INVESTIGATIONAL DEVICE and/or DRUG USAGE

1. **PURPOSE:** To establish a service level policy for the use of investigational devices and drugs, including emergency or one-time treatment use, at the Portland VA Health Care System (VAPORHCS).

2. **POLICY:**
   A. The Food and Drug Administration (FDA) regulations require Institutional Review Board (IRB) review and approval for investigations, clinical investigations (both as defined in Section 3) and certain clinical treatments (as outlined in this policy) involving products regulated by the FDA. FDA-regulated products include "foods, dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products."
   B. VA investigators are expected to fulfill all of the responsibilities delineated in the FDA regulations. Investigations, clinical investigations and certain clinical treatments regulated by the FDA may only be conducted at the VAPORHCS after:
      i. The IRB of record has:
         a. received documentation that the research will be conducted under an applicable investigational new drug application (IND) or investigational device exemption (IDE); or
         b. formally determined and documented that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or
         c. formally determined that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.
      ii. The research project and associated documentation have been approved by the IRB and the Research & Development Committee (R&DC).
      iii. The patient or legally authorized representative has signed the approved VA Research Informed Consent Form (VA Form 10-1086) and, as applicable, HIPAA authorization, excluding the exceptions outlined in this policy.

3. **DEFINITIONS:**
   A. A **Biologic** is a biological or related product, regulated by the FDA, including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Studies of unlicensed biologics are regulated according to the IND regulations, except in some cases when the biologic is in a combination product with a medical device.
   B. A **Clinical** Investigation is defined by the FDA, under the IND regulations, as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human

subjects. For the purposes of [the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice."

C. An **Investigation** is defined by the FDA, under the IDE regulations, as "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device."
D. An **Investigational Device**, as defined by the FDA, is a device, including a translational device, that is the object of an investigation. A mobile application may be considered applicable for FDA oversight if it meets the definition of a device under section 201(h) of the Federal Food, Drug, and Cosmetic Act and is intended to be used as an accessory to a regulated medical device or to transform a mobile platform into a regulated medical device.
E. An **Investigational Drug**, as defined by VHA, is a chemical or biological drug that is used in a clinical investigation. An investigational drug can be:
   i. a new chemical compound, which has not been released by the FDA for general use; or
   ii. an approved drug that is being studied for an approved or unapproved use, dose, dosage form, administration schedule, or under an IND application, in a controlled, randomized, or blinded study.
F. An **Investigational (New) Drug,** as defined by FDA regulations, is a new drug or biological drug that is used in a clinical investigation; the term also includes a biological product that is used in vitro for diagnostic purposes.
G. An **Investigator** is defined by the FDA regulations as an "individual who actually conducts a clinical investigation (i.e. under whose immediate direction the test article is administered or dispensed to, or used involving, a subject), or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team".
H. A **Non-significant Risk (NSR)** Device is one that does not present significant risk to the human subjects.
I. **Off-Label** means the use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label uses requires IND or IDE applications.
J. A **Significant Risk (SR) Device** is defined by the FDA as an investigational device that presents a potential for serious risk to the health, safety or welfare of the human subjects and that:
   i. is intended for use as an implant;
   ii. is purported or represented to be for a use in supporting or sustaining human life;
   iii. is for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
   iv. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
K. **Sponsor** means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

L. A **Sponsor-investigator** is defined by FDA regulations as an individual who both initiates and actually conducts, alone or with others, an investigation and under whose immediate direction the investigational drug or device is administered, dispensed, or used. The term does not include any person other than an individual. Under FDA regulations, the obligations of a sponsor-investigator include those of both an investigator and those of a sponsor.

M. An **Unapproved Device** is defined in FDA guidance as "a device that is used for a purpose, condition or use for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 360e)(the act) or an approved IDE under section 520(g) of the act [21 U.S.C. 360 j(g)]."

4. RESPONSIBILITIES:

A. The **Associate Chief of Staff/Research & Development** is responsible for developing and managing policies and procedures related to the use of investigational devices and investigational drugs at the Portland VA Medical Center.

