SOP Title	**WAIVER OF INFORMED CONSENT IN GREATER THAN MINIMAL RISK EMERGENCY RESEARCH**	SOP No.	UWS-HP-608
		Version	.02
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Signatures and Dates:

Signature on file

Author:	Human Subjects Protection Branch	Date
QA Review:	Human Subjects Protection Branch	Date
Approving Authority:	Human Subjects Protection Branch	Date

Review/Approval for unchanged documents

	Author/Date	QA Review/Date	Approving Authority/Date
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1. Purpose and Applicability

This Standard Operating Procedure (SOP) describes the criteria and processes by which the Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) may waive the requirement for consent in greater than minimal risk emergency research as per 21 CFR 50.24. This waiver applies to research involving an intervention that is an investigational drug, device, or biologic regulated by the United States Food and Drug Administration (FDA), and research that is either sponsored by a Common Rule federal agency or conducted by an institution that has chosen to apply federal regulations to its research activities. This waiver does not apply to research involving fetuses, pregnant women, human *in vitro* fertilization, prisoners, children, or other vulnerable populations as defined by federal regulation. Protocols involving a waiver of consent must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent.

This SOP does not apply to the exception from informed consent procedures provided by 21 CFR 50.23(a) and (b) and 21 CFR 812.35(a)(2) in order to use an investigational test article in an attempt to save a patient's life (See SOP UWS-HP-605 Humanitarian Use Devices and SOP UWS-HP-607 Emergency Use Notification and Reporting Procedures).

Per Title 10 United States Code (USC) 980, a waiver of informed consent is not permitted for "research involving experimental subjects." Department of Defense (DoD) Instruction 3216.02 defines "research involving experimental subjects" as activities where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction. A waiver of consent may be granted under 10 USC 980 when there is a direct benefit to each subject, when the project is intended to advance the development of a medical product necessary to the armed forces, and the Secretary of Defense grants a waiver from this requirement.

This SOP applies to the WRAIR Principal Investigator (PI), the WRAIR Human Subjects Protection Branch (HSPB), the WRAIR IRB, the WRAIR Scientific Review Committee (SRC), and the WRAIR Institutional Official (IO).

2. Responsibilities

a. The WRAIR PI or WRAIR Point of Contact (POC):

1) Reviews this SOP;

2) Requests waiver; and

3) Ensures that written permission from the FDA and all applicable approvals are obtained prior to initiating a study that includes a waiver of consent for emergency research.

b. The WRAIR HSPB:

1) Provides technical assistance to PIs on the requirements for a waiver of consent for emergency research that is greater than minimal risk; and

2) Documents waiver determinations.

c. The WRAIR SRC is responsible for determining that the study design of a protocol that includes a waiver of consent for emergency research is adequate for evaluating whether the test article has the hypothesized effect and that the scientific evidence available justifies the length of the therapeutic window cited in the protocol.

d. The WRAIR IRB reviews and approves, if appropriate, a waiver of consent for emergency research.

e. The WRAIR IO reviews and authorizes implementation of a waiver of consent for emergency research that is greater than minimal risk (GTMR) in accordance with this SOP.

3. Materials and Equipment

Not applicable.

4. Procedures

a. The PI or WRAIR POC:

1) Includes a request to the HPSB for a waiver of informed consent for emergency GTMR research described in the Consent section of the protocol. Ensures that the submission contains the elements required by Title 21, Code of Federal Regulations, Part 50, Section 24 (21 CFR 50.24).

2) Files, if applicable, a separate IND or IDE submission with FDA for the research that clearly states the investigation may include subjects who are unable to consent; OR ensures that the Sponsor has filed such an application.

3) Defines the therapeutic window in the protocol, and the portion of the therapeutic window that will be devoted to seeking informed consent. Provides clear and complete scientific evidence to justify the length of the therapeutic window.

4) Provides a sound rationale for the study design if it involves a placebo-controlled trial that includes subjects to whom neither treatment nor the test article is given.

