

Research Stepchildren: **Humanitarian Use Devices and Expanded Access to Investigational Medical Products**

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About the Presenters . . .

Deneice Kramer is the Human Research Protection Program (HRPP) and Compliance Manager, at Essentia Health

Cathy Murray, is a compliance specialist dedicated to the Essentia Health Institutional Review Board (IRB)

Kim Wold, is a compliance specialist dedicated to Essential Health's Research Compliance & Assistance Program (RCAP)

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About the Title . . .

Research Stepchildren:

- Humanitarian Use Devices (HUDs)
- Expanded Access Programs

Both, by regulatory definition, are not research

However,

Both require institutional review board oversight and commitments from clinical teams as if these programs were research

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Objectives

- Review related laws and regulations which help define HUDs and Expanded Access
- Describe IRB and institutional challenges when reviewing and monitoring HUDs and Expanded Access projects
- Essentia Health's approach, lessons learned and yet to be learned

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Disclaimer

It is possible to interpret the regulations and guidance documents in multiple, appropriate ways. We will be presenting processes that we have developed and feel represent best practices for our organization.

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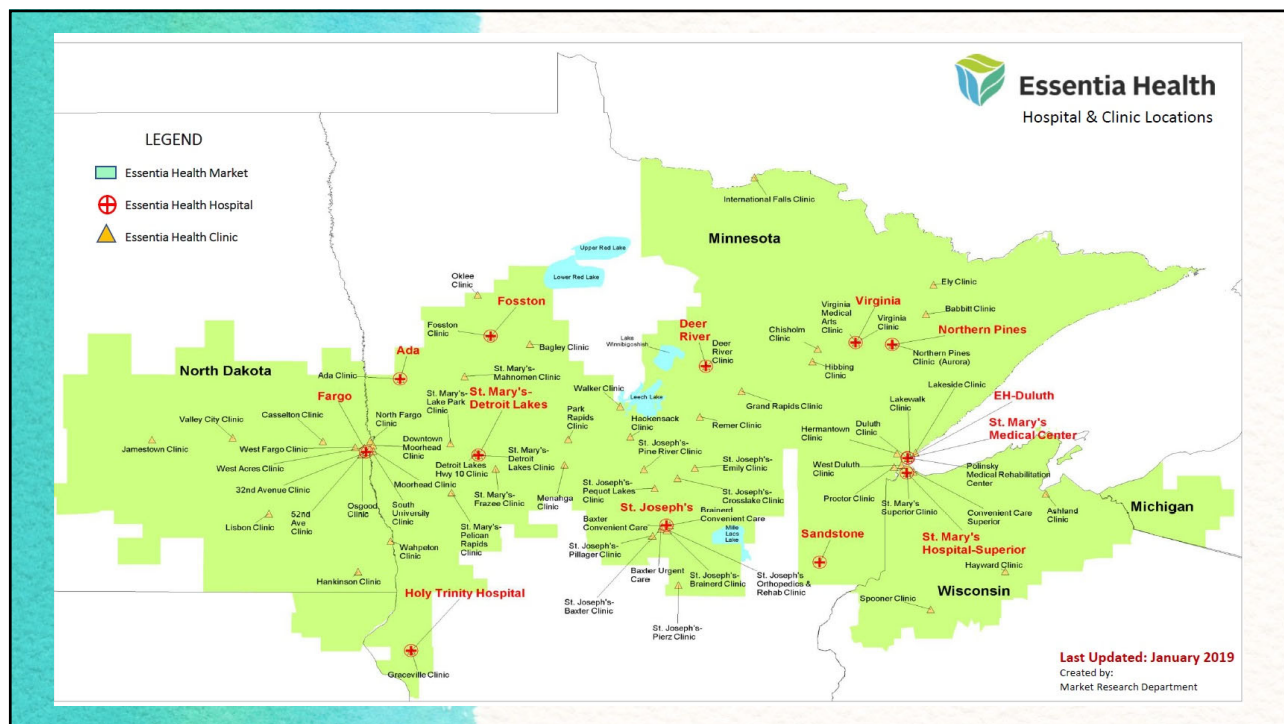
A little about Essentia Health . . .