B. The **Research & Development Committee** is responsible for assuring that all necessary subcommittee approvals are in place for studies involving investigational drugs and/or devices with human subjects and providing final approval of those studies.

C. The **Institutional Review Board** is responsible for approving or disapproving research projects involving investigational drugs and/or devices in accordance with the procedures outlined in this policy.

D. The **Chief of Staff** is responsible for evaluating and providing clearance for the emergency use of a drug or device.

E. **Physicians/Principal Investigators (PIs)** are responsible for:

i. Adhering to FDA regulations regarding drugs and/or devices, as well as the requirements and procedures outlined in this policy.

ii. Submitting the scientific protocol (when applicable) and all required documentation, which may include an informed consent form (ICF), IRQ Appendices for investigational drugs and/or devices and/or an Investigational Drug Information Record (VA Form 10-9012) to the Research Administration Office and obtaining IRB review and approval, prior to beginning the investigation or other use of the drug(s) and/or device(s) outlined in this policy.

iii. Submitting continuing review documentation (as appropriate) and all reportable events (including adverse events) to the IRB in a timely manner.

iv. Using the device(s) and/or drug(s) only after notification of IRB and R&DC approval (except for emergency uses, as per Section 5.D.iii) and after obtaining informed consent and, when applicable, a HIPAA authorization from individuals (expect as per Section 5.D.iii.h or when the IRB approves a waiver of the requirements for informed consent and, if applicable, HIPAA authorization).

v. Forwarding the original signed ICF (VA Form 10-1086) and, when applicable, HIPAA authorization for each individual enrolled into the research project, or treated under an expanded access use, to the Research Administration Office as soon as possible

(preferably within 3 days) for scanning into the patient's electronic medical record. The patient must initial the original signed ICF acknowledging receipt of a copy of the informed consent form. A copy of the ICF must also be provided to the Research Pharmacy.

vi. Providing secure storage for all investigational devices and/or drugs according to their storage requirements as outlined by the sponsor and/or, as appropriate, the Research Pharmacy.

vii. Providing accountability of all investigational devices and drugs and ensuring proper dispensing, utilization, storage, security and use of the investigational devices and/or drugs, as outlined in the approved IRB submission (when applicable).

viii. Registering applicable studies at http://www.clinicaltrials.gov/. Clinical trial information must be submitted for inclusion in the clinical trial registry databank. The applicable clinical trials are:

a. Drug or biologic trials: controlled clinical investigations (except for Phase 1 trials) of drugs or biologics subject to FDA regulation; and

b. Device trials: controlled trials (except for small feasibility studies) with health outcomes of devices subject to FDA regulation.

5. PROCEDURES:

A. Research with Investigational Drugs

i. An investigational new drug application (IND) is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." An investigational drug must have an IND before it can be shipped, unless it falls under one of the categories of clinical investigations that are exempt from the IND requirements.

ii. Categories of clinical investigations that are exempt from the IND requirements:

a. Certain research involving marketed drug products, if all of the following criteria for an exemption are met:

(1) the drug product is lawfully marketed in the United States;

(2) the investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(3) the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(4) the investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(5) the investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50;

(6) the investigation is conducted in compliance with the requirements of 21 CFR 312.7 (promotion of investigational drugs); and
(7) the investigation does not intend to invoke an exception from informed consent requirements for emergency research.

b. Bioavailability or bioequivalence (BA/BE) studies using unapproved versions of approved drug products, if all of the following conditions are met:
(1) the drug product does not contain a new chemical entity, is not radioactively labeled, and is not cytotoxic;
(2) the dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
(3) the investigation is conducted in compliance with the requirements for review by an IRB and the requirements for informed consent; and
(4) The sponsor meets the requirements for retention of test article samples.

c. Radioactive drugs (approved and unapproved), if they are generally recognized as safe and effective for those uses, under the following conditions:
(1) A Radioactive Drug Research Committee, composed and approved by the FDA, has made certain determinations regarding the dosage and has approved the use of the radioactive drug in human subjects.
(2) The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.
(3) The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

iii. A clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR 312 if the investigation does not otherwise require submission of an IND.

