Institutional Review Board Procedure No. 14

EFFECTIVE DATE: ***August 28, 2020***

PROCEDURE TITLE:

Expanded Access to Investigational Drugs and Biologics
And Off-Label Use

To be reviewed every three years by:
Institutional Review Board

REVIEW BY: ***August 27, 2023***

PROCEDURE

This Procedure implements the requirements of Institutional Review Board Policy No. 1 *Authority of the Institutional Review Board*, which requires the Trinity Health Mid-Atlantic (THMA) Institutional Review Board (IRB) establish policies and procedures to ensure that the THMA's IRB operations fully comply with applicable laws, regulations and professional standards, including promoting the conduct of ethical and compliant research.

Expanded access is the use of an *investigational* drug or biologic external to an FDA approved clinical trial. Federal research regulations do not limit or interfere with the authority of a clinician to provide emergency medical treatment using an *investigational* drug or biologic product for one patient in a life-threatening medical emergency, where there is no standard acceptable treatment available **and** insufficient time to obtain IRB approval. In this circumstance the federal research regulations grant an exemption from prior review and approval by the IRB.

However, all research that involves expanded access to an investigational drug or biologic must be submitted to the IRB. The type of expanded access (emergency or non-emergency use) determines whether an IRB acknowledgement will suffice either before or after the use *or* whether prospective IRB review and approval prior to the use is required. At the earliest opportunity the clinician will notify the IRB of his/her intent to use or use of an investigational drug or biologic *in an emergency* (but no less than 5 working days after the use). Informed consent will be obtained from the patient or his/her legally authorized representative unless the federal research requirements for waiver or exception from the informed consent requirements are satisfied.

The *treatment use* of an *FDA-approved* drug or biologic in a manner that is not consistent with the 'for use' labeling (and does not meet the FDA definition of a clinical investigation) is not under the purview of an IRB and, thus, does not require the review of the IRB.

I. Overview

Expanded access is the use of an investigational drug or biologic (referred to by some as "compassionate use", however this is a term used by the FDA to describe a class of access to

investigational devices only). Wherever possible, the use of an investigational drug or biologic by a patient as part of a clinical trial is preferable because clinical trials can generate data that may lead to the approval of products and, consequently, to wider availability. However, when patient enrollment in a clinical trial is not possible (e.g., a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials), patients may be able to receive the product, when appropriate, through expanded access.

The FDA regulations (21 CFR part 312 subpart I) provide general requirements, describes criteria that must be met to authorize expanded access, lists requirements for expanded access submissions, and describes safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the investigational drug or biologic.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, physicians and investigators should recognize that such applications would be suitable when *all* of the following criteria apply:

1. Patient(s) have 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 and the potential risks are not unreasonable in the context of the disease or condition to be treated; ***AND***
3. The expanded use of the investigational drug or biologic for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product.

Sponsor: Please be aware that the party who (1) submits a request to open an expanded access IND application and (2) receives FDA's authorization to use the investigational product is considered the **sponsor** of the IND application. In the absence of any other sponsor (e.g., pharmaceutical company), the treating physician is the sponsor of the expanded access IND application. When "sponsor" is used, it refers to the above person or party.

The Investigators' Responsibilities described for sponsors of IND applications intended for clinical investigations also apply to sponsors of expanded access IND applications intended for clinical treatment with investigational products.

A. Types of Access

Under FDA's current regulations for investigational drugs (including biologics), there are three categories of expanded access:

1. Expanded access for individual patients, *including for emergency use*;
2. Expanded access for intermediate-size patient populations; and
3. Expanded access for widespread use.

B. Types of FDA Submissions

For each of the above:

- The medical product company (typically a pharmaceutical company) can amend its existing IND to include an ***access protocol*** or

- The physician may submit for a ***new access IND***.

An expanded access IND application intended for IND use in non-emergency setting will go into effect 30 days after FDA receives the application or on earlier notification by FDA that the expanded access use may begin. Expanded access IND applications submitted for the purpose of emergency use may begin as soon as the use of investigational drug or biologic is authorized by an FDA reviewing official.

C. Emergency use and the definition of research under OHRP and FDA regulations

Emergency use of an investigational drug or biologic is not considered research under OHRP Regulations. OHRP 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." Therefore, a person receiving an emergency use of a drug or biologic is not considered a research participant *by OHRP regulation*, and such emergency use is not "research" as covered under 45 CFR 46.

