IRB Reliance on the CDC IRB and Implementation of the Expanded Access Program: "Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections"

C. Karen Jeans, PhD, CCRN, CIP, Director of Regulatory Affairs,
Office of Research Protections, Policy, & Education
VHA Office of Research and Development (ORD)

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- ✓ A recording of this session and the associated handouts will be available on ORPP&E's Education and Training website approximately one-week post-webinar

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- ✓ Please use the Q&A feature to submit questions.
  - ✓ **Please do not use Chat to send in questions.**
  - ✓ **Be sure to send questions to "All panelists".**

- ✓ We would be ever so grateful if you would complete the post-webinar evaluation survey that pops up once you exit the webinar.

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Objectives

- Describe the purpose of using Tecovirimat (TPOXX®) as a treatment for Monkeypox
- Identify the type of U.S. Food and Drug Administration (FDA) expanded access program utilized for this specific Centers of Disease Control and Prevention (CDC) Program
- Apply the steps required to rely upon the CDC IRB for initiating the CDC Expanded Access Investigational New Drug Application (IND) Protocol for Tecovirimat in the treatment of Monkeypox
- Identify key issues directly related to regulatory implementation of the CDC Expanded Access Program
  - Institutional responsibilities
  - Informed consent requirements
  - HIPAA authorization requirements

Monkeypox

- Monkeypox is a rare disease caused by infection with the monkeypox virus.
- Monkeypox virus is part of the same family of viruses as variola virus, the virus that causes smallpox.
- Monkeypox symptoms are similar to smallpox symptoms, but milder, and monkeypox is rarely fatal.
- Monkeypox is not related to chickenpox.

Reference: https://www.cdc.gov/poxvirus/monkeypox/about.html

Origin of Monkeypox

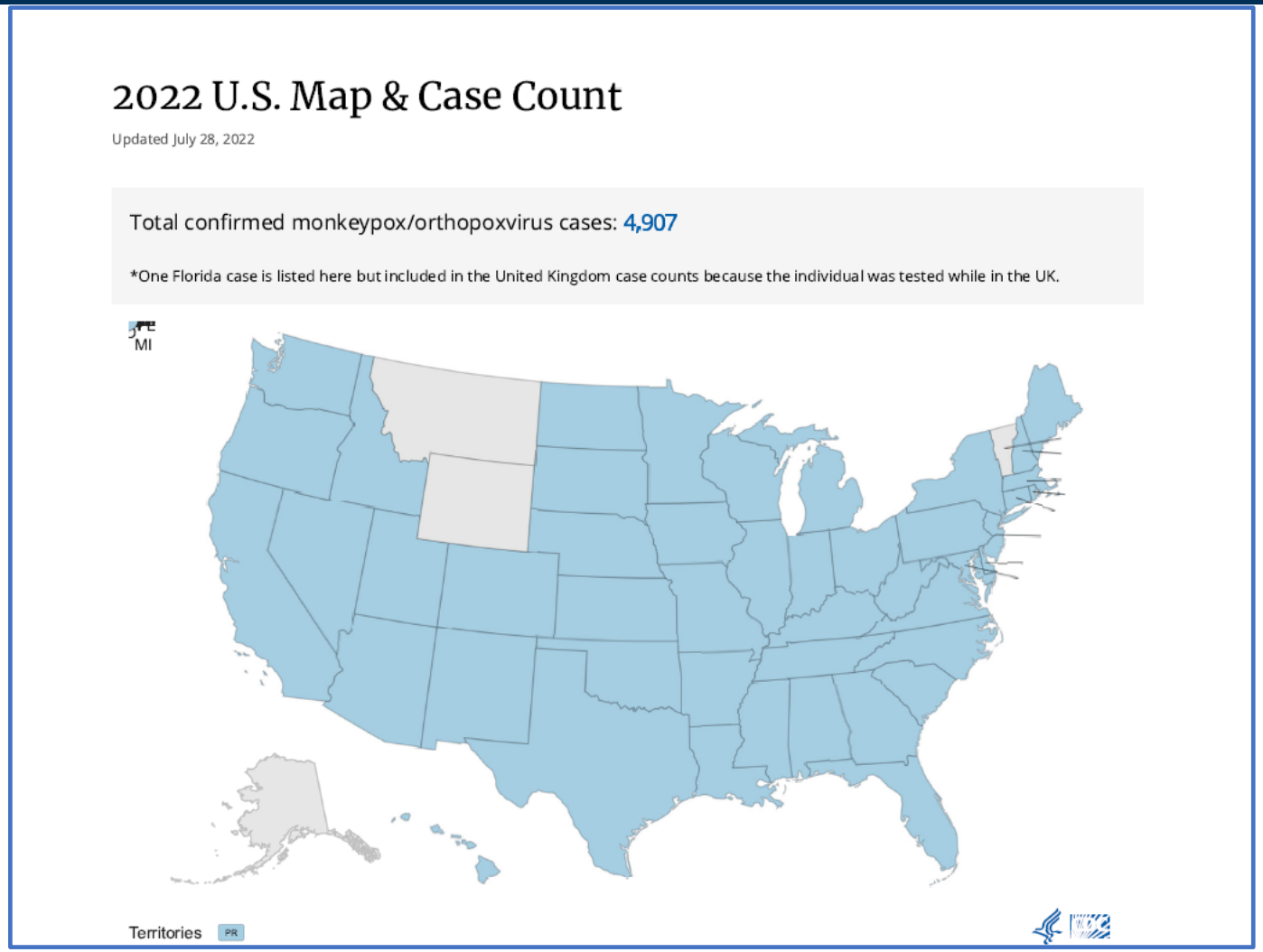
- Monkeypox was discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research.
- Despite being named "monkeypox," the source of the disease remains unknown.
- However, African rodents and non-human primates (like monkeys) might harbor the virus and infect people.