5) Ensures that participation in the emergency research study holds out the prospect of direct benefit for the individual subjects and demonstrates that this project is conducted with the intent to advance the development of a medical product necessary to the armed forces.

6) Provides a clear and complete written description of the steps that will be taken to learn the identity of the subject and the subject's legally authorized representative (LAR) and to obtain consent from the LAR. Documents a commitment to obtain consent from the subject or the subject's LAR, whenever possible, rather than proceeding without consent and makes this information available to the WRAIR IRB at the time of continuing review according to the SOP UWS-HP-618, Continuing Review and Continuation Determination.

7) Provides a clear and complete written description of the steps that will be taken, in cases when obtaining informed consent is not feasible and LAR is not available, to locate and provide a family member with the opportunity to object to the subject's participation. Documents a commitment to contact the family member within the therapeutic window.

8) Provides a clear and complete written procedure for informing the subject, or the subject's LAR (if the subject remains incapacitated), or the subject's family member (if the LAR is not available), at the earliest feasible opportunity, of the following:

   a) The subject's inclusion in the clinical investigation;

   b) The subject's right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;

   c) The details of the investigation and other information contained in the consent document; and

d) A request to allow the subject to continue to participate in the study and an opportunity to discontinue participation. The decision to continue or withdraw from the study must be obtained in writing from the subject/LAR. In the event that the subject and the LAR are not available, a reasonably available family member must be asked whether he or she objects to the subject's participation in the research.

9) Provides a clear and complete written procedure for informing the subject's LAR or family member of the subject's participation and provide information about the study, when feasible, in the event that the subject dies and consent was waived.

10) Develops strategies and plans for community consultation. Effective community consultation ensures that the target community is involved in the WRAIR IRB's decision-making process and requires that the investigator:

a) Define the community in which the research will be conducted and from where the subjects will be drawn;

b) Determine the most effective ways of consulting with the community (e.g. face to face meetings with the PI and WRAIR IRB, random surveys, focus groups, consulting with local political organizations and civic groups), considering the characteristics of the target community;

c) Set goals with the WRAIR IRB for community consultation and determine how the results of the consultation effort will be used (e.g. assessing whether the community agrees the study should be done, gather information from the community on how to design and implement the study);

d) Ensure that consultation activities are widely advertised and promoted so that as many different groups in the community as possible are represented (e.g. newspaper, radio, television and internet advertisements);

e) Ensure that community consultations include the minimum information outlined in the current FDA Guidance on this topic (see Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research); and

f) Develop a plan to inform the community about the research conducted, to include research population demographic information and study results, after the study has been completed.

11) Include in the continuing review report (see UWS-HP-618, Continuing Review and Continuation Determination) a case-by-case summary of the following:

a) Attempts to identify the subject and locate the subject's LAR to obtain consent within the therapeutic window; and

b) Attempts to locate and identify the subject's family member and provide the subject's family member with an opportunity to object to the subject's participation in the study, as well as, the family member's decision.

12) In the event that the WRAIR IRB disapproves the request for a waiver of consent for emergency research, ensure that the Sponsor of the research is promptly notified, so that the Sponsor may then disclose this information to the FDA, to other investigators on this or substantially equivalent research protocols, and to other IRBs who have been or are asked to review this or substantially equivalent research protocols.

b. The HSPB Staff:

1) Review the request for a waiver of informed consent for emergency research to ensure that it contains the elements required by 21 CFR 50.24 and 10 USC 980.

2) Notify the PI in writing of the following review results for a waiver of informed consent for emergency research:

a) Approval – The convened WRAIR IRB approves the waiver of informed consent and the Commander approves implementation of the waiver.

b) A request for additional information – A written request from the convened WRAIR IRB for additional information to resolve issues prior to further action.

c) Disapproval – Document criteria for disapproval of the waiver and provide these findings promptly in writing to the PI and the Sponsor of the clinical investigation.