Essentia Health

- Health system serving northeastern, north central and northwestern Minnesota, southeastern North Dakota and northwestern Wisconsin
- 12 hospitals system-wide
- Level 1 Trauma Center – Duluth Minnesota

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*A little about
research at
Essentia Health...*

Essentia Institute of Rural Health (EIRH)

... oversees institutional research

- PhD research scientists and support staff
 - Supports Level 1 Trauma Center accreditation with research and quality assurance projects
- Consortium and collaborative public health research
 - Large Scale Multi-Center NIH Funded Trials; All of Us, ADAPTABLE
- Oncology Clinical Trials (NCORP site)
- Heart & Vascular and Multi-Specialty Clinical Trials

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*A little more about
research at
Essentia Health...*

Essentia Health Institutional Review Board:

- 11 members (plus 3 alternates)
 - 3 physicians
 - 3 PhD scientists
 - 2 pharmacists
 - 2 advanced practice nurses
 - 1 community member/clergy member
- Oversees more than 100 studies in addition to reliance on external/central IRBs for more than 120 studies

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HRPP/IRB/RCAP Work

- Research compliance: federal, state, and institutional requirements governing human subjects research, including research privacy
- Evaluation of research integrity and human subjects protections
- Institutional Review Board administration
- Education, training, and research submissions
- Protocol and consent development guidance
- Research project quality assurance, best practices and corrective actions

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Annual IRB Review Volumes

More than 500 per year:

- Initial Reviews > 50
- Continuing Reviews > 100
- Amendments and Changes > 180
- Key Personnel Changes > 100
- Event Reports > 25
- Safety Information/DSMB/Annual & Progress Reports > 10
- Permanent Closures > 40

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**Who do we have
in the audience
today?**

- ☐ Health Care Systems
- ☐ Academic Medical Centers
- ☐ Commercial Research Organizations
- ☐ Commercial Institutional Review Boards
- ☐ Other

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Introductory Notes

In our presentation today, we will first discuss humanitarian use devices (HUD) and then expanded access programs (EAP) based on the following format for each:

- **Basic Overview/Regulations**
- **Getting Started**
- **IRB Processes (Initial, Ongoing, Closure)**
- **Essentia Health (EH) Approach**
- **Operational Challenges**

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Introductory Notes, continued

The regulations covering both programs describe the general criteria that must be met for each program; the requirements for regulatory submissions and the safeguards applicable to both, such as informed consent, ethics/institutional review board oversight, and reporting requirements

- One thing that both these programs have in common is the ability for a licensed physician to use HUDs and investigational medical products in an emergency
 - The physician must notify FDA and the appropriate review boards within 5 days and the appropriate applications and submissions be completed

Today we are focusing on non-emergency use and treatment

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Let's Talk About HUDs

What is a humanitarian use device?

- As defined in 21 CFR 814.3(n), and updated by the 21st Century Cures Act, a 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 not more than 8,000 individuals in the United States per year.”

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FDA Requirements

21 CFR 814 Subpart H: Humanitarian Use Devices

- Sec. 814.124 Institutional Review Board requirements
- HDE holder (in our experience, the manufacturer) is responsible for ensuring that a HUD approved under 21 CFR 814 Subpart H is administered only in facilities having an Institutional Review Board (IRB) constituted and acting pursuant to 21 CFR 56, including continuing review of use of the device.
 - The 21st Century Cures Act (passed December 2016) allows for an appropriate local committee to review and approve use of HUD at an institution

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FDA Requirements, continued

- A HUD may be administered only if its use has been approved by the institution's IRB, a similarly constituted IRB that has agreed to oversee such use (and to which the local IRB has deferred in a letter to the HDE holder signed by the IRB chair or an authorized designee), or an appropriate local committee
 - If a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval; however the physician must provide written notice the IRB chair within 5 days after the use of the HUD
- HDE holder must notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.

