communities in which the clinical investigation will be conducted and from which the participants will be drawn;
    (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the participants will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
    (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and study results;
    (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
    (v) If obtaining informed consent is not feasible and a LAR is not reasonably available, the Investigator has committed, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a LAR, and asking whether he or she objects to the participant's participation in the clinical investigation. The Investigator will summarize efforts made to contact family

members and make this information available to the IRB at the time of continuing review.

Additional IRB Responsibilities for Research Subject to FDA Regulation

1. The IRB is responsible for ensuring that procedures are in place, at the earliest feasible opportunity, to inform each participant, or a LAR of the participant if the participant remains incapacitated, or a family member if such a representative is not reasonably available, of: (i) the participant's inclusion in the clinical investigation, the details of the investigation, and other information contained in the informed consent document; and
   (ii) the right to discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
2. If a LAR or a family member is told about the clinical investigation and the participant's condition improves and regains capacity for informed consent, the participant is also to be informed as soon as feasible.
3. If a participant is entered into a clinical investigation with waived consent and the participant dies before a LAR or a family member can be contacted, information about the clinical investigation is to be provided to the participant's LAR or family member, if feasible. Note: For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the participant is the equivalent of a family relationship.
4. The IRB must retain the records of documentation required during the review on waiver of consent for at least 3 years after completion of the clinical investigation, and the records must be accessible to FDA for inspection and copying.
5. Protocols involving a waiver of the informed consent must be performed under a separate IND or IDE that clearly identifies as protocols that may include participants who are unable to consent. The submission of those protocols in a separate IND or IDE is required even if an IND or IDE for the same drug product or device already exists.
6. If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception of because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly (no longer than within 30 days) in writing to the clinical Investigator and to the sponsor. The sponsor must promptly disclose this information to FDA and to the sponsor's Investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor of the clinical investigation.

Research <u>Not</u> Subject to FDA Regulation

When research is not subject to FDA regulations, but follows DHHS regulations, the IRB finds, documents, and reports to DHHS that the following conditions have been met relative to the research:

1. The IRB found and documented that the research is not subject to regulations codified by the FDA at 21 CFR 50.
2. The research participants are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

3. Obtaining informed consent is not feasible because:
    (i) The participants will not be able to give their informed consent as a result of their medical condition;
    (ii) The intervention involved in the research is administered before consent from the participants' legally authorized representatives (LARs) is feasible; and
    (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
4. Participation in the research holds out the prospect of direct benefit to the participants because:
    (i) Participants are facing a life-threatening situation that necessitates intervention;
    (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual participants; and
    (iii) Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
5. The research could not practicably be carried out without the waiver.
6. The proposed research defines the length of the potential therapeutic window based on scientific evidence; the Investigator has committed to attempting to contact a LAR for each participant within that window of time and, if feasible, to asking the contacted LAR for consent within that window rather than proceeding without consent; the Investigator will summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review.
7. The IRB has reviewed and approved consent procedures and a consent document in accord with 45 CFR
   46.116 and 46.117.
    (i) These procedures and the consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documented is feasible.
    (ii) The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a participant's participation in the research consistent with the paragraph of this waiver.
8. Additional protections of the rights and welfare of the participants will be provided, including, at least:
    (i) Consultation, including that carried out by the IRB where appropriate, with representatives of the communities in which the research will be conducted and from which the participants will be drawn;
    (ii) Public disclosure to the communities in which the research is conducted and from which the participants will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits;
    (iii) Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and study results;
    (iv) Establishment of an independent data monitoring committee to exercise oversight of the research; and
    (v) If obtaining informed consent is not feasible and a LAR is not reasonably available, the Investigator has committed, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a LAR, and asking

whether he or she objects to the participant's participation in the research. The Investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

Additional IRB Responsibilities for Research <u>Not</u> Subject to FDA Regulation

1. The IRB is responsible for ensuring that procedures are in place, at the earliest feasible opportunity, to inform each participant, or a LAR of the participant if the participant remains incapacitated, or a family member if such a representative is not reasonably available, of: (i) the participant's inclusion in the research, the details of the research, and other information contained in the informed consent document; and
   (ii) the right to discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
2. If a LAR or a family member is told about the research and the participant's condition improves and regains capacity for informed consent, the participant is also to be informed as soon as feasible.
3. If a participant is entered into research with waived consent and the participant dies before a LAR or a family member can be contacted, information about the research is to be provided to the participant's LAR or family member, if feasible. Note: For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the participant is the equivalent of a family relationship.

For further information

FDA Regulated Research: 21 CFR 50.24: Exception from informed consent requirements for planned emergency research; FDA Guidance, April 2013: Exception from Informed Consent Requirements for Emergency Research; Federal Register, Vol. 61, pp. 51531-51533: Waiver of Informed Consent in Certain Emergency Research

Non-FDA Regulated Research: OPRR Reports, October 31, 1996: Informed Consent Requirements in Emergency Research; Federal Register, Vol. 61, pp. 51531-51533: Waiver of Informed Consent in Certain Emergency Research