Expanded Access
Treatment Use of an Unapproved Investigational Drug/Biologic
Policy and Procedure

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I. Policy

A. Nothing in this policy is intended to prevent a physician from preserving life, for example, if in the investigator's opinion, immediate use of the test article is required to preserve the patient's life, and if time is not sufficient to conform to the policies as outlined in OIRB policies (e.g., Emergency use procedures such as IRB notification, obtaining an independent physician's determination or Treatment Use of an Unapproved Investigational Drug (Including Single Patient Use) Policy and Procedure), the clinical investigator should make the determination and then follow the procedures outlined in the Emergency Use of an Investigational Drug or Device Policy and Procedure, e.g., 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, then notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

B. This policy, in accord with FDA recommendations, seeks a balance between administrative burden and ensuring patient safety and welfare and does not seek to be a deterrent to obtaining access to investigational drugs for treatment use. For single patients, physicians will generally be relying heavily on the sponsor's IND and minimal additional information that should be readily available to the physician in the course of the care of that patient is all that is required by the FDA and therefore a similar package with minor variations will be required by the IRB. For small group (multi-patient) INDs the UTHSCSA IRB will make all reasonable efforts to follow FDA recommendations regarding the use of centralized IRBs and standardized documentation across sites to minimize the administrative burden. Full Treatment Protocols will likely be submitted in the usual manner with the understanding that at some point an emergency may arise calling for invoking the Emergency Use of an Investigational Drug or Device Policy and Procedure. In all cases, sponsors and sponsor-investigators must comply with all applicable responsibilities under all applicable regulations.

C. Use of an investigational drug or biologic requires an IND. Several mechanisms are available. Some are described in this policy, others are described in Research Involving a Drug Policy and Procedure. As mentioned in section I above, emergency use may be necessary at any point during submission of any type of Expanded Access Treatment Protocol or request and other mechanisms are described in the Emergency Use of an Investigational Drug or Device Policy and Procedure to enable investigators to meet this requirement which may include obtaining a telephonic emergency IND from the FDA. If the physician determines criteria are not met for submitting a request for an emergency IND or if the FDA does not authorize shipment of the test article in advance of the IND submission in the form of an Emergency IND the FDA may authorize shipment for those patients with a serious disease or condition, regardless of whether the patient would currently be considered seriously ill with that disease or condition as treatment use under a Single patient IND, Small group Treatment IND or a full protocol Treatment IND (other mechanisms include: Open Label Protocol or Open Protocol IND, Group C Treatment IND, or under the FDA's Parallel Track policy. In all other cases a standard submission to the FDA for an IND may be required, see the Research Involving a Drug Policy and Procedure. Only the three most common forms of Treatment IND, Single patient IND, Small group Treatment IND or a full protocol Treatment IND will be
thoroughly discussed under this policy since all other treatment use can be submitted under the Initial Review of Research Policy and Procedure.

1. Treatment Use

a) Single patient Treatment IND, Multi-patient (small group) Treatment IND and full Treatment Use Protocol:

(1) All of these Treatment Use requests for an investigational drug or biologic must meet the criteria for a Treatment IND, Single patient IND. The FDA considers the use to meet criteria if:

(a) The drug is intended to treat a serious or immediately life-threatening disease;

(b) There is no comparable or satisfactory alternative drug or other therapy to diagnose, monitor or treat the disease or condition;

(c) 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

(d) 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.

(e) Expanded access use may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin. However, it is also possible that the FDA may place any expanded access IND or protocol on clinical hold as described in § 312.42.

(f) For a drug intended to treat an immediately life-threatening disease, the Commissioner of the FDA may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug: (i) May be effective for its intended use in its intended patient population; or (ii) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

b) Additional criteria for each specific type of Expanded Access Investigational Drug Use

(1) Single patient, including emergency use (see the Emergency Use of an Investigational Drug or Device Policy and Procedure).

(a) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(b) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(c) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).
(d) A physician may request a waiver from the FDA’s requirement to obtain IRB approval for single patient expanded access use of an investigational drug or biological product after obtaining concurrence by the IRB Chair or another designated IRB member before treatment begins so long as there are alternative methods of ensuring protection of rights and welfare of subjects.

(2) **Small Group (Intermediate-size population)**, including if necessary while awaiting approval, emergency use (see the [Emergency Use of an Investigational Drug or Device Policy and Procedure](#)).