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Additional considerations based on FDA Guidance

- FDA does not require informed consent, but permits at the discretion of the IRB
- HUDs may be used in different ways
 - Medical Practice: used according to approved labeling and indication(s) to treat or diagnose patients. It can also be used "off label" as part of medical practice
 - Clinical Investigation (Research!): collection of safety and effectiveness data; a HUD may be studied in a clinical investigation in accordance with its approved indication(s) or for a different indication

Today our focus is on clinical applications in medical practice

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Additional considerations for the institution

- Physician/Lead Clinician training and acknowledgement of responsibilities
 - FDA refers to physicians and health care providers – we use “Lead Clinician” to designate the physician who will oversee access to and use of HUDs at a given facility
- Approval for HUD use is specific to each site/facility at which the device will be used (FDA & manufacturer requirements)
- Reports of adverse events and deviations/violations
 - Since the Lead Clinician is required to submit Medical Device Report (MDR) information to Manufacturer, the EH IRB has determined that a related event report should be submitted to IRB
- Since informed consent is at the discretion of the institution/IRB EH has chosen to require informed consent
 - Developed process by which patient is advised of the use of the device either pre- or post-procedure: a cover sheet in addition to the manufacturer's patient information brochure
 - Easily addresses use of an approved HUD in a clinical emergency

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Does your institution require research compliance training for HUD clinicians?

- ☐ Yes
- ☐ No
- ☐ Other

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Getting Started – Physician/Lead Clinician

- Physician identifies device that has received a Humanitarian Device Exemption (HDE) from FDA
 - a list of approved HDEs along with the approval order, summary of safety and probable benefit, labeling and patient information is available at: <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm>
- Completes Humanitarian Use Device training through CITI
- Reviews & acknowledges Lead Clinician Roles & Responsibilities
- Seeks assistance of regulatory support staff
- Works with HDE holder / manufacturer to acquire device
- Identify clinical support staff to track and monitor devices
 - Device storage and labeling

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Humanitarian Use Devices & the IRB – Initial Review

FDA recommends the IRB follow the review criteria in 21 CFR 56.111, and elsewhere in part 56, where applicable

Humanitarian Use Device (HUD) application must include these materials:

- FDA HDE approval order
- Protocol = manufacturer's Instructions for Use / Package Label
- IRB Information Brochure
- Patient Information Brochure or Packet (often includes patient information card for easy reference)
 - Pre- or Post- Procedure informed consent materials

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HUD Informed Consent Policy & Process

Using FDA's required elements of informed consent as a guide, the IRB determines what information must be presented to the HUD recipient

- Informed consent materials must be consistent with the approved labeling for the device and must contain the appropriate elements of consent
- Coversheets can be used with Patient Information Brochure or Packets and include institution-specific information and signature blocks for patients to acknowledge and that they consent to or understand the use of the HUD

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HUD Informed Consent Policy & Process, continued

Most physicians using HUDs are not engaged in research and are not familiar with research informed consent processes typically approved by the IRB

- HUDs can become "rescue devices" in emergencies, which further complicates the traditional informed consent process
- Needed to create a process that was easy for physicians to comply with and appropriately informative for patients
- Found that manufacturer-supplied patient information material and brochures are very informative and include the elements of informed consent
- If these materials are sufficient a pre- or post-procedure coversheet is added, which may also include elements of consent not present in the manufacturer-supplied materials

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Pre-Procedure Patient Information Sheet

Page 1



Essentia Health

<Name of HUD
Version Date: 06/03/2020

COVER PAGE FOR PATIENT INFORMATION SHEET

Humanitarian Use Device (HUD) Information:		
HUD Device	<Full Name of Device>	
Lead Clinician	Dr. Lead Clinician	###-###-####

Dr. Lead Clinician and his colleagues from the Essentia Health Department of <???> are offering you treatment with <Full Name of Device> (<device acronym>). <Device acronym> is a Humanitarian Use Device (HUD).

Your doctor provided you with the document titled "A Patient's Guide to <device acronym>." The guide will give you the information that you need to make an informed decision whether to consent to its use, such as the risks and benefits of the device. The guide includes information regarding the <device acronym> and its designation as a HUD by the Food and Drug Administration (FDA).

A Humanitarian Use Device is used to diagnose or treat a disease or condition that affects fewer than 8,000 individuals in the United States per year and for which no comparable device is available. The FDA approves Humanitarian Use Devices based on evidence that it does not pose a significant risk of injury and that the potential benefit of the device to the health of the patient outweighs the risks of its use.

The use of this HUD at Essentia Health and any associated complications are being monitored by the Essentia Health Institutional Review Board.

The doctor involved in your care will be available to answer any questions you have concerning the <device acronym>. In addition, you are free to ask Dr. Lead Clinician any questions concerning the device that you wish in the future or if at any time you feel you have experienced a procedure-related injury or a reaction to the device. Dr. Lead Clinician can be contacted at (###) ###-####.