iv. Clinical investigations that are exempt from IND regulations still require IRB review and approval.

v. Even when there is no immediate intent to change product labeling or advertising, investigators who are planning rigorous, carefully controlled clinical investigations of off-label uses of approved drugs or biologics should contact the FDA regarding obtaining an IND before submitting a protocol to the IRB.

vi. The PI must provide information to the VAPORHCS Research Pharmacy for each participant receiving an investigational drug. The signed ICF is used by the Research Pharmacy to locate records in CPRS and assure that documentation is available on allergies, toxicities, and adverse drug events related to the investigational drug, and the potential for interactions with other drugs, foods, or dietary supplements. In cases where any of this information is missing, the Research Pharmacy will follow-up with the PI. The PI is also responsible (and may work with the Research Administration Office) to assure that the Research Pharmacy receives the following:

a. Documentation of IRB initial and continuing review approvals and any other relevant approvals.

b. A copy of VA Form 10-9012, Investigational Drug Information Record (when applicable), that has been signed by all required parties.
c. A copy of the currently approved protocol.
d. Copies of sponsor-related correspondence specific to the drug(s), as appropriate;
e. Copies of all correspondence addressed to the investigator from the FDA and other involved authorities, specific to the investigational drug(s), as appropriate.
f. Notification to the Chief of Pharmacy Service, the Research Pharmacy and the IRB in writing when a study involving investigational drugs is suspended, terminated, or closed.

vii. The PI must comply with all dispensing requirements and all documentation requirements, including making relevant records accessible to the Research Pharmacist when requested.
viii. The PI must comply with all VHA pharmacy requirements regarding receiving, dispensing, storing and record-keeping for investigational drugs.

B. **Research with Investigational Devices**

i. An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization, or PMA) or cleared to market [via 510(k)] by the FDA to be shipped in order to conduct investigations of that device.
ii. Research with investigational devices falls into three categories:
a. Investigations of Significant Risk (SR) devices to determine safety and effectiveness; an IDE must be approved by the FDA before the study may proceed.
b. Investigations of Non-Significant Risk (NSR) devices to determine safety and effectiveness; if the IRB agrees with the sponsor that the device meets the criteria for a NSR device, or if the FDA has already made the NSR determination, then an approved IDE is not required.
c. Investigations exempted from the IDE regulations.
iii. If the sponsor or FDA has determined a device to be SR, the IRB must also consider the device to be SR during the IRB review. If the FDA has determined a device study to be NSR, the IRB must also consider the device study to be NSR during the IRB review. Otherwise, the IRB must determine whether an investigational device is either SR or NSR.
a. The determination of level of risk of the device is based on the proposed use of the device, rather than just the device itself.
b. The designation of SR or NSR may be considered as a factor in, but is independent of, the risk level designation for a study as a whole and the determination for frequency of continuing review.
c. The IRB makes its decision of SR or NSR level of the device based on the review and evaluation of the following:
(1) the risk evaluation provided by the sponsor or sponsor-investigator;
(2) the investigator's brochure, if applicable;
(3) federal regulations;

(4) the FDA Information Sheet, "Significant Risk and Non-Significant Risk Medical Device Studies;"
(5) any additional correspondence regarding the device from the FDA, sponsor, and/or investigator;
(6) the nature of the harm that may result from use of the device;
(7) if participants must undergo a procedure as part of the investigational study, the potential harm that could be caused by the procedure in addition to the potential harm caused by the device; and
(8) when applicable, the information and justification given by the sponsor for any NSR determination.

d. The rationale for the IRB's NSR or SR determination must be documented in the IRB minutes.
e. If the IRB disagrees with a sponsor's NSR assessment and decides that the study is SR, the IRB shall inform the PI and, where appropriate, the sponsor.