Reference: https://www.cdc.gov/poxvirus/monkeypox/about.html

Example of Monkeypox Rash

Reference: https://www.cdc.gov/poxvirus/monkeypox/resources/graphics.html

Monkeypox/Orthopoxvirus Cases: July 28, 2022



Reference: https://www.cdc.gov/poxvirus/monkeypox/response/2022/us-map.html#print

Tecovirimat: Medical Countermeasure for Treatment of Monkeypox

- Also known as TPOXX® or ST-246.
- Antiviral medication that is approved by the United States Food and Drug Administration (FDA) for the treatment of smallpox in adults and children.
- Data are not available on the effectiveness of tecovirimat in treating monkeypox infections in people, but studies using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses.
- CDC holds an expanded access protocol (sometimes called “compassionate use”) that allows for the use of stockpiled tecovirimat to treat monkeypox during an outbreak.
- Tecovirimat is available as a pill or an injection.

Tecorivimat - Expanded Access Program

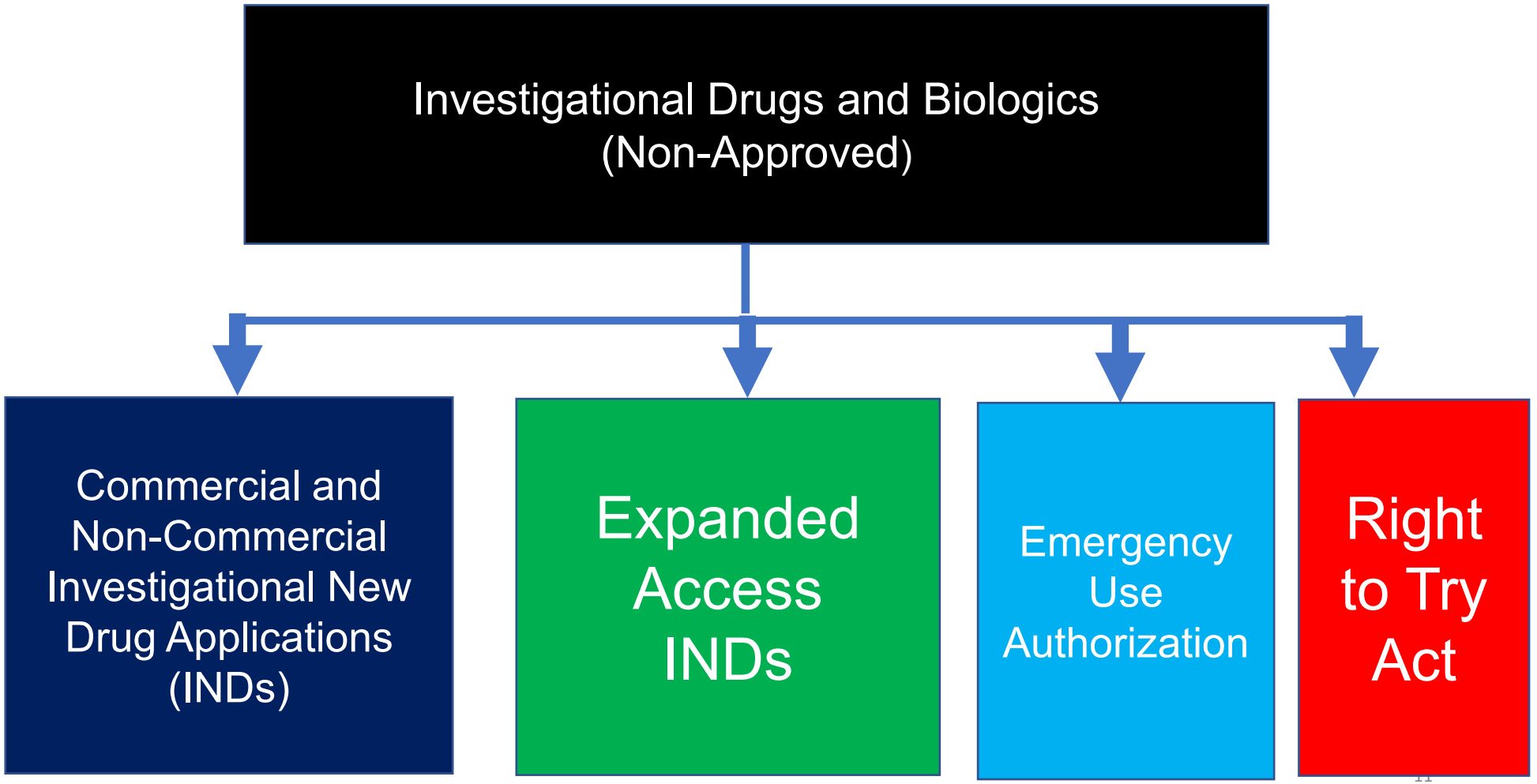
- The Centers for Disease Control and Prevention (CDC) has an intermediate-size expanded access Investigational New Drug Application (EA-IND) for the use of Tecoivimat for Monkeypox.
- This EA-IND protocol allows access to and use of TPOXX for treatment of orthopoxvirus infections, including monkeypox.
- The EA-IND provides an umbrella regulatory coverage so that clinicians and facilities do not need to request and obtain their own INDs.
- The name of the CDC Protocol: Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children.

When Investigational Drugs or Biologics Are Used Under FDA's Expanded Access Regulations