3) Ensure that the determinations and documentation required by this SOP are included in the WRAIR IRB meeting minutes, in the protocol file, and are

retained for at least three years after the completion of the clinical investigation.

4) Ensure that records pertaining to the waiver are accessible for inspection by the FDA in accordance with 21 CFR 56.115(b).

5) Ensure that the Sponsor is provided with a copy of any study information that is publicly disclosed (e.g., copies of newspaper advertisements, tapes or transcripts of radio/television shows, minutes of community meetings) so that the Sponsor is aware that such disclosure has occurred and can provide copies of the disclosed information to the FDA.

c. To grant approval of the waiver of informed consent, the WRAIR IRB:

1) Determines and documents that the following specific conditions with respect to the research have been met (per 21 CFR 50.24):

a) The subjects are in a life-threatening situation;

b) Available treatments are unproven or unsatisfactory; and

c) The collection of valid scientific evidence, which may include evidence obtained through a randomized placebo-controlled investigation, is necessary to determine the safety and effectiveness of the intervention.

2) Determines and documents that informed consent is not feasible since:

a) The subjects will not be able to give their informed consent as a result of their medical condition;

b) The intervention under investigation must be administered before consent from the subject's LAR is feasible; and

c) There is no reasonable way to prospectively identify the individuals likely to become eligible to participate in the clinical investigation.

3) Determines and documents that participation in the emergency research holds out the prospect of direct benefit for each individual subject since:

a) Subjects are facing a life-threatening situation that requires intervention;

b) Appropriate animal and other preclinical studies have been conducted, and the information from those studies and related evidence support the

potential for the intervention to provide a direct benefit to individual subjects; and

c) Risks associated with the investigation are reasonable in relation to what is known about: the medical condition of the potential class of subjects; the risks and benefits of the standard therapy; and the risks and benefits of the proposed intervention or activity.

Note: The research must hold out the prospect of direct benefit for all subjects enrolled in the research, to include those subjects randomized to the placebo or control treatment arm (as applicable), in accordance with 10 USC 980.

4) Determines and documents that the clinical investigation could not practicably be carried out without a waiver of consent.

5) Determines that the protocol adequately defines the length of the therapeutic window, based on scientific evidence, and defines an appropriate period of time within the window for seeking informed consent from the subject or the subject's LAR or providing the opportunity for a family member (who is not an LAR) to object to the subject's participation.

6) Reviews and approves informed consent procedures and an informed consent document, containing the elements required by 21 CFR 50.25, for use with the study subject or the subject's LAR, when feasible.

7) Reviews and approves the proposed plan and procedures for contacting the subject's LAR or a family member who is not an LAR.

8) Determines that the PI is committed to attempting to contact the subject's family member within the therapeutic window to determine whether the family member objects to the subject's participation in the study if informed consent is not feasible and an LAR is not reasonable available.

9) Works with the PI to develop an effective community consultation plan that may include any of the following:

a) Face to face meetings with community representatives to answer questions and obtain firsthand knowledge of the community's reaction to and concerns about the research;

b) Invitations to community representatives to attend specific meetings of the WRAIR IRB at which the study is discussed;

c) Community members serving as consultants to the WRAIR IRB; and

d) Establishment of a panel whose members come from the study community.

10) Determines that adequate community consultation has occurred (i.e. meaningful feedback was obtained) and consider community feedback when reviewing the protocol.

11) Determines and documents that the plan for public disclosure prior to study initiation is adequate and contains all the information that a reasonable person would want to know in order to decide about research participation, to include:

a) A summary of the research protocol and study design that includes the purpose of the study;

b) Information about the test article's use;

c) How potential study subjects will be identified;

d) The sites or institutions that will be participating in the research;

e) A balanced description of the study's risk and potential benefits;

f) The fact that informed consent will not be obtained for most research subjects; and

g) Information about an individual's right to refuse to participate and ways in which individuals wishing to be excluded from the research may indicate his/her preference.