(3) FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use. (a) Need for expanded access. Expanded access under this section may be needed in the following situations:

(a) Drug not being developed. The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

(b) Drug being developed. The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

(c) Approved or related drug. (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or (ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage. (b) Criteria. The criteria in § 312.305(a) must be met; and FDA must determine that: (1) 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 (2) 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.

(d) **Full Treatment Protocol**, including if necessary while awaiting approval an emergency use (see the [Emergency Use of an Investigational Drug or Device Policy and Procedure](#)).

(i) FDA may permit an investigational drug to be used for widespread treatment use.

(ii) 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 (ii) All clinical trials of the drug have been completed; and

(iii) Marketing status. The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(iv) Evidence. (i) 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. Such evidence would ordinarily consist of
data from phase 3 trials, but could consist of compelling data from
completed phase 2 trials; or (ii) 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. This evidence would ordinarily consist of clinical data from phase 3
or phase 2 trials, but could be based on more preliminary clinical evidence.

c) Other Treatment Use INDS for Investigational Drugs and Biologics that do not require
special processing outside the scope of the Initial Review of Research Policy and
Procedure.

(1) **Open Label Protocol Or Open Protocol IND** These are usually uncontrolled
studies, carried out to obtain additional safety data (Phase 3 studies). They are
typically used when the controlled trial has ended and treatment is continued so that
the subjects and the controls may continue to receive the benefits of the
investigational drug until marketing approval is obtained. These studies require
prospective Institutional Review Board (IRB) review and informed consent and are
submitted under the Initial Review of Research Policy and Procedure.

(2) **Group C Treatment IND** The “Group C” treatment IND was established by
agreement between FDA and the National Cancer Institute (NCI). The Group C
program is a means for the distribution of investigational agents to oncologists for the
treatment of cancer under protocols outside the controlled clinical trial. Group C drugs
are generally Phase 3 study drugs that have shown evidence of relative and
reproducible efficacy in a specific tumor type. They can generally be administered by
properly trained physicians without the need for specialized supportive care facilities.
Group C drugs are distributed only by the National Institutes of Health under NCI
protocols. Although treatment is the primary objective and patients treated under
Group C guidelines are not part of a clinical trial, safety and effectiveness data are
collected. The usage of a Group C drug is described in the FDA’s "Guideline
Protocol" document. Because administration of Group C drugs is not done with
research intent, FDA has generally granted a waiver from the IRB review
requirements [21 CFR 56.105]. Even though FDA has granted a waiver for these
drugs, the UTHSCSA IRB still chooses to conduct a review under this policy and
procedure. The Guideline Protocol contains an FDA-approved informed consent
document which must be used if there has been no local IRB review however
although the UTHSCSA IRB chooses to conduct a local review the FDA
approved informed consent may still be used. Local review will occur under the Initial Review of
Research Policy and Procedure.

(3) **Parallel Track** The Agency’s Parallel Track policy [57 FR 13250] permits wider
access to promising new drugs for AIDS/HIV related diseases under a separate
"expanded access" protocol that "parallels" the controlled clinical trials that are
essential to establish the safety and effectiveness of new drugs. It provides an
administrative system that expands the availability of drugs for treating AIDS/HIV.
These studies require prospective IRB review and informed consent and are
submitted under the Initial Review of Research Policy and Procedure.

d) Physicians and sponsors are responsible for meeting all responsibilities under applicable
regulations and may be required to submit to additional safeguards (additional monitoring,
reporting, etc.) by the FDA during the IND review or by the IRB during IRB review.

D. Treatment Use Protocols require prior IRB review and approval. “A Waiver of Local IRB Review” is
allowed under FDA [21 CFR 56.105]. The FDA may approve a waiver of local IRB review if it can
be shown to be in the best interest of the subject(s), and if a satisfactory alternate mechanism for
assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. The UTHSCSA IRB still opts to review such studies even when FDA has granted a waiver therefore in the event of a waiver of local IRB review the physician must still contact the IRB (Office, Director, Associate Director or Chair) directly as soon as possible.

a) Whether or not the waiver applies:

1) Treatment use must meet criteria for a treatment IND and must provide sufficient data to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

2) Prior notification by the physician is required. The physician must notify the IRB Chair, alternate chair or designated physician member concerning the proposed treatment use of the investigational drug or biologic.

b) Where the waiver applies, the UTHSCSA IRB makes no exception to local review requirements unless there is an existing agreement in place with the central IRB.

c) Where the waiver does not apply or the UTHSCSA IRB has not entered into the applicable agreements necessary with the central IRB in question, IRB approval must be by a convened IRB. [However, although the FDA regulations do not provide for expedited IRB approval in treatment use or emergency situations, the physician should keep in mind that a letter may be sent to the sponsor as described in the Emergency Use of an Investigational Drug or Device Policy and Procedure, if sufficient time does not exist to organize a convened IRB meeting and the condition of the patient changes such that criteria for emergency use are now met, (the letter would include a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). This is not an "IRB approval," the acknowledgment letter is only intended to be acceptable to manufacturers to allow shipment of the product to proceed as described in Emergency Use of an Investigational Drug or Device Policy and Procedure.]

