Appendix A-9 ***Expanded Access (Emergency Use) of Drugs, Biologics, and Devices***

This Emergency Use guidance outlines the responsibilities of the physician/investigator when an emergency requires that a patient be treated with an investigational Test Article such that there is not sufficient time to obtain IRB review and approval at a convened meeting. At Seattle Children's, emergency use procedures are used to provide access to investigational products under state and federal "Right to Try" provisions.

Emergency Use Information:

- An Emergency Use is an exception to the general rule that investigational Test Articles may only be used in human subjects who are participating in a clinical investigation/research.
- Emergency Uses are exempt from the requirement to obtain prior IRB review and approval, provided that the use is reported to the IRB within 5 working days after initiation of the Emergency Use. 21 CFR 56.104(c).
- Whenever possible, informed consent should be obtained before the investigational Test Article is used. Please see HRP-506 Template Consent Document: Emergency Use.
- The physician should check with the Investigational Drug Service about the cost of drugs as they can be charged for in certain circumstances.
- The physician should complete as many of the patient protection measures detailed in this guidance as possible before using the investigational article.
- If a physician anticipates using an investigational Test Article more than one time at Seattle Children's, the physician should contact IRB@seattlechildrens.org about the need to submit an IRB application for prospective IRB review and approval of a research study.

Emergency Use Procedure:

Step 1: Determine whether an Emergency Use is appropriate.

Note: Table Continued on next Page

Criteria for Emergency Use of a Test Article	
Drugs/Biologics	**Devices**
Treating physician determines that all of the following are met: (1) Life-threatening or serious* disease or condition that needs immediate treatment; (2) No generally acceptable alternative for treating the patient is available; and (3) Due to the immediate need to use the test article, there is no time to follow existing procedures to obtain IRB approval prior to the use. **Additional determinations:** (4) FDA also expects the physician to make the determination that the **probable risk** to the person from the investigational test article is not greater than the probable risk from the disease or condition. 21 CFR 312.310(a)(1). **Relevant definitions in the Drug/Biologic context:* • ***Immediately life-threatening disease or condition*** *means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.* • ***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. 21 CFR 312.300(b).*	**Treating physician** determines that all of the following are met: (1) The patient has a life-threatening* condition that needs immediate treatment; (2) No generally acceptable alternative treatment for the condition exists; and (3) Because of the immediate need to use the device, there is no time to use existing procedures to get IRB and FDA approval for the use. **Additional determinations:** (4) FDA also expects the physician to assess the **potential for benefit** from the use of the unapproved device, and to have **substantial reason to believe that benefits will exist**. *See* FDA Device Guidance. **Relevant definitions in the Device context:* • ***Life-threatening condition*** *includes serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity (e.g., blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke).* FDA Device Guidance

Criteria for Emergency Use of a Test Article	
Drugs/Biologics	**Devices**
FDA must determine (based on information physician provides) that: • The patient 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; 21 CFR 312.305(a)(1). • 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; 21 CFR 312.305(a)(2). • Providing the investigational test article 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. 21 CFR 312.305(a)(3). • The patient cannot obtain the test article under another IND or protocol. 21 CFR 312.310(a)(2).	An **uninvolved physician** (not participating in the emergency use) determines that all of the above emergency use criteria are met. • **Obtain documentation** of the uninvolved physician's determination whenever possible (usually via email). • If it is not possible to obtain a second opinion from an uninvolved physician (and/or documentation), the treating physician should make the determination and proceed with the emergency use process.

Step 2: Take steps to obtain the investigational test article.