- Sometimes called "compassionate use", expanded access is a potential pathway for a patient to gain access to an investigational drug or biologic for treatment outside of clinical trials conducted in accordance with FDA's expanded access regulations.

Reference: https://www.fda.gov/news-events/expanded-access/expanded-access-information-physicians

Pathways for Use of Investigational Drugs and Biologics



Summary of Different Types of Expanded Access: Drugs and Biologics

Summary of Expanded Access Request Types (Drugs or Biologics)

Request Type	Who May Request Expanded Access	
	Industry*	Physician
1. Individual Patient IND	✓	✓
2. Emergency Use Individual Patient IND	✓	✓
3. Intermediate-Size Population IND	✓	✓
4. Treatment IND	✓	✓*
5. Individual Patient Protocol	✓	
6. Emergency Use Individual Patient Protocol	✓	
7. Intermediate-Size Population Protocol	✓	
8. Treatment Protocol	✓	

Source: https://www.fda.gov/news-events/expanded-access/expanded-access-how-submit-request-forms

CDC Intermediate-Size IND- Expanded Access Program – Not "Research"

- Research under the Federal Policy For the Protection of Human Subjects ["Common Rule'] in 38 CFR §16.102 is defined as a

" . . . systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge . . ."

- This program is not "research" under the Common Rule definition.
- This program is under FDA regulations in 21 CFR §312.315.
- This program requires prospective IRB approval under 21 CFR §56 and IRB continuing review.
- This program requires IRB-approved informed consent from the patient or patient's legally authorized representative unless an exception from informed consent as described in 21 CFR § 50.23 applies as defined in this protocol.