For questions about your rights as a Humanitarian Use Device patient, please contact the Human Protections Administrator for Essentia Health at (218) 786-2540.

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Pre-Procedure Patient Information Sheet

Page 2

Signatures

I have received the patient information brochure about this device, and I understand the use of the device and its HUD designation. I have signed the Essentia Health surgical consent form.

Patient or Legally Authorized Representative

Signature _____ Date _____

Printed Name _____

Relationship to Patient _____

Individual Explaining the HUD

I have explained the use of this humanitarian use device to the patient or his/her representative before requesting the signature above. A copy of this form has been given to the patient or his/her representative.

Provider (or designee) Signature _____ Role _____

Printed Name of Provider (or designee) _____ Date/Time _____
Obtaining Consent

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Post-Procedure Patient Information Sheet

Page 1



Essentia Health

<Name of> HUD
Version Date: 06/03/2020

POST PROCEDURE PATIENT INFORMATION SHEET

Humanitarian Use Device (HUD) Information:

HUD Device	<Full Name of Device>
Lead Clinician	Dr. Lead Clinician (###) ###-####

During your procedure, your doctor found it necessary to use the <Full Name of Device> (<device acronym>) to close a coronary artery perforation caused by a tear in the artery wall, which is a rare but serious complication that can occur during a procedure like yours. The <device acronym> maintains the opening of the artery while sealing the perforated vessel wall. The device will remain in the artery permanently, and over time, tissue from the coronary artery wall covers the device.

The Food and Drug Administration (FDA) has authorized the <device acronym> for Humanitarian use only. A Humanitarian Use Device (HUD) is a medical device. The FDA decides if a device is a HUD. To receive HUD approval, the device must meet the following conditions:

- The device is expected to help not more than 8,000 people in the United States per year, and
- No similar device, other than another HUD, or a device not yet approved by the FDA, is available to treat or diagnose the condition.

Humanitarian use authorization provides the opportunity for a small group of patients who may need the product to have access to it without having to wait for a large research study to be conducted. The FDA bases its authorization on safety information obtained from small studies and current use of the product in hospitals. Although the device is authorized for use, the effectiveness of the <device acronym> device has not yet been demonstrated. The FDA has approved use of the device because the information that is known suggests the risks of using the device are reasonable compared to the possible benefits and compared to other treatments for conditions like yours.

The use of this HUD at Essentia Health and any associated complications are being monitored by the Essentia Health Institutional Review Board.

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Post-Procedure Patient Information Sheet

Page 2

Who can answer my questions?

The doctor involved in your care will be available to answer any questions you have concerning the <device acronym>. In addition, you are free to ask Dr. Lead Clinician questions concerning the device that you wish in the future or if at any time you feel you have experienced a procedure-related injury or a reaction to the device. Dr. Lead Clinician can be contacted at (###) ###-####.

For questions about your rights as a Humanitarian Use Device patient, please contact the Human Protections Administrator for Essentia Health at (218) 786-2540.

Signatures

I have received the patient information booklet about this device, and I understand the use of the device and its HUD designation. I have signed the Essentia Health surgical consent form.

Patient or Legally Authorized Representative:

Signature _____ Date _____

Printed Name _____

Relationship to Patient _____

Individual Explaining the HUD

I have explained the use of this humanitarian use device to the patient or his/her representative before requesting the signature above. A copy of this form has been given to the patient or his/her representative.

Provider (or designee) Signature _____ Role _____

Printed Name of Provider (or designee) _____ Date/Time Obtaining Consent _____

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Does your institution require informed consent from HUD recipients?