To Use Drugs/Biologics → IND	To Use Devices → IDE
Identify the sponsor: There are two scenarios, depending on whether the manufacturer previously obtained an IND for the drug/biologic: • Manufacturer has an IND → Manufacturer serves as the "sponsor" of the emergency use. • Manufacturer has no plans to get an IND → Physician serves as the "sponsor-investigator" of the emergency use.	***Identify the sponsor****:* Generally there will be a manufacturer who has applied for an IDE and will serve as the "sponsor" of the emergency use.
Contact the manufacturer/sponsor to determine whether they are willing to provide the investigational drug/biologic.	***Contact the sponsor*** to determine whether they are willing to provide the investigational device.
Contact the FDA for an Emergency IND: • If the manufacturer will serve as the "sponsor," manufacturer/sponsor will usually contact the FDA on the physician's behalf for approval of an emergency IND. • If the physician will serve as the "sponsor," the physician contacts the FDA directly to obtain an emergency IND. An emergency use may be requested by telephone, facsimile, or other means of electronic communications. Contact information is provided below. • The physician or sponsor must explain how the expanded access use will meet the above criteria for emergency use.	***Not Required to Contact the FDA in Advance for an Emergency IDE:*** • For devices, prior FDA approval for shipment or emergency use of an investigational device is <u>not</u> required. 21 CFR 812.35(a)(2). • Treating physician may contact the Office of Device Evaluation (ODE) at FDA to discuss his/her patient's condition. In this situation, ODE acts in an *advisory* role, rather than in an *approving* role. The responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the investigational device should be used lies with the treating physician. Contact information is provided below.
The FDA usually provides a new IND number for the specific emergency use.	If no IDE exists, the physician should follow the above procedures and report the emergency use to CDRH as directed in Step 6.

Type of Test Article (Branch)	FDA Office/Division to Contact
Drugs (CDER)	Division of Drug Information 301-796-3400, or 301-827-4570 Email: druginfo@fda.hhs.gov *See* FDA Guidance, Physician Request for an Individual Patient IND under Expanded Access for Emergency Use
Biologics (CBER)	Office of Communication, Outreach and Development, 301-827-1800 or 1-800-835-4709 Email: ocod@fda.hhs.gov
Devices (CDRH)	Office of Device Evaluation, Program Operations Staff, 301-796-5640 Email: dsmica@fda.hhs.gov
All Products, after normal working hours (8am – 4:30pm ET)	FDA Emergency Call Center 1-866-300-4374 or 301-796-8240 or 301-443-1240 Email: emergency.operations@fda.hhs.gov

Step 3: Follow as many patient protection measures as possible

Patient care should not be compromised in the event there is insufficient time to complete all of these measures:

1. **Concurrence of the Institutional Review Board Chair or designee**.
   - Please ***email*** the Emergency Use Report Form (HRP-2141) to the IRB representative before calling, if possible, so the IRB representative can reference the form during the call. This form can be found in the Click Document Library.
   - Please contact the IRB representatives in the following order:
     1. IRB Chair, Douglas Diekema, MD, MPH, diek@u.washington.edu.
     2. IRB Vice-Chair, Danielle Lewis, MD, MPH, danielle.lewis@seattlechildrens.org or at 206-884-1427.
     3. Investigational Drug Service, Ada Kong, PharmD, ada.kong@seattlechildrens.org. Note that IDS serves as an IRB representative for emergency uses of drugs/biologics *and* devices.
     4. Senior Vice-President, Chief Medical Officer, Ruth McDonald, MD, ruth.mcdonald@seattlechildrens.org
        Senior Vice President, Surgeon-in-Chief, Jeff Ojemann, MD, jeff.ojemann@seattlechildrens.org
   - Once you have emailed the Emergency Use Report Form to an IRB representative, please **call the paging operator at 206-987-2131 or call the designee at the number listed above** to consult with the IRB representative (in the order listed above).

2. **Written informed consent** from the patient or their legally authorized representative. Use the Seattle Children's template Emergency Use Consent Form (HRP-506) or a form provided by the manufacturer or sponsor. This template can be found in the Click Document Library.

- Since the FDA exempts emergency uses from the usual requirements for prior IRB approval, there is no requirement to obtain IRB approval of the emergency use consent form before using it with the patient.