iv. **Significant Risk (SR) Device Research**

a. SR device studies must follow all applicable IDE regulations. Applications to the IRB for research on the use of an SR device must be accompanied by a copy of the FDA's approval of the IDE application..
b. Research projects involving SR devices do not qualify for expedited review during the initial review.
c. Research projects involving SR devices may be considered for expedited review during the continuing review, if the IRB determines that the study meets one of the following three criteria:
(1) The research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects;
(2) No subjects have been enrolled and no additional risks have been identified; or
(3) The remaining research activities are limited to data analysis.

v. **Non-significant Risk (NSR) Device Research**

a. Because NSR studies do not require an IDE, a clinical investigation involving an investigational device classified by the sponsor as NSR may be submitted to an IRB for review without an IDE. The sponsor should provide the IRB with a risk assessment and the rationale used in making its NSR risk determination. The IRB will review that information, in conjunction with IRQ Appendix E, to determine whether the device fulfills the requirements to be considered an NSR device and, thus, may be used following the abbreviated IDE requirements. In cases when the investigator applies to the IRB for a NSR determination for a device study, but the IRB determines that the device is SR, the IRB will notify the investigator and, where appropriate, the sponsor.

vi. **Exempt Device Research**

a. Clinical investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories:

(1) A device legally marketed in the U.S. that is used for investigation in accordance with the indications in the FDA-approved labeling.
(2) An in vitro diagnostic device, if the testing is: 1) 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. Note: An in vitro diagnostic device to support an application for research or marketing of the device is considered a human subject investigation, regardless of whether samples to be used are individually identifiable or not. Such studies require IRB review but may be eligible for expedited review and waiver of informed consent, when appropriate.
(3) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more medical devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
(4) A custom device [as defined in 21 CFR812.3 (b)], unless the device is being used to determine safety or effectiveness for commercial distribution.
(5) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
(6) 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 indications in the labeling the FDA reviewed under subpart E of part 807 in determining substantial equivalence.

C. Sponsor-Investigator Research

i. In reviewing research involving test articles, the IRB evaluates whether a VAPORHCS investigator holds his or her own IND or IDE. If so, the IRB confirms that the investigator understands his or her additional responsibilities as the sponsor of the research, including reporting requirements to the FDA. The IRB may contact or site visit the sponsor-investigator as deemed necessary. A sponsor-investigator must follow all FDA regulations applicable to sponsor responsibilities. Sponsor-investigators of NSR device studies have abbreviated sponsor responsibilities.
ii. Sponsor-investigators who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE. In addition, they must document in writing that the product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP) or any modification to those standards approved by the FDA in issuing the IND or IDE.

D. Expanded Access to Investigational Drugs and Devices

i. **Investigational and Approved Drugs**: Expanded access use (often referred to as “compassionate use”) of drugs involves the use of investigational new drugs and

approved drugs, where availability is limited by a risk evaluation and mitigation strategy, when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. Expanded access uses are not primarily intended to obtain information about the safety or effectiveness of a drug.

a. All expanded access drug use, other than emergency uses (see Section 5.D.iii), requires prior IRB review and approval. The IRB review must occur at a convened IRB meeting, and the IRB must determine that informed consent will be sought from each prospective individual or the individual's legally authorized representative, in accordance with FDA regulations.
b. All expanded access drug use must meet the following basic criteria:
   (1) The patient(s) to be treated has 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;
   (2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
   (3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
c. Categories of Access:
   (1) **Individual patient access** is generally limited to a single course of therapy for a specified duration, unless the FDA expressly authorizes multiple courses or chronic (i.e., ongoing) therapy. The treating physician should request an individual patient IND for treatment use on FDA form 1571 (specifying whether it is an emergency IND or individual patient IND).
      (a) Additional criterion for individual patient access:
         (i) The physician must determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition, and the FDA must determine that the patient cannot obtain the drug under another IND or protocol.
   (2) **Intermediate-size patient population access programs** are intended generally to accommodate population sizes smaller than the large populations typical of treatment access and larger than the limited number of patients who might obtain treatment under individual patient access. When the requested drug is being developed, intermediate-size patient population access programs generally are used earlier in drug development than treatment access. Also, in contrast to treatment access, an intermediate-size patient population access program can be used to obtain access to a drug that is not being developed or an approved or related drug that is not available through marketing channels. A drug may also be under study in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial for various reasons.