E. Treatment Use Protocols require Informed consent. FDA regulations note that treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR part 50).

II. Overview

A. This procedure starts upon a physician identifying the need for the treatment use of an Unapproved Investigational Drug or Biologic. Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process (whether previously existing or a treatment IND/single patient IND is obtained); , including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) (Waiver of Local IRB Review may be allowed) and the applicable provisions of 21 CFR 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

B. This procedure ends when the IRB has reviewed the information provided by the physician on the treatment use of the Unapproved Investigational Drug or Biologic in the form of a Treatment Use Protocol (as submitted to the FDA) or as a full UTHSCSA IRB Submission packet under the Initial Review of Research Policy and Procedure.

III. Procedure
A. When IRB review and approval is sought for a Treatment Use Protocol and before administering the investigational drug:

1. The physician must identify an available IND or the physician or the sponsor must obtain a Single, Multiple-Patient or Full Treatment IND or a standard IND from the FDA:

a) If the physician finds the intended patient meets criteria of an existing study protocol open at the institution in question:

   (1) The physician contacts the PI on the study in question

   (2) The PI on the study in question may enroll the subject and initiate the investigational drug treatment or the local physician may opt to open the study at this location through the normal submission process.

b) If an approved study protocol does not exist or if the subject does not meet enrollment criteria for an existing study, the physician may either contact the manufacturer who may be able to allow use under an existing company Treatment IND or contact the FDA for a Single, Multiple-Patient or Full Treatment IND. In either case, the manufacturer must be contacted.

   (1) The manufacturer determines whether the drug or biologic can be made available for the treatment use under a company Treatment IND. If so, the physician compiles the necessary documentation and follows the submission procedures in III.A.2 below.

   (2) If the need for an investigational drug or biologic represents an emergency situation that does not allow time for submission of an IND or if the FDA does not authorize shipment of the test article under a Single, Multiple-Patient or Full Treatment IND, the physician may choose proceed as described in the Emergency Use of an Investigational Drug or Device Policy and Procedure if criteria as an emergency are met.

2. The physician must submit the following information to the IRB for convened IRB review and approval for a Treatment Use Protocol (If the sponsor has not applied for a waiver of local IRB review under the treatment IND (such a waiver must be accepted by the UTHSCSA IRB under applicable agreements):

   (1) A full submission package as described in Initial Review of Research Policy and Procedure.

   (2) Or alternately the UTHSCSA IRB Chair, Director or Associate Director may allow the physician to submit to the convened IRB, the completed package sent to the FDA for approval of the Treatment IND or Single Patient Use IND.

   (3) Contact must be made with other HSC administrative units in accordance with the Coordination with Other Committees or Offices Policy and Procedure as soon as possible in the process (e.g., South Texas Veterans Health Care System, Institutional Biosafety Committee, Radiation Safety Committee, and the Office of Sponsored Projects) as some may have expedited review (e.g., possibly RSC) or administrative review (e.g., possibly STVHCS) procedures available to expedite the review process.

B. When Waiver of Local IRB review is sought and before administering the investigational drug:

1. The physician must still identify an available IND or obtain a Treatment IND or Single Patient Use IND from the FDA (This will likely have been done prior to a satisfactory alternate
mechanism for assuring the protection of human subjects was obtained, e.g., review by a central IRB.)

2. The physician must still contact the IRB Chair, Director or Associate Director concerning the planned treatment use of a test article in the following manner:
   a) A written memorandum, email, or telephone call summary of explanation which justifies administration of the test article is required;
   b) A copy of the informed consent form may still be required;
   c) Applicable agreements must be in place. See Cooperative Off-Site Research Policy and Procedure. Procedures described in those applicable agreements must be followed.

C. See the IRB Minutes Policy and Procedure for details concerning documenting Treatment Use Protocols.

IV. References

A. Definitions (see Glossary)

B. Regulatory (see Policy on Policies Policy and Procedure)