CDC Intermediate-Size IND- Expanded Access Program – Not "Research"

- CDC holds the IND as sponsor of this intermediate-size IND program.
- Brett Petersen, M.D., M.P.H is the Sponsor Principal Investigator.

What Research Committees or Subcommittees are Required to Review or Approve When a VA Physician Wants to Request an Investigational Drug or Biologic Through Expanded Access?

Emergency Expanded Access IND

- **No Prospective Institutional Review Board (IRB) Approval.**
- **IRB Notification <u>Required</u> 5 Working Days After Beginning Administration.**
- **No VA Research and Development Committee approval or notification required.**

Non-Emergency Expanded Access IND For CDC EA-IND for Tecovirimat for Monkeypox

- **Prospective IRB Approval <u>Required.</u>**
- **Prospective VA Research and Development Committee approval <u>required.</u>**
- ***Designated Review can be used by the R&D Committee for any non-emergency expanded use.**

VA Research and Development Committee Review for Expanded Access: Primary Review Components

- Verifying that an IRB approval was obtained with an executed IRB reliance agreement if applicable.
- Ensure privacy and information security review done.
  - **Note**: Central Privacy and Information Security Reviews have been done and will continue for any amendments to the program.
- Resources available to support the program (pharmacy).
- No evaluation of scientific merit as this is a treatment protocol under FDA's expanded access regulations; the evaluation has been done by FDA as part of the intermediate-size population IND approval.
- No evaluation of hypotheses; non applicable.

CDC IRB Reliance for CDC EA-IND Tecovirimat Program for MonkeyPox

- ORD and the Office of Research Oversight (ORO) have established a mechanism for VHA Facilities to rely upon the CDC Institutional Review Board (IRB) to participate in the expanded access program.

CDC IRB Reliance for CDC EA-IND Tecovirimat Program for Monkeypox: VA Facilities Relying upon other IRBs

- Some VA Facilities have already obtained IRB approvals from their own VA Facility IRBs or another VA Facility's IRB or University IRB which have been approved as IRBS for the VA Facility.
- There is no requirement for a VA Facility which has already obtained IRB approval of this program to transition IRB oversight to the CDC IRB.
- However, if your VA facility wishes to transition oversight, the VA Facility must follow the same steps that VA Facility initially seeking reliance will follow with an additional requirement.
  - The current IRB of Record must agree in writing to the transition, with written documentation of the transition after the VA Facility has obtained CDC IRB reliance.
  - If there are questions about transitioning IRB oversight, please email irbrelianceandsirbexceptions@va.gov

ORD Webpage – CDC IRB Reliance for CDC EA-IND Tecovirimat Program for Monkeypox

- ORD has established a webpage describing the steps and current forms supporting implementation of this program located at

  https://www.research.va.gov/programs/orppe/CDC-IRB-TPOXX-EAIND-Program.cfm

- The webpage contains the steps described in this webinar and other related ORPP&E tools and guidance supporting this program.
  - Master National CDC IRB reliance agreement executed between the CDC and ORD
  - Facility Director Concurrence Form for CDC IRB reliance
  - Central privacy reviews
  - Central information security reviews
  - ORD-training that serves as an alternative to CITI training for personnel conducting this program.

ORD Webpage Supporting CDC IRB Reliance and Human Subject Related Issues for CDC EA-IND Tecovirimat Program Program

https://www.research.va.gov/programs/orppe/CDC-IRB-TPOXX-EAIND-Program.cfm

Steps for VA Facilities to Establish IRB Reliance for the CDC IRB and Obtain VA Facility Approval

This Can Occur in Hours (as has already been done by VA Facilities)
It does not take Days or Weeks.

Step 1	**Step 2**	**Step 3**	**Step 4**
Facility Director Signs the Concurrence Memo after Reviewing the IRB Reliance Form; VA Facility submits to ORD and ORO	Update CDC IRB SOP template for your VA Facility and Submit to ORO Note: Does not require completion to move to Step 3	Obtain VA Research and Development Committee Approval *Designated Review	**Implement the Program** Informed Consent HIPAA Authorization

Step 1. VA Facility Director Signs the Concurrence Memo after Reviewing the IRB Reliance Agreement

- The CRADO has signed a National IRB Authorization Agreement Between the CDC and ORD. Your VA Facility Director should review the terms of the Agreement prior to signing and dating the form titled:

  "Concurrence with the Office of Research and Development (ORD) Agreement with Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB) For CDC IRB Oversight For Participation in the Expanded Access Program: "Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections".

