

NAVMEDCEN SDIEGO INSTRUCTION 6710.19

From: Commander

Subj: EMERGENCY USE OF AN INVESTIGATIONAL AGENT

Ref: (a) BUMEDINST 6710.69 (Use of Investigational Agents in Humans)
(b) Code of Federal Regulations, Title 21 (Food and Drugs), Part 56 (Institutional Review boards) (21 CFR 56)
(c) Code of Federal Regulations, Title 21 (Food and Drugs), Part 50 (Protection of Human Subjects) (21 CFR 50)
(d) Food and Drug Administration Information Sheets Guidance for Institutional Review Boards and Clinical Investigators 1998 Update
(e) United States Code, Title 10 (Armed Forces), Section 980 (Limitations on Use of Humans As Experimental Subjects) (10 USC 980)

Encl: (1) Directions for Emergency Investigational Agent Use
(2) Emergency Investigational Agent Cover Sheet
(3) Statement of Investigator Form (FDA 1572)
(4) Individual Consent Form
(5) Third Party Consent Form
(6) Investigational Agent Status Report (NAVMED 6710/9)

1. Purpose. To define the procedure for emergency one-time use of an investigational agent at the Naval Medical Center, San Diego (NMCS) per references (a) through (e).

2. Cancellation. NAVMEDCEN SDIEGOINST 6710.16F (Procedure for Securing Authorization/Approval for an Emergency One-Time Use of an Investigational Drug in a Single Patient).

3. Definitions

a. Emergency use. The use of an investigational agent on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain Institutional Review Board (IRB) approval.

b. Investigational Agent. Investigational drug, biologic or device.

c. Investigator. An individual under whose immediate direction the investigational agent is administered to, or used involving, a subject.

d. Life threatening includes the scope of both life threatening and severely debilitating. Life threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes. The criteria for life threatening do not require the condition to be immediately life threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

e. Sponsor. A person or other entity that initiates a clinical investigation but does not actually conduct the investigation.

4. Emergency Use of Investigational Drugs or Biologics. The emergency use of an unapproved investigational drug or biologic requires an Investigational New Drug (IND) application. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's Investigational New Drug (IND) application.

5. Emergency Use of Investigational Devices. The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an Investigation Device Exemption (IDE) for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, the FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to the FDA that an emergency actually existed. After an unapproved device is used in an emergency, if an IDE for the use does exist, the physician should notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use and provide FDA with a written summary of the conditions constituting

the emergency, subject protection measures, and results.

6. Emergency Exemption from Prospective IRB Approval. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described under emergency use above exist, allows for one emergency use of an investigational agent without prospective IRB review. FDA regulations require that any subsequent use of the investigational agent at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

7. Institutional Approval and IRB Notification

a. Reference (b) requires that the IRB be notified of the emergency use of an investigational agent. Reference (d) states that "Institutional procedures may require that the IRB be notified prior to such use, however, this notification should not be construed as IRB approval." The institutional oversight exercised by NMCS D of the emergency use of investigational agents as below requires endorsement by the Chair, IRB (or his/her designee). By this procedure, the IRB is notified prior to the emergency use of an investigational agent. However, the Chair, IRB, acting in this capacity is not providing IRB approval.

b. The Chair, IRB will provide the first review of requests for emergency use of an investigational agent. The Chair, IRB must favorably endorse the application by signature. If the Chair, IRB is not available, then the Vice Chair, IRB or another IRB member designated by the Chair will endorse the request. This endorsement by the Chair, IRB must be obtained prior to "By direction" approval by the Head, Clinical Investigation Department (CID). If the Head, CID is not available, then the next available individual up the administrative chain of command (the Director for Medical Education, the Deputy Commander or the Commander) will sign if approved. The original signed documents must be provided to CID after an approval is granted. This institutional approval should not be construed as IRB approval.

c. If the emergency situation cannot wait until normal working hours, the investigator may obtain a copy of this instruction with enclosures (1) through (6) at <http://nmcsdintranet.med.navy.mil/cid/protocol/default.htm> from the NMCS D Intranet or from the Central Files office located in the Command Suite. The investigator may then complete enclosure (2) and obtain verbal endorsement by the Chair, IRB and verbal institutional approval from the Head, CID per paragraph 7b above, and indicate these on enclosure (2). Under these circumstances, informed consent must still be obtained using enclosure

(4) or (5). Verbal endorsement and approval must be followed-up with actual signatures and by the complete approval process as described in paragraph 9 below on the next working day.

d. The Chair, IRB will report all emergency uses of investigational agents to the full IRB at the next regularly scheduled meeting, however, this should not be construed as IRB approval.

8. Informed Consent Requirement. Even for the emergency use of an investigational agent, the clinician is required to obtain informed consent of the subject using enclosure (4) or the subject's legally authorized representative using enclosure (5). Templates for enclosures (4) and (5) are updated periodically and the most recent versions, found at <http://nmcsdinstranet.med.navy.mil/cid/protocol/default.htm> should be used.

9. Approval Process. The procedures required for the emergency use of an investigational agent are as follows:

a. Obtain enclosures (1) through (6) from CID. CID will assign an emergency agent use number to enclosure (2).

b. The Principal Investigator (PI) must complete enclosures (2) and (3) and prepare enclosure (4) or enclosure (5). The complete packet should also include:

(1) A copy of the protocol for administration/use provided by the sponsor.

(2) A copy of the manufacturer's brochure and any relevant literature.

(3) Curriculum vitae for the PI and any Associate Investigator (AI) who could possibly administer/use the agent.

c. Institutional approval should be obtained per paragraph 7 above.

d. Informed consent should be obtained as described in paragraph 8 above. The original signed consent must be maintained in the patient's medical record. A copy of the signed consent must be included in the complete packet submitted to CID.

e. The drug/device may be used after completion of all of the above steps.

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10. Administrative Follow-up Procedure

a. CID is responsible for ensuring that all completed documents are forwarded to the Commanding Officer, Naval School of Health and Sciences (NSHS) (Code OP6), Bethesda, MD 20889-5612 within two weeks of the investigational agent being used.

b. The PI must report adverse reactions or unexpected events via memorandum to CID at the earliest possible date. These reports will then be forwarded to NSHS.

c. Until the emergency investigational agent use is completed, annual reviews will be conducted using enclosure (6). These reports will then be forwarded to NSHS.

d. Upon termination or completion of the emergency investigational agent use by the PI, a report must be submitted to CID stating the results using enclosure (6). A case summary must be included as an attachment. These reports will then be forwarded to NSHS.

e. The PI should submit a research protocol for this investigational agent use if the investigator foresees future use of the agent for the same conditions in other patients.

f. CID will maintain a log referencing all emergency investigational agent use requests, approvals, CID numbers, name of the investigational agent, name of PI, patient's last name/initial, and the closing report. Copies of the emergency investigational agent use approvals will be provided to the PI and the Pharmacy. CID, as specified above, will maintain all completed forms, indefinitely.

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