Emergency Use 201: A Higher Bar

Ben Mooso
Susan Garrow-Sloan
Human Research Protections Clubhouse
Continuing our 101 and 102 series....

Recap of our 101 and 102 Series

Expanded Access

- Process for treatment use of unapproved medical products
- Requires a life-threatening (months) or serious disease/condition
- There cannot be an appropriate or effective alternative
- There cannot be an appropriate clinical trial to enroll in
- Still counts as a “clinical investigation”
- Requires FDA and IRB approval
- IRB must apply 21 CFR 50 and 21 CFR 56

ReCap…Questions we have received…

Are expanded access “protocols” required to be listed on clinicaltrials.gov?

- Small and intermediate population INDs and treatment IDEs – Yes!
- Single-patient INDs and compassionate use – No!

Do these have to be reviewed by the full board?

- Small and intermediate population INDs and treatment IDEs – Yes!
- Single-patient INDs and compassionate use – No, if the FDA allows for chair concurrence or expedited review

Case Study: Pediatric Patient with Sepsis

4 pm on a Friday before a 3-day weekend

Pediatric patient with worsening sepsis

Failed all standard antibiotic therapies

Culture shows a multi-drug resistant bacteria with no available antibiotic

Treating physician wants to use phage therapy in the next 2 hours

Phage can be available in that time frame

Manufacturer has agreed to provide phage under expanded access

No FDA or IRB submission yet

Case study

A 77-year-old Jehovah's witness with life threatening anemia secondary to hemorrhage.

The primary therapy for severe, life-threatening anemia was unavailable to this patient due to religious beliefs regarding blood transfusions

The treating physician contacted the FDA and acquired over the phone permission to administer the investigational product known as Hemopure.

The product was administered within 24 hours of confirmation from the FDA

IRB chair concurrence was acquired after administration of the product.

Emergency Use: A higher bar

- Must meet all expanded access criteria
- Generally, for only 1 person
- Disease or condition must be life-threatening or severely debilitating
  - Likelihood of death is high unless interrupted (e.g. actively dying); or
  - Will cause major irreversible morbidity unless interrupted
    - E.g. will result in blindness, loss of limb, loss of hearing, paralysis, stroke.
- Not enough time for IRB approval
- Product can not have been used for emergency use at the institution before
- Situation must necessitate the use of the investigational product

BUT if you had a week instead of an immediate situation…

- Then it's not emergency use!
- Use the appropriate expanded access pathway for a single patient
- If it is anticipated there will be more patients, consider converting to small group/intermediate-size or treatment protocol

- IRB Professionals – Expanded access & emergency use is tricky!
  - Keep documentation of your conversations with the physician.
  - Follow-up via email so they have instructions in writing.
  - Consider posting a checklist and/or instructions somewhere publicly.

Comparison

Emergency Use	Expanded access
• LAST RESORT • 1 time • 1 person • FDA specificized course: (2 weeks, 2 doses, etc.) • Usually, a phone call instead of written submission to the FDA • Done without IRB approval	• One time or more than one time • One person or more than one person • FDA specificized course: (2 weeks, 2 doses, etc. – course would be longer) • Written submission to FDA ALWAYS • Chair concurrence/approval

Emergency Use Process (Drugs & Biologics)

- Higher bar to be met
- The FDA must issue an IND to physician PRIOR to administration of drug or biologic
  - FDA may also approve access via a new protocol for 1 patient added to an existing IND (less common)
- The FDA may issue authorization without a written submission over the phone.
  - Physician should document conversation for the record and retain any communications (e.g. email)
  - If no written submission was made, within 15 working days the physician has to submit to the FDA
- Treating physician reports to IRB within 5 working days
- Subsequent uses of the product must be under IRB review and approval

Emergency Use Process (Device)

- There is no IDE, the use is not approved under an existing IDE, or the treating physician is not part of the IDE study
  - If any of the above not true, enroll the patient in the clinical trial or treatment program
- Insufficient time to obtain FDA approval of an IDE
- There is a substantial reason to believe benefits exist
- Treating physician reports to IRB within 5 working days
- Sponsor (if there is an IDE) or treating physician reports to FDA within 5 working days
- Subsequent uses of the product must be under IRB review and approval