- ☐ Full informed consent
- ☐ No informed consent
- ☐ Informed consent “lite”
- ☐ Other

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Humanitarian Use Devices & the IRB

Ongoing Oversight & Approval

- FDA requires IRB approval for use of a HUD at an institution but does not give much guidance regarding ongoing monitoring and/or review. EH has chosen to require:
 - Continuing review to the IRB which can be expedited
 - Lead Clinician responsible for making annual use reports to manufacturer(s); manufacturers report to FDA
 - Reports of unanticipated problems / non-compliance including serious adverse events (must also be reported to the manufacturer)

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Humanitarian Use Devices & the IRB

Ongoing Oversight & Approval, continued

- Permanent closure notice
 - Must include any notice from manufacturer and number of HUDs used
 - Manufacturer may receive Pre-Market Approval (PMA) and the HUD no longer qualifies for HDE
 - Will notify sites, check inventory
 - Device expiration or conversion to regular therapies

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**Does your institution
conduct post
approval
monitoring of
HUD use?**

- ☐ Yes
- ☐ No
- ☐ Other

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Operational challenges identified through post-approval monitoring

- Adequate lead clinician oversight
 - Address through physician / staff training requirements
- Appropriate recording keeping
 - Especially informed consent
- Patient instruction / information / education
 - Clarified importance of informed consent processes
 - Find ways to make access to consent and patient materials easy for all involved in caring for patient
- Regular communication with cath lab managers, supply chain/purchasing personnel

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Wrapping Things Up - HUD

- Manufacturer may receive Pre-Market Approval (PMA) and the HUD no longer qualifies for HDE
 - Will notify sites, check inventory
 - Device expiration or conversion to regular therapies
 - Must close the HUD approval with the IRB

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Let's Talk About Expanded Access

What is expanded access?

- Sometimes called “compassionate use,” expanded access is a potential pathway for a patient with an **immediately life-threatening condition or serious disease or condition** to gain access to an **investigational medical product** (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

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More on expanded access

- Expanded access programs are not intended to obtain information about the safety or effectiveness of a drug
- Expanded access to an investigational drug can only be provided under a treatment IND or protocol if the sponsor is actively pursuing, with due diligence, marketing approval of the drug for the expanded access use
- Expanded access, access, and treatment use may also refer to
 - Use in situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks
 - Use of a similar, but unapproved/unapproved/off label for certain use drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage of the approved drug
 - Use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug under the REMS

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Expanded Access by Any Other Name

Alternative terms for expanded access programs used elsewhere but not defined or described in FDA regulations:

- Single Patient IND or “SPIND”
- Compassionate Use
- Preapproval Access
- Limited Access Protocol
 - May be converted to Single Patient IND
- Post Trial Access “PTA”

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FDA Requirements

21 CFR 312 Subpart I—Expanded Access to Investigational Drugs for Treatment Use

FDA regulations at 21 CFR 312 Subpart I remind us that drugs offered through EAPs are investigational drugs, and they are subject to the following requirements:

- **Protection of Human Subjects (informed consent)**
- **Institutional Review Boards (IRB)**
- **Clinical Holds based on safety**
- **Reporting requirements (adverse event reports, annual reports)**

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FDA Requirements, continued

FDA requirements for IRB review and research compliance are more prescribed for expanded access than for HUDs

- Investigational Drugs/Biologics - 21 CFR 312 Subpart I and Investigational Medical Devices - 21 CFR 812 Subpart B
 - Direct sponsors and investigators to ensure appropriate informed consent processes (21 CFR § 50.24) and IRB oversight (21 CFR §§ 56.110 and 56.111)

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FDA Requirements, continued

§ 312.300 General

Primary purpose is to diagnose, monitor, or treat a patient's disease or condition

Aim is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

Important Definitions

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

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FDA Requirements, continued

§ 312.305 Requirements for all expanded access uses

FDA must determine that:

- 1) The patient or patients to be treated 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 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

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FDA Requirements, continued

Regulations define three main categories for access to investigational new drugs (IND):

1. Expanded access for individual patients, including emergency use (21 CFR 312.310)
2. Expanded access for intermediate-size patient populations (21 CFR 312.315)
3. Expanded access for large patient populations under a treatment IND or treatment protocol (21 CFR 312.320)

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FDA Requirements, continued

Part 812—Investigational Device Exemptions Subpart B, section 812.36 Treatment use of an investigational device

States in part: “. . . , it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment investigational device exemption (IDE). The purpose of this section is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness.” (The same application determination criteria of 21 CFR 312.305 apply.)

See also: <https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices>

We have not had experience or seen literature on this expanded access option

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Does your institution require physicians who wish participate in expanded access programs to complete research compliance training?