(a) Additional criteria for intermediate-size patient population access programs: The FDA must determine that:
(i) there is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and
(ii) there is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(3) **Treatment access** involves hundreds to thousands of patients receiving the treatment.
(a) Additional criteria for treatment access:
(i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or all clinical trials of the drug have been completed; and
(ii) The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and
(iii) When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use (e.g. data from phase 3 trials, or compelling data from completed phase 2 trials); or when the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury (e.g. clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence).

d. Types of regulatory submissions for expanded drug access:
(1) An **Access Protocol** is submitted as a protocol amendment to an existing IND if the sponsor seeking access has an existing IND in effect.
(a) For an individual patient or intermediate-size patient population access protocol, access to the drug can begin once the protocol has been submitted to FDA and has been approved by an IRB. For a treatment access protocol, however, access may not begin until 30 days after FDA receives the protocol or on earlier notification by FDA, and IRB approval has been obtained consistent with 21 CFR 56.
(2) An **Access IND** is a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use when: there is no existing IND in effect for the drug; or there is an existing IND in effect for the drug, but the sponsor of the existing IND declines to be the sponsor of the access use (e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's physician submit a separate individual patient IND).

(a) When an access IND (not for emergency use) is submitted, the treatment use of the drug may begin when the IND goes into effect and IRB approval has been obtained consistent with 21 CFR 56. An access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA.

e. Prior approval or authorization from the FDA is required for every category of the expanded access use program.

f. Reporting and monitoring requirements for investigators and sponsors for expanded access use drugs are outlined at 21 CFR 312.

ii. **Investigational Devices**: There are three types of expanded access to devices.

a. **Compassionate use**: A physician can use an unapproved device to treat, diagnose, or monitor a patient with a serious disease or condition. The use is typically approved for individual patients but may be approved to treat a small group.

(1) Compassionate use must meet the following basic criteria:

(a) The patient must have a serious disease or condition and no alternative treatment available. The patient does not meet the requirements for inclusion in the clinical investigation.

(b) The probable risk to the patient is not greater than the probable risk from the disease.

(c) The treating physician believes the device may provide a benefit in treating and/or diagnosing the patient's disease or condition.

(2) Prior to treatment, the physician must obtain:

(a) an independent assessment from an uninvolved physician;

(b) authorization from the sponsor for the use;

(c) approval from the FDA for the use;

(d) concurrence from the IRB chair for the use; and

(e) clearance from the VAPORHCS Chief of Staff.

(3) The IRB Chair's concurrence involves:

(a) ensuring sponsor authorization and FDA approval for the proposed use; and

(b) reviewing the independent assessment from uninvolved physician, the consent document, the device brochure and any other relevant documents (e.g. treatment plan).

(4) For an individual patient, the sponsor should submit an IDE supplement to the FDA requesting approval for a protocol deviation. The supplement should include:

(a) a description of the patient's condition and the circumstances necessitating treatment;

(b) a discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;

(c) an identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and

(d) the patient protection measures that will be followed (e.g. informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor).

(5) For a few patients, the physician should request access to the investigational device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

(6) Consent from the patient(s) must be obtained. The attending physician should devise an appropriate schedule for monitoring the patient(s), considering the investigational nature of the device and specific patient needs. The patient(s) should be monitored to detect any possible problems arising from the use of the device.

(7) Following compassionate use of a device, the physician must:

(a) write a summary of the use and provide it to the IRB and the sponsor; a follow-up report should be submitted to the FDA, as an IDE supplement, in which summary information regarding patient outcome is presented; and

(b) report any problems as a result of the device use to the IRB and sponsor; any problems which occurred as a result of the device use should be discussed in the supplement and reported to the IRB as soon as possible.

b. **Treatment Use**: An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of a clinical trial with the device, if the data suggests that the device is effective, then it may be appropriate to use the device in the treatment of patients, who have life-threatening or serious diseases but are not in the trial, under the provisions of the treatment investigational device exemptions IDE regulation.