12) Determines that the plan for public disclosure to the community (both scientific and lay) after the study is completed is adequate and includes the following information:

a) Demographic characteristics of the research population;

b) Study results; and

c) Comprehensive summary data for the research community.

13) Ensures that adequate written procedures are in place to:

a) Inform the subject or an LAR at the earliest feasible opportunity that the subject has been included in the clinical investigation [information conveyed should include sufficient information to obtain informed consent for continued participation];

b) If the subject remains incapacitated and consent was waived, inform the subject's LAR or family member that the subject may discontinue participation at any time without penalty or loss of benefits;

c) If the subject dies and consent was waived, inform the subject's LAR or family member of the subject's participation and provide information about the study.

14) In cooperation with WRAIR HSPB staff, ensures that the WRAIR IRB meeting minutes summarize the discussion of controverted issues and their resolution. The summary should include issues raised during community consultations, particularly discussions of community opposition to, or concern about, the emergency research study, and how the WRAIR IRB addressed and/or resolves such concerns about the study.

15) Obtains and documents the concurrence of a licensed physician who is a member or consultant to the WRAIR IRB, but not involved in the research, that the criteria of 21 CFR 50.24 are met.

16) Determines and documents prior to study initiation that the Sponsor has established an independent Data Monitoring Committee (DMC) or retained the services of an already established DMC to serve as an advisory body to the Sponsor.

d. The WRAIR IO:

1) After the WRAIR IRB has granted approval, officially transmits a request for waiver of consent for emergency research to the US Army Medical Research and Development Command (USAMRDC), Office of Research Protection (ORP), Human Research Protection Office (HRPO).

2) After approval by the HRPO approving authority and approval by the Secretary of Defense are received, authorizes implementation of a waiver of consent for emergency research.

5. Explanation of Abbreviations, Acronyms, and Definition of Terms

Clinical Investigation	For drugs/biologics: Any experiment in which a drug or biologic is administered or dispensed to, or used involving, one or more human subjects. For devices: Any investigation or research involving one or more subjects to determine the safety or effectiveness of a device. For this SOP, the terms clinical investigation, research, clinical research, clinical study, and study are deemed to be synonymous.
Community	A group or groups of people who live and work in a particular region and who may be linked by common interests; an interacting population of different kinds of individuals constituting a society or association; or simply an aggregation of mutually related individuals in a given location.
Community Consultation	For this SOP, community consultation means providing the opportunity for discussions with, and soliciting opinions from the community (communities) in which the study will take place and from which the study subjects will be drawn. Community consultation refers to ensuring that the community (communities) is (are) involved in the IRB's decision-making process. As such, the IRB needs to provide an opportunity for the community (communities) to discuss the proposed study, its risks and potential benefits, and provide feedback to the IRB. The IRB should consider this community discussion when reviewing the protocol. The "community in which the research will take place" is the geographic area, e.g., city or region, where the hospital or clinical investigation study site is located. The "community from which the study subjects will be drawn" may be characterized by analyzing the demographics of previous hospital patients with the emergent condition under study. These communities may not always be the

	same; when they are not the same, both communities should be consulted.
Direct Benefit	A benefit to each individual subject that is realized by the subject's participation in the research, which is supported by valid and current scientific evidence.
DMC	Data Monitoring Committee – Sometimes called a data and safety monitoring board (DSMB), a DMC is a group of experts established by the Sponsor to assess at intervals the progress of a clinical trial (the safety data and efficacy endpoints), and recommend to the Sponsor whether to continue, modify, or stop the trial. DMCs for trials implemented under 21 CFR 50.24 must be composed solely of individuals without financial interest in the study and without involvement in the design or conduct of the study.
Emergency Research	A planned clinical investigation that is subject to FDA authorization in advance and involves subject(s) who are experiencing immediately life-threatening conditions for which available treatments are unproven or unsatisfactory.
Family Member	Any one of the following legally competent persons: spouse, 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 subject is the equivalent of a family relationship [21 CFR 50.3(m)]. The definition of "legally competent" may vary from state to state but in general includes an age of majority and an assessment of mental capacity.
FDA	Food and Drug Administration.
Full Board Review	For this SOP, the review of emergency medicine research that includes a waiver of informed consent, at a convened meeting at which a majority of the membership of the IRB is present including at least one member whose primary concerns are in nonscientific areas. For the research to be