However; the FDA regulations regards emergency use of an investigational drug or biologic to meet the definition of a clinical investigation (research) and may require data from an emergency use to be reported in a marketing application, although this is not generally the purpose of expanded access. Emergency use of an investigational drug or biologic meets the criteria for an exemption from IRB review per FDA regulation, provided that such emergency use is reported to the IRB within 5 working days. Any further use of the investigational drug or biologic at SJMHS is subject to IRB review.

D. Definitions

Immediately life-threatening disease or condition: For the purposes of FDA regulations 21 CFR 56.102(d), this includes both life-threatening and severely debilitating, as defined below.

- **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, where the end point of clinical trial analysis is survival. 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.

Serious disease or condition: Means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Emergency use: Means the use of an investigational drug or biologic in a human being in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. See the FDA Q & A document for more explanation: *Expanded Access to Investigational Drugs for Treatment Use-Questions and Answers.*

Investigational New Drug (IND): The IND is a type of submission that the FDA uses to grant permission so that an investigational new drug or biologic may be used in humans, and upon execution will provide clinical data that supports safety and effectiveness for a specific use. The FDA's permission is documented via an assigned IND number or the granting of an IND exemption, both by the FDA.

E. Consent and HIPAA Authorization

1. Informed consent and HIPAA Authorization must be obtained from each participant (or the Legally Authorized Representative) in advance of the use. The consent must include all required elements of consent, including a statement that the study involves research, an explanation of the purposes of the research, and identification of any procedures which are experimental [21 CFR 50.25(a)(1)]. These requirements extend to emergency use;

OR

2. Exception from Informed Consent Requirements [21 CFR 50.23(a)]: FDA regulations permit ***emergency use*** of an investigational drug or biologic without informed consent where the investigator **and an independent physician**, who is not otherwise participating in the clinical investigation, certify in writing:

    a. The patient is confronted by a life-threatening or severely debilitating situation (see definitions above), necessitating the use of an investigational drug or biologic;

b. Informed consent cannot be obtained from the patient (because the patient cannot communicate or is incompetent to give consent);

c. Time is not sufficient to obtain consent from the patient's legally authorized representative; ***AND***

d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

If, in the physician's opinion, immediate use of an investigational drug or biologic is required and if time is not sufficient to obtain the independent physician determination, the physician should make the determination and, ***within 5 working days*** after the use of an investigational drug or biologic, have the determination reviewed and evaluated in writing by an independent physician.

F. Submitting to the IRB

After contacting the FDA, the appropriate forms must be submitted to the IRB within the timeframes indicated for each type:

1. Emergency use- submits the *Emergency Use of an Investigational Drug or Biologic* form before or up to 5 days after the use.

2. Expanded access for individual patients, intermediate-size patient populations, and widespread use must submit to the IRB a *New Project Application,* protocol, informed consent document and all other related documents. The *New Study Application* form is located on the IRB forms page of the website. All expanded access use (that is not emergency use) must receive full board review (convened IRB meeting). It may be appropriate for your application to be accepted past the deadline to get it to the next IRB meeting, contact the IRB Administrator for awareness of this urgent need. You will also need to meet several FDA requirements - refer to the FDA website.

3. FDA approval is required.

II. Expanded Access for Individual Patients

There are two types of expanded access for individuals: single patient expanded access and emergency single patient expanded access. Both involve serious and/or immediately life-threatening disease or condition; emergency expanded access is reserved for cases where more immediate use is required and there is not sufficient time to obtain IRB approval and use is limited to a one time investigational drug or biologic use (only used one time, with one patient, per

institution). See the definitions section above and the explanation below for the distinction in terms.

A. Non-emergent, but urgent

If you are seeking expanded access for an individual patient and your situation is urgent, but not yet an emergency, and:

- it is feasible (enough time) to undergo a full board IRB review in the time frame before use and,
- generally, you have more than a few days before you will need to use the drug or biologic;
- you will need to seek an individual access IND from the FDA or an access protocol from the FDA.

The criteria for use are as follows:

1. **Criteria for Use:**

The FDA and the physician must determine that the 3 criteria listed above in the overview section are met. Additionally:

- The FDA must determine that the patient cannot obtain the drug or biologic under another IND or protocol.
- Treatment is generally limited to a single course of therapy for a specified duration unless the FDA expressly authorizes multiple courses for chronic therapy.