- ☐ Yes
- ☐ No
- ☐ Other

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Getting Started – Physician/Principal Investigator

- Physician identifies drug, biologic, or medical device
 - Must confirm that there are no approved drugs or clinical trials available
- CITI training – historically, only physicians involved in research have been those requesting EAP, so no additional training requirements
- Review & acknowledge Roles & Responsibilities
- Submit Form FDA 1571 for intermediate-size or large patient populations
 - Submit Form FDA 3926 individual patient
- Seek assistance of regulatory support staff
- Assure drug accountability
- Work with sponsor to acquire investigational medical product
- Make periodic and annual reports to sponsor and FDA

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Expanded Access and the IRB – Initial Review

The IRB reviews the protocol and consent to ensure the materials are consistent with 21 CFR parts 56 and 50 before treatment with the investigational drug may begin

An application to the IRB for approval of expanded access must include:

- Protocol and/or treatment plan
- Sponsor approval
- FDA approval
 - Form FDA 1571 for intermediate-size or large patient populations
 - Form FDA 3926 individual patient
- Informed consent/assent forms
 - Must include the basic elements of informed consent as prescribed by FDA, but avoiding reference to “research”
- Participant materials
- Investigator brochure/package insert/package labeling
- Other things to consider:
 - State health agency requirements as needed (usually disease-related; reportable diseases)

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Expanded Access and the IRB

Ongoing Oversight & Approval

- Continuing review
- Changes to treatment plan/protocol must be reviewed and approved by the IRB
 - Physician responsible for submitting to sponsor(s) and FDA
- Unanticipated problems / non-compliance including serious adverse events and/or adverse drug reactions (which must also be reported to the sponsor)
- Permanent closure notice
 - To include any notice from sponsor / manufacturer

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Does your institution conduct post approval monitoring of expanded access programs?

- ☐ Yes
- ☐ No
- ☐ Other

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Operational challenges identified through post-approval monitoring

- Physician and clinical staff may not have research experience
- Regular communication with pharmacy personnel
- HRPP/IRB may not be notified if or when drug has arrived
- Treatment plan changes not reported to IRB
- Appropriate recording keeping
- Adverse event tracking and reporting

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References/Guidance - HUD

- FDA Presentation: IRB Oversight of Humanitarian Use Devices (What's an IRB to do?)
 - <https://www.fda.gov/media/87321/download>
- FDA Presentation: Institutional Review Boards and Humanitarian Use Device (HUD)
 - <https://www.fda.gov/media/77468/download>
- Advarra Presentation: Humanitarian Use Devices Made Simple
 - <https://www.advarra.com/wp-content/uploads/HUDs-Made-Simple-5-25-17.pdf>
- FDA Guidance Document: Humanitarian Device Exemption (HDE) Program Guidance for Industry and Food and Drug Administration Staff, issued September 6, 2019 **supersedes "Guidance for HDE holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff, Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers," issued July 8, 2010
 - <https://www.fda.gov/media/74307/download>
- Advarra: Making Sense of the New HUD Guidance NOVEMBER 20, 2019
 - <https://www.advarra.com/new-hud-guidance/>

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References/Guidance - EAP

- FDA GUIDANCE DOCUMENT: Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers - Guidance for Industry JUNE 2016
 - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expanded-access-investigational-drugs-treatment-use-questions-and-answers>
- FDA Webpage – Information about Expanded Access
 - <https://www.fda.gov/news-events/public-health-focus/expanded-access>
- DDI Webinar: An Overview of FDA's Expanded Access Program - A FOCUS ON INDIVIDUAL PATIENT EXPANDED ACCESS
 - <https://www.fda.gov/media/111341/download>
- Expanded Access Contacts:
 - FDA's Office of Health & Constituent Affairs at 301-796-8460 or PatientNetwork@fda.hhs.gov
 - CDER's Division of Drug Information at 855-543-3784 or druginfo@fda.hhs.gov
 - CBER at 800-835-4709 or industry.biologics@fda.gov
- SACHRP Recommendations: Attachment B: Recommendation on Single Patient Treatment Use
 - <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-b/index.html>
- Clinical Research Pathways: Intermediate-size Patient Population Expanded Access Use A Flexible Alternative to Multiple Single Patient Uses
 - <https://clinicalresearchpathways.org/wp-content/uploads/2018/09/Intermediate-size-Patient-Population-Expanded-Access-Use-9.24.18.pdf>