OR

- **Determine that the criteria are met to waive consent** for the emergency use. ***Before*** using the test article, ***determine*** and, if possible, ***document*** (in writing/email) that criteria for waiving emergency use consent (see below) are met, in the opinion of both the:
  - Physician treating the patient with the test article; ***and***
  - Physician not participating in the emergency use (independent/uninvolved physician)

- If it is not possible to obtain consent, FDA regulations (21 CFR 50.23) allow a waiver of emergency use consent under the following conditions:
  - The patient is confronted with a life-threatening situation necessitating the use of the test article;
  - Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally effective consent from, the patient;
  - Time is not sufficient to obtain consent from the patient's legally authorized representative; ***and***
  - No alternative method of approved or generally recognized therapy is available that provides equal or greater likelihood of saving the patient's life.

3. If immediate use of the test article is needed to preserve the patient's life, and there is not sufficient time to secure an independent physician's determination that the four conditions for a waiver of emergency use consent (described above) apply, the treating physician should **make the determination that consent cannot be obtained and proceed**, but must have his/her written determination reviewed in writing by an independent physician within five working days after the emergency use of the test article. 21 CFR 50.23(b) & (c); 21 CFR 812.150(a)(5).

4. DEVICES ONLY (not required for drugs/biologics): As noted above in Step 1, obtain a **written assessment from an uninvolved physician** that the criteria for emergency use (this is not about waiving consent) are satisfied for the patient.

5. DEVICES ONLY: As noted above in Step 2, obtain **authorization from the IDE sponsor**, if an approved IDE exists for the device.

Step 4: Initiate treatment with the investigational agent.

Initiate Use of Drug/Biologic (IND)	Initiate Use of Device (IDE)
Treatment may begin when the emergency use is authorized by the FDA reviewing official. 21 CFR 312.305(d)(2)(i).	Emergency use of the device may begin when the use is authorized by the IDE sponsor.

Step 5: Submit a follow-up report to the IRB within 5 working days of initiating treatment with the investigational agent. The report form is located in the Click Document Library.

The report should include the following:

- Completed Emergency Use Report Form (HRP-2141) (found in Click Document Library);
- All relevant attachments requested in the report form.

Step 6: Submit a follow-up report to the FDA or sponsor within 5 working days.

Reports for Drugs/Biologics = IND	Reports for Devices = IDE
Physician must submit an expanded access submission to FDA within 15 working days of FDA's authorization of the emergency use. 21 CFR 312.310(d)(2). See Form FDA 1571 and Instructions, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm .	Deviations from the investigational plan: An investigator shall **notify the IDE sponsor (who will notify the FDA**) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than **5 working days after the emergency use occurred**. 21 CFR 812.35(a)(2); 812.150(a)(4). - The report should contain a **summary of the conditions** constituting the emergency, the **patient protection measures** that were followed, and patient **outcome** information. - If no IDE exists, the physician should follow the above procedures and report the emergency use to CDRH or CBER. - Informed consent: If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs. 21 CFR 812.150(a)(5).

Step 7: Convened IRB reviews follow-up report of the emergency use.

- The IRB will review whether the situation satisfied the emergency use criteria, whether the physician followed reasonable patient protection measures under the circumstances, the patient outcome information, and whether future uses of the investigational test article are anticipated such that an application should be submitted to the IRB.
- Subsequent emergency uses of the investigational test article for the same indication should not occur unless the physician or another Seattle Children's provider obtains **FDA and IRB approval** for the drug/biologic/device and its use. (FDA acknowledges that it would be inappropriate to deny emergency treatment to a second patient if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the application.)
- If an IND or IDE application for subsequent use has been filed with FDA and FDA *disapproves* the application, the drug/biologic/device may not be used even if the circumstances constituting an emergency exist.

Step 8: Physician/investigator receives IRB correspondence.

The IRB outcome letter will either confirm that all regulatory requirements have been satisfied, or will highlight deficiencies and request additional actions.

References:
SOP HRP-001 Definitions
SOP HRP-023 All Emergency Use and Compassionate Use (Device Only) Review
SOP HRP-027 All Emergency Use and Compassionate Use (Device Only) Post-Review
Worksheet HRP-322 Emergency UseForms HRP-2141 Emergency Use Submission