2. FDA approval is required:

- The pharmaceutical company/drug or biologic manufacturer must agree to provide the investigational drug for expanded access use. The FDA cannot require the company to do this;
- A sponsor (as defined above) may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access;
- A licensed physician may satisfy the submission requirements by obtaining from the sponsor (as defined above) 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).

3. IRB review and approval is required:

Prospective IRB review and approval is required prior to use. Submit a New Project Application form plus FDA approval letter, sponsor acknowledgement letter, and consent with HIPAA authorization. The IRB must ensure that the FDA granted approval before the expanded access use at THMA may be approved by the IRB.

4. The FDA requires:

- Submit to the FDA all serious and reportable Adverse Events or Unanticipated Problems (IND safety reports) promptly, and annual reports if the protocol continues for one year or longer.
- At the conclusion of the treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.
- The FDA may require the sponsor (as defined above) to monitor an individual patient expanded access use if the use is for an extended duration.
- Please note that the FDA may ask the sponsor (as defined above) to submit an IND or protocol for the use under 21 CFR 312.315 or 21 CFR 312.320 when the FDA determines that a significant number of similar individual patient expanded access requests have been received by the FDA.

B. Emergency use

1. One emergency use per investigational drug or biologic:

The FDA regulations allows for one emergency use of an investigational drug or biologic at an institution [21 CFR 56.104(c)]. Any subsequent use of the investigational drug or biologic at the institution is subject to prospective IRB review and approval. However, the FDA also acknowledges 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 (FDA Information Sheet, 2003 Update). Investigators/physicians should plan for the anticipated scenario for the use.

2. Criteria for Use:

The FDA and the physician must determine that the 3 criteria listed above in the overview section are met. Additionally, the FDA and the physician must determine that the following criteria are met:

- Emergency use means the use of a test article 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 IRB approval (review at a convened meeting is not feasible).

- Probable risk to the person from the investigational drug or biologic is not greater than the probable risk from the disease or condition.

Additionally:

- The FDA must determine that the patient cannot obtain the drug or biologic under another IND or protocol.
- One use per institution is allowable (see statement above).

3. FDA approval is required:

- Contact the sponsor to obtain permission to use and obtain the investigational drug or biologic.
- The physician will need to gain an emergency IND from the FDA or an amendment to existing IND. In an emergency, the FDA may authorize the expanded access use to begin without a written submission to the FDA. The FDA reviewing official may authorize the emergency use by telephone. For investigational biological drug products under the Center for Biologics Evaluation and Research, physician contacts the FDA's Office of Communication, Outreach & Development, 301-827-1800 or 1-800-835-4709, ocod@fda.hhs.gov – tell them it is an emergency.
- For all other investigational drugs, physician contacts the Division of Drug Info: 301-796-3400, druginfo@fda.hhs.gov –tell them it is an emergency. After hours (8 a.m. to 4:30 p.m.), contact FDA Emergency Call Center: 866-300-4374, emergency.operations@fda.hhs.gov.
- The physician or sponsor must explain how the expanded access use will meet the requirements of 21 CFR 312.305 and 21 CFR 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

4. Use is reported to and acknowledged by the IRB:

The IRB must be notified prior to emergency use, however, this notification should not be construed as an IRB approval. Notification is used by the IRB to initiate tracking to ensure that the physician files a report within the five-day time-frame required by the FDA [21 CFR 56.104(c)].

When emergency use is reported to the IRB within 5 working days and meets the criteria above, the IRB will *acknowledge the use.* Misuse will be evaluated for non-compliance. The FDA regulations do not provide for expedited IRB approval in emergency situations. IRB *approval* is not required because emergency use of an investigational drug or biologic is exempt from IRB *review* (but not acknowledgement), when these conditions are met, per FDA regulation.

Any further use of the investigational drug or biologic at THMA is subject to IRB review, as one emergency use of a drug per institution is the general practice.

Submit the *Emergency Use of a Test Article* form to the IRB before the use or within 5 working days after the use. If a research consent is available or there is time to create one, this is preferred for the emergency use. The investigational drug or biologic administration brochure (Investigator Brochure) is typically submitted to give guidance on how to suspend the investigational drug or biologic.

The investigator will provide documentation of the FDA approval to the SJMHS IRB. The required FDA approval of emergency use will be provided by the physician in whatever format that it was received from the FDA (i.e., e-mail, documentation of telephone call, emergency IND, amending an existing IND, etc.) to the IRB when it is available.