Concurrence Form for VA Facilities to rely upon the CDC IRB

Name of VA Facility

Concurrence with the Office of Research and Development (ORD) Agreement with Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB) For CDC IRB Oversight For

Participation in the Expanded Access Program: "Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections"

BACKGROUND

1. The FDA is working in conjunction with the CDC to implement an expanded access protocol to treat patients with Orthopoxvirus (Monkeypox) infections. To meet VA requirements and enable VHA facility participation the VHA Office of Research and Development (ORD) has executed a national level agreement between ORD and the CDC IRB for IRB review of the Expanded Access Program (EAP) of IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections" for treatment of VA Patients with Monkeypox.

2. The national IRB Reliance Agreement between CDC IRB and ORD clearly defines the responsibilities of the IRB and each VA medical facility.

3. The VHA Medical Center Director's signature on this document serves as written Concurrence with the national IRB reliance agreement which allows your VA Facility to rely upon the CDC IRB for the above-named expanded access program.

SIGNATURES:

By signing this MOU, the VHA Facility named in this MOU agrees to:

a. Rely upon the CDC IRB for the Expanded Access Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections, to follow the requirements specified in the ORD agreement with the CDC IRB.

b. Disseminate CDC IRB SOPs relevant to this expanded access program. Maintain written IRB Reliance SOPs for communication with, and reporting to, the IRB.

SIGNATURES ON NEXT PAGE

Signature Blocks:

Name and Title of Signatory Official for the VHA Medical Facility:

Name of Signatory Official:

Date:

Electronic Signature:

Name of Facility Director

Facility Director Signature

Attachment: IRB Authorization Agreement between the CDC IRB and the VHA Office of Research and Development

Routing of CDC IRB Concurrence Form to ORD and ORO

- Retain a copy for your files and send a copy of the signed and dated agreement by email to these four(4) addresses within ORD and ORO.
  - ORO: Priscilla Craig: priscilla.craig@va.gov
  - ORO: Elizabeth Clark: Elizabeth.clark3@va.gov
  - ORD: Don Workman: don.workman@va.gov and
  - ORD: irbrelianceandsirbexceptions@va.gov

Note: Do Not Submit This Concurrence Form Directly to the CDC IRB

Routing of CDC IRB Concurrence Form to ORD and ORO (cont.)

- Please also include in your email to ORD and ORO the following:

  (a) the name and position of the primary point of contact for the CDC IRB for administrative issues, and

  (b) email and phone number of the VA Facility's point of contact.

What will VA Facilities Receive Once the Concurrence Form is Submitted?

- Your VA Facility's reliance upon the CDC IRB for this program is in effect once the concurrence form signed and dated by the VA Facility Director has been received by ORD and ORO.

- ORD will send a copy of the VA Facility(ies) concurrence forms with contact information and the VA Facility Point of Contact's information to the CDC IRB, within three days of receipt of the Concurrence agreement and the Supplemental SOP, and will send an acknowledgement back to the Facility when the information has been sent.

Your VA Facility does not have to wait upon ORD sending a written confirmation by email to confirm the CDC IRB Reliance once the form has been sent by email.

Step 2. Update CDC IRB SOP template for your VA Facility

- Your VA Facility must have procedures on how to utilize the CDC IRB for this program.
- ORO and ORD have developed a standardized policy and procedure (SOP) that can be customized for your VA Facility (fill in the indicated sections).
- The SOP template will be sent to VA sites by ORD to the points of contacts when your VA Facility returns the signed concurrence form to ORD and ORO.
- The SOP must be completed with your VA Facility information and provided to ORO to the ORO contacts (Ms. Craig and Ms. Clark).

Patient treatment under the program can begin prior to the SOP being reviewed by ORO.

Step 3. Obtain VA Research and Development Committee Approval

- R&D Committee review and approval can be done by
  - designated review (VHA Directive 1200.01, Paragraph 9.e.(5)) or by
  - a convened R&D Committee (ad hoc meeting may be convened).

- R&D Committee approval is not patient-specific.
  - Subsequent uses for other patients at the VA Facility in this program do not require separate R&D Committee approval.