(1) FDA would consider the use of an investigational device under a treatment IDE if:

(a) the device is intended to treat or diagnose a serious or immediately life-threatening disease or condition (i.e. a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment);

(b) there is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;

(c) the device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed;

(d) the sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

(2) Applications for treatment use must include all items listed in 21 CFR 812.36(c)(1).
(3) A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under FDA regulations governing IDEs, IRBs and informed consent. Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the FDA regulations governing informed consent and IRBs.
(4) Contingent upon IRB review and approval, treatment use may begin 30 days after FDA receives the treatment IDE submission. The FDA may notify the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. The FDA may approve the treatment use as proposed or approve it with modifications.
(5) Reporting requirements: The sponsor of a treatment IDE must submit progress reports on a semi-annual basis to all reviewing IRB's and the FDA, until the filing of a marketing application, and is responsible for submitting all other required reports, such as unanticipated adverse device effects and final reports.

c. **Continued Access ("extended investigation")**: FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed, in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA. There must be a public health need, or preliminary evidence that the device will be effective and no significant safety concerns.
(1) The Continued Access Policy may be applied to any clinical investigation that meets the criteria identified above but is intended to be applied late in the device development process (i.e. after the controlled clinical trial has been completed).
(2) A sponsor's request for an extended investigation should be submitted as an IDE supplement and include the following information:
(a) A justification for the extension;
(b) A summary of the preliminary safety and effectiveness data generated under the IDE;
(c) A brief discussion of the risks posed by the device;
(d) The proposed rate of continued enrollment (the number of sites and subjects);
(e) The clinical protocol, if different from that used for the controlled clinical trial, as well as the proposed objectives for the extended study; and
(f) A brief discussion of the sponsor's progress in obtaining marketing approval/clearance for the device.
(3) If the FDA approves the IDE supplement, IRB approval must be maintained, and informed consent must be obtained from future subjects.

iii. **Emergency Use of Unapproved Devices or Investigational Drugs**

a. Emergencies may arise where an unapproved device or drug may offer the only possible life-saving alternative, but an IDE for the device or IND for the drug does not

exist, the proposed use is not approved under an existing IDE or IND, or the physician or institution is not approved under the IDE or IND.

b. Emergency use of a test article, meeting the requirements below, is exempt from prior IRB review and approval, provided that such emergency use is reported to the IRB in writing within 5 working days after the use (whenever possible, the IRB should be notified prior to such use). Expedited IRB approval is not permitted for emergency uses. The FDA regulations allow for one emergency use of a test article at an institution but then any subsequent use of the investigational product at the institution is generally required to have prospective IRB review and approval.
c. The FDA may require data from an emergency use to be reported in a marketing application. However, the Department of Health and Human Services (DHHS) states "emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity." Thus, a patient receiving an emergency use of a test article is not considered a research participant by DHHS regulation. .
d. Additional Requirements for Emergency Use of an Investigational Drug:
   (1) The patient needs treatment before a written submission can be made – i.e. treatment of the patient must occur within a very limited number of hours or days.
   (2) The licensed physician or sponsor must contact the FDA (via phone, facsimile or other electronic communications) in advance to request and obtain authorization for the use and agree to submit an expanded access IND or protocol within 15 working days of FDA's authorization of the use. The FDA must determine that the patient cannot obtain the drug under another IND or protocol.
e. Requirements for Emergency Use of an Unapproved Device:
   (1) A patient is in a life-threatening or severely debilitating condition that needs immediate treatment.
   (2) No generally acceptable alternative for the condition exists.
   (3) Assessment by the treating physician of the potential benefits from the unapproved use indicates a substantial reason to believe that benefits will exist for the patient(s).
   (4) Sufficient time is not available to obtain prior FDA approval through existing procedures, prior to using the device because of the immediate need.
   (5) An independent assessment by an uninvolved physician is obtained. If time is not sufficient to obtain an uninvolved physician's assessment, the treating physician should make the determination and have the determination reviewed and evaluated in writing by an uninvolved physician; all of the documentation from the treating physician and uninvolved physician must be submitted to the IRB within 5 working days after the use of the test article.
   (6) Concurrence from the IRB Chairperson is obtained prior to the use.
f. Expectations of Physicians for Emergency Uses:
   (1) Determine whether all requirements for emergency use have been met.