The IRB must ensure that the FDA granted approval before the expanded access use at SJMHS may be acknowledged by the IRB. The IRB Chair or designee (who is an IRB member) will review documents for emergency use and provide an acknowledgement of concurrence on whether the conditions listed above were met. The IRB Chair or designee's acknowledgement of the emergency use will be reviewed at the next convened IRB meeting.

The IRB determinations that all criteria were met and acknowledgments, as well as consent or waiver of consent, will be documented in the minutes and in IRB correspondence to the investigator in the same fashion as other research that is reviewed.

For emergency use, the IRB will send a written statement to the physician (and manufacturer, if this is their requirement) that the IRB is aware of the proposed/past use and considers the use to meet the requirements of 21 CFR 56.104(c). Note that this is not an "IRB approval" letter, but rather an acknowledgment letter. An acknowledgement letter is generally acceptable to manufacturers and has allowed the shipment to proceed.

5. FDA and IRB follow-up are required:

The physician or sponsor must submit to the FDA a new Emergency Access IND, or amendment to an existing IND (access protocol), within 15 working days of the FDA's authorization of the use. Clearly mark "Emergency IND" on top of Form 1571 (new form coming soon from the FDA; 21 CFR 312.310).

The physician must also submit to the IRB the outcome of use, including any adverse events.

III. Expanded Access for Intermediate-size Patient Populations

A. Criteria for Use

The FDA and the investigating physician must determine that the 3 criteria listed above in the overview section are met. Additionally, these criteria must be met:

- There is enough evidence that the investigational drug or biologic is safe at the dose & duration proposed for expanded access use to justify a clinical trial of the investigational drug or biologic in the approximate number of patients expected to receive the drug under expanded access; *AND*
- There is at least preliminary clinical evidence of effectiveness of the investigational drug or biologic, or of a plausible pharmacologic effect of the investigational drug or biologic to make expanded access use a reasonable therapeutic option in the anticipated patient population.

B. FDA approval is required

The submission to the FDA may be a new access IND or a protocol amendment to an existing IND (access protocol). Information required for a submission may be supplied by referring to pertinent information contained in an existing IND, if the sponsor of the existing IND allows for the investigator to read the IND. See the requirements.

C. IRB review and approval is required

Prospective IRB review and approval are required. Submit to the IRB a *New Project Application* form plus FDA approval letter, sponsor acknowledgement letter, and research informed consent with HIPAA authorization. The IRB must ensure that the FDA granted approval before the expanded access use at THMA may be approved by the IRB.

D. FDA follow-up is required

All reportable adverse events and unexpected problems (IND safety reports) must be submitted to the FDA promptly. Annual reports must also be submitted when the protocol continues for one year or longer.

IV. Expanded Access for Widespread Use

A. Criteria for Use

The FDA and the physician must determine that the 3 criteria listed above in the overview section are met. Additionally, the FDA and the physician must determine that the following criteria are met:

1. Trial status:

    a. The drug or biologic is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, OR
    b. All clinical trials of the investigational drug or biologic have been completed; AND

2. Marketing status: The sponsor is actively pursuing marketing approval of the investigational drug or biologic for the expanded access use with due diligence; AND

3. Evidence:

    a. 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*

    b. 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.

B. FDA approval is required

The submission to the FDA may be a new access IND or a protocol amendment to an existing IND (access protocol). Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND allows the investigator to see the IND. See the FDA website for 21 CFR 312.305(b)2&3 for detailed list of submission requirements.

C. IRB review and approval are required

Prospective IRB review and approval are required. Submit a *New Project Application form* plus FDA approval letter, sponsor acknowledgement letter, and consent with HIPAA authorization to the IRB. The IRB must ensure that the FDA granted approval before the expanded access use at THMA may be approved by the IRB.

D. FDA follow-up is required

Submit to the FDA all IND safety reports promptly, and annual reports if the protocol continues for one year or longer.

The sponsor (or sponsor/investigator) is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

RESPONSIBLE DEPARTMENT

Further guidance concerning this Procedure may be obtained from the Trinity Health Mid-Atlantic Institutional Review Board.

RELATED PROCEDURES AND OTHER MATERIALS

FDA requirements:
http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm20080392.htm

APPROVALS

Initial Approval: August 28, 2020

Subsequent Review/Revision(s):