Emergency Use (Consent Considerations)

- Consent should be obtained from the patient or their legally authorized representative (LAR) whenever possible
- If prospective consent is not possible, the treating physician and a physician uninvolved must document:
  - The patient is confronted by a life-threatening situation necessitating use of the medical product
  - Informed consent is not possible because of an inability to communicate with, or obtain legally effective informed consent from, the patient
  - Time is insufficient to obtain consent from the patient's LAR
  - There is no alternative or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient

Emergency Use (Subsequent Use)

- Regulations require that subsequent uses of a medical product must be conducted under an approved clinical trial or expanded access protocol
- This includes any use beyond the treatment plan originally agreed to by FDA
- A recent warning letter from June 7, 2024 states:
  - "Under IND #**(b)(4)**, FDA authorized the subcutaneous administration of the investigational drug, **(b)(4)**, weekly for up to two weeks. Subject **(b)(6)** was administered **(b)(4)** on May 15, 2020 (Day 0, Baseline), and on **(b)(6)** (Day 7), as authorized. However, Subject **(b)(6)** continued to receive the investigational drug, **(b)(4)**, between May 29, 2020, and March 28, 2022, instead of during the authorized two weeks only. … As a result, you failed to maintain an effective IND for the expanded access use [per 21 CFR 312.305(c)(5)]."

Other Considerations

HIPAA

- Expanded access is still a “clinical investigation” so HIPAA provisions apply when sharing data

Research

- Sometimes manufacturers and sponsor will want to include research with the expanded access (e.g. PK draws) or ask for data beyond safety
- Treat like any other research protocol and review accordingly

What to do When You Get the Call/Email?

- If the treating physician isn't sure:
  - Contact IRB leadership or search electronic system for prior emergency use
  - Clinicaltrials.gov to search for open clinical trials
  - Ask an IRB chair for medical decision making
- Remind the treating physician of their responsibilities
  - Consent is still required
    - Use emergency use template and modify as necessary
  - If consent is not possible, must document as described previously
  - Must report to IRB within 5 working days
  - For drugs/biologics – Must get approval from FDA first
    - If done without written submission, report to FDA within 15 working days
  - For devices – FDA pre-approval not required
    - If there is an IDE, Sponsor reports to FDA within 5 working days
    - If there isn't an IDE, treating physician reports to FDA within 5 working days
  - Send all of this to them in writing (email, checklist, etc.) so they don't mess up

What to do When You Get the Call/Email Continued…

- Verify emergency use criteria are met
  - Is it a life-threatening or severely debilitating disease or condition?
  - Verify the timeframe – Is it really an emergency?
  - Is the investigational product necessary?
  - Are there any alternatives available?
  - Is there a clinical trial available?
  - Medical product has not been through emergency use at this institution previously
  - For devices:
    - Is the device's probable risk not greater than the probably risk from the disease?
    - Is there substantial reason to believe that benefits of using the device exist?

What should an application ask?

- Questions to verify eligibility
  - Documentation of life-threatening or severely debilitating condition
  - Documentation that the investigational product was necessary
  - Documentation that there were no alternatives
  - Documentation that there were no clinical trials
  - For drugs/biologics - Confirmation of FDA approval
  - For devices – Confirmation of risks and benefits
- Documentation of consent – Can provide unsigned version
- Documentation of consent waiver criteria by treating physician
- Certification of consent waiver criteria by uninvolved physician

What to do when the 5-day Report to the IRB is Submitted

- Verify emergency use criteria were met
  - If comes to you but someone else in the office discussed with the physician, talk to your colleague
- Verify consent was obtained or waiver criteria were documented
  - If wrong consent used, can they re-consent?
  - If waiver criteria weren't documented by uninvolved physician, can be documented post-hoc
- If investigational product use will persist for same or other patients – request expanded access submission
- If all verified and good – Acknowledge

Questions????

Resources

- The FDA Expanded Access webpage
  - Summarizes categories and initial requirements of Expanded Access process to include information for treating physicians and patients
- Expanded Access consent templates:
  - UC San Diego
  - UC Davis
- Emergency Use Worksheets:
  - UC San Diego
  - UC Davis