(2) Exercise reasonable foresight with respect to potential emergencies and make appropriate arrangements under the IDE or IND procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.
(3) If an approved IDE or IND exists for the device or drug, obtain authorization from the sponsor.
(4) Obtain institutional clearance from the VAPORHCS Chief of Staff or designee.
(5) Obtain informed consent from the patient or the patient's legally authorized representative, except as noted in Section 5.D.iii.g.
(6) Notify the IRB as soon as possible, within 5 working days, of the use of the drug or device.

g. Informed Consent Requirements for Emergency Uses
(1) Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative, unless both the investigator and a physician, who is not otherwise participating in the clinical investigation, certify in writing all of the following:
(a) The subject is confronted by a life-threatening situation necessitating the use of the test article.
(b) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
(c) Time is not sufficient to obtain consent from the subject's legal representative.
(d) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
(2) If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. All of the documentation from the investigator and non-participating physician must be submitted to the IRB within five working days after the use of the test article.

h. Notification to the Center for Devices and Radiological Health (CDRH)
(1) The device developer must notify the Center for Devices and Radiological Health (CDRH) Program Operation Staff immediately after the shipment is made when a device is to be used in an emergency situation meeting all justifiable requirements.
(2) An unapproved device or drug may not be shipped in anticipation of an emergency.
(3) CDRH Business Hour Contact Information: (301) 594-1190. Nights and Weekends Contact Information: Division of Emergency and Epidemiological Operations: (202) 857-8400

i. Procedures After Emergency Use
(1) The investigator must report the use to the IRB as soon as possible, within 5 days, of usage and otherwise comply with provisions of the IRB regulations.

(2) The investigator should evaluate the need for the device or drug in the future, and if future use is likely, obtain IRB approval and an approved IDE or IND for future use.
(3) If the device or drug does have an IDE or IND, the physician must notify the sponsor of the emergency use.
(4) For drugs, the physician must submit an expanded access IND or protocol within 15 working days of FDA's authorization of the use.
(5) For devices, if the device has an IDE, the use should be reported to FDA by the sponsor, via a supplemental application to the IDE, within 5 working days from the time the sponsor learns of the use; in addition, the physician should provide the sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulations. If an IDE does not exist, the investigator must notify the FDA of the emergency use and provide the FDA with a written summary of the conditions constituting the emergency, patient protection measures, and results.

E. Humanitarian Use Devices (HUDs)

i. As defined by the FDA, a Humanitarian Use Device (HUD) is a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year."
ii. A **Humanitarian Device Exemption (HDE)** is an application that is similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of the FDA Act. FDA approval of an HDE authorizes an applicant to market an HUD, subject to certain profit and use restrictions. Approval is based on safety and probable benefit. HUDs can only be used in a facility after an IRB has approved their use in that facility, except in certain emergencies.
iii. An applicant should submit to the FDA a request for an HUD designation before submitting an application to the FDA for an HDE.
iv. The FDA will consider an HDE application for any of the following situations:
    a. no comparable device is available to treat or diagnose the disease or condition; or
    b. a comparable device is available under another approved HDE application; or
    c. a comparable device is being studied under an approved IDE.
v. An HUD may be used:
    a. according to its approved labeling and indication(s) to treat or diagnose patients; or
    b. in a clinical investigation to collect safety and effectiveness data, in which case the use is subject to the same requirements that apply to all FDA-regulated clinical studies and, if the HUD is being studied for a use other than its approved indication(s), the IDE regulations apply.
vi. **IRB Initial Review of HUDs**: For initial review of an HUD, IRBs are required to perform their review at a convened meeting. The following materials should be submitted to the IRB for initial review of an HUD application:
    a. a VAPORHCS HUD Initial Application;
    b. a copy of the HDE approval order;