	approved, it must receive the approval of a majority of those members present at the meeting.
HRPO	Human Research Protection Office, Office of Research Protection, U.S. Army Medical Research and Development Command.
HSPB	Human Subjects Protection Branch, WRAIR, the administrative branch of the WRAIR IRB.
IDE	An investigational device exemption application - An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA.
IND	Investigational new drug – An IND application is the means through which a Sponsor technically obtains an FDA exemption from the Federal requirement for an approved marketing application prior to transport or distribution of an investigational drug across state lines.
Informed Consent	A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. The informed consent document (consent form) communicates the necessary information in a meaningful, understandable way. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the Sponsor, the institution or agents thereof from liability for negligence.
Intervention	Includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
IO	Institutional Official

IRB	Institutional Review Board - a specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research
IRB Approval	The determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.
LAR	Legally authorized representative – 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.
Licensed Physician	A member of or consultant to the IRB, professional licensed to practice medicine, who is not otherwise participating in the clinical investigation.
Life-Threatening	Diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted. 21 CFR 50.24 applies only to life-threatening EMERGENCY situations.
Office of Research Protections	Office that houses the HRPO, within US Army Medical Research and Development Command
PI	Principal Investigator or WRAIR POC – For this SOP, an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to a subject.
POC	Point of Contact
Public Disclosure	For this SOP, public disclosure means informing the community(ies), the public, and researchers about the study (1) prior to its commencement and (2) following its completion. The dissemination of information about an emergency research study must be sufficient to allow a reasonable assumption that the communities are aware

	that the study will be conducted, and later, communities and scientific researchers are aware of the study's results.
SOP	Standard Operating Procedure
Sponsor	A person or other entity that takes responsibility for and initiates a clinical investigation. A Sponsor may be an individual, a company, a governmental agency, an academic institution, a private organization, etc.
SRC	Scientific Review Committee
Therapeutic Window	The time period, based on available scientific evidence, during which administration of the test article might reasonably produce a demonstrable clinical effect.
Test Article	Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act, as amended, or under sections 351 and 354-360F of the Public Health Service Act.
WRAIR	Walter Reed Army Institute of Research
WRAIR IRB	WRAIR Institutional Review Board (IRB), an ethical review committee for research involving human subjects at WRAIR its CONUS detachments or Overseas Laboratories, or when WRAIR funding, facilities or personnel are involved in any way (i.e., investigator). This includes protocols for which recruitment of subjects is through WRAIR.
USAMRDC	US Army Medical Research and Development Command

6. References

Reference Number or Authors	Document Title
21 Code of Federal Regulations (CFR) 50	Food and Drug Administration, Protection of Human Subjects
21 Code of Federal Regulations (CFR) 56	Food and Drug Administration, Institutional Review Boards
21 Code of Federal Regulations 812	Food and Drug Administration, Investigational Device Exemptions
10 US Code (USC) 980	Limitation on use of humans as experimental subjects
Department of Defense (DoD) Instruction 3216.02	Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research
SOP UWS-HP-605	Humanitarian Use Devices
SOP UWS-HP-607	Emergency Use Notification and Reporting Procedures
SOP UWS-HP-618	Continuing Review and Continuation Determination
	Food and Drug Administration, *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research,* Guidance, April 2013

7. Appendices and Attachments

Not applicable.

8. Document Revision History

Version Number	Brief Description of Changes	Effective Date
.00	New	30 October 2007
.01	Updated names and titles, replaced PI responsibilities and procedures with guidance for PI	Not signed
.02	Updated regulatory requirements and convert to current SOP template	