c. a description of the device;
d. the product labeling;
e. the patient information packet that may accompany the HUD; and
f. a summary of how the physician proposes to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.
g. If the HUD is being used according to its approved labeling and indication(s) to treat or diagnose patients, the following must also be submitted: a sample clinical consent form for the use of the HUD.
h. If the HUD is being used in a clinical investigation to collect safety and effectiveness data, the following must also be submitted:
(1) protocol;
(2) abstract;
(3) VAPORHCS IRB Initial Review Questionnaire (IRQ);
(4) any items prompted on the IRQ; and
(5) informed consent form (on VA Form 10-1086) and HIPAA authorization, as applicable.

vii. A list of approved HDEs may be found at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2. The approval order, labeling, and patient information may be found by selecting the number of the appropriate HDE.
viii. Reporting requirements:
a. Device user facilities and/or manufacturers are required to submit medical device reports to FDA and to the IRB of record whenever an HUD may have caused or contributed to a death or a serious injury. The device user facility must also report such occurrences to the manufacturer (or record if the manufacturer is unknown).
b. The HDE holder must provide the FDA with updated information on a periodic basis, demonstrating that the HUD designation is still valid, based on the most current and authoritative information available.
ix. **IRB Continuing Review of HUDs**: For continuing review, IRBs may use the expedited review procedures, if applicable.
a. If the HUD is being used according to its approved labeling and indication(s) to treat or diagnose patients, a VAPORHCS HUD Continuing Review form must be submitted.
b. If the HUD is being used in a clinical investigation to collect safety and effectiveness data, a VAPORHCS Continuing Review Questionnaire (CRQ) and any items prompted on the CRQ must be submitted.

6. REFERENCES:
21 CFR 50 – Protection of Human Subjects:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50&showFR=1

21 CFR 56 – Institutional Review Boards:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=56&showFR=1
21 CFR 312 - Investigational New Drug Application (IND):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1
21 CFR 314 – Applications for FDA Approval to Market a New Drug:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1
21 CFR 315 – Diagnostic Radiopharmaceuticals:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=315&showFR=1
21CFR 320 - Bioavailability and Bioequivalence Requirements:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320&showFR=1
21 CFR 361 - Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=361&showFR=1
21 CFR 812 - Investigational Device Exemptions:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1
21 CFR 814 – Premarket Approval of Medical Devices:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1&subpartNode=21:8.0.1.1.11.7
ClinicalTrials.gov's FDAAA 801 Requirements: http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa
DHHS's Institutional Review Board Guidebook, Chapter II, Regulations and Policies:
http://www.hhs.gov/ohrp/archive/irb/irb_chapter2.htm
FDA's Clinical Trials Guidance Documents:
http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm
FDA's Emergency Use and Compassionate Use of Unapproved Devices:
http://www.fda.gov/downloads/Training/CDRHLearn/UCM180888.pdf
Guidance for Industry and Food and Drug Administration Staff: Mobile Medical Applications:
http://www.fda.gov/medicaldevices/productsandmedicalprocedures/connectedhealth/mobilemedicalapplications/default.htm
FDA's Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use - Qs & As:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf

FDA's IDE Guidance:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm
FDA's Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors:
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm
FDA's Selected FDA GCP/Clinical Trial Guidance Documents:
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219433.htm
VHA Handbook 1108.04 – Investigational Drugs and Supplies:
http://vaww1.va.gov/vhapublications/publications.cfm?Mode=CURRENT&pub=2&order=asc&orderby=pub_Number
VHA Handbook 1200.05 - Requirements for the Protection of Human Subjects in Research:
http://vaww1.va.gov/vhapublications/publications.cfm?Mode=CURRENT&pub=2&order=asc&orderby=pub_Number

7. CONCURRENCES: Endorsed by the Research & Development Committee on 02/02/2015.

8. RESCISSION: HRPP Policy & Procedure Investigational Device and/or Drug Usage, endorsed by the R&D Committee on 04/07/2014.

9. FOLLOW-UP RESPONSIBILITY: ACOS/Research & Development (R&D)

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ACOS/R&D