VA Research and Development Committee Review for Expanded Access.

- Verify that an IRB approval was obtained with an executed IRB reliance agreement if applicable.
- Ensure privacy and information security review done.
  - ORD's Privacy Officer has conducted a central privacy review.
  - ROTC-D has conducted a central information security review.
  - All privacy and information security reviews are available to any VA Facility conducting this program (regardless of whether the CDC IRB is used. Central reviews will be done throughout the life of this program.
- Resources available to support the program (pharmacy).
- No evaluation of scientific merit or hypotheses as this is a treatment protocol under FDA's expanded access regulations.

Training for Treating Clinicians and Staff Conducting the Program: Used in Lieu of CITI

- ORD has established a training slide set for healthcare providers participating in this expanded access program who have not previously completed human subjects training in human subjects protections.
- A certificate of completion is issued that can be retained by the VA health provider and/or VA Facility's research office.
- This slide set will be uploaded on the ORD website for the CDC Expanded Access Tecorivimat Program for Monkeypox located at https://www.research.va.gov/programs/orppe/CDC-IRB-TPOXX-EAIND-Program.cfm.

Example of Certificate of Completion – Learner Fills in Fields

Certificate of Completion

This certifies that

[Enter full name here]

Has successfully completed

The VHA Research and Development Course:

Human Subjects Protection Training:

For VA Research Personnel:
For VA Research Personnel Conducting Expanded Access Program Activities for the Treatment of Patients with Monkeypox

On

[Enter date here]

Step 4. Implement the Program: Informed Consent and HIPAA Authorization

- The CDC IRB has approved the Informed Consent Form for this program. The informed consent document is located at
  - Information for Healthcare Providers on Obtaining and Using TPOXX (Tecovirimat) for Treatment of Monkeypox | Monkeypox | Poxvirus | CDC
- Three are three options (in order to be used) for obtaining informed consent as approved by the CDC IRB for this program.
  - Written informed consent obtained from the patient.
  - Written informed consent obtained from the patient's legally authorized representative.
  - An exception from informed consent to be documented by the patient's treating physician and a second physician who is not part of the patient's team participating in the program.

Written Informed Consent

- No alterations in the CDC IRB-approved informed consent document are permitted.
- For VA subjects, a VA Informed Consent Addendum approved by the CDC IRB will also be used that is signed and dated by the patient or patient's legally authorized representative; it is not yet approved.

Written Informed Consent – VA Addendum

- Until the CDC IRB has approved the informed consent addendum, please convey the following information to the patient:

  #1: The patient and/or his or her insurance will not be charged for any treatments or procedures that are part of this Expanded Access IND. If the patient has co-payments for VA care and medications, these co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this treatment program.

  #2. The VA will provide necessary medical treatment should the patient be injured by being in this program. The patient will be treated for the injury at no cost. This care may be provided by the local VAMC, or arrangements may be made for contracted care at another facility. The patient has not released the VA Facility from liability for negligence. In case of injury resulting from being in this program, the patient should contact their treating clinician.

Exception from Informed Consent

- CDC IRB has approved an exception from informed consent that may be used In the event that obtaining informed consent is not feasible because the
  - (A) patient is unable to respond and make wishes known about tecovirimat treatment and
  - (B) no legal guardian or next-of-kin is present.

An Exception From Informed Consent is

Not an Exception for IRB approval.

Exception from Informed Consent (cont.)

- The treating physician can make a clinical determination to treat with tecovirimat provided that the treating physician and an independent physician certifies to the following within 3 working days of initiating treatment with tecovirimat:

  1. Patient is confronted by a life-threatening situation necessitating the use of tecovirimat.

  2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.

  3. Time is not sufficient to obtain consent from the patient's legal representative.

  4. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

Exception from Informed Consent (cont.)

- The CDC IRB-informed consent document includes check boxes to be completed when an exception from informed consent occurs.
- CDC must be notified by email (regaffairs@cdc.gov) within 3 working days of tecovirimat initiation when an exception of informed consent is used for a patient receiving Tecovirmat under this program.

IF OBTAINING INFORMED CONSENT IS NOT FEASIBLE

In the event that obtaining informed consent is not feasible because the patient is unable to respond and make wishes known about tecovirimat treatment *and* no legal guardian or next-of-kin is present the following provides for the treating physician to make a clinical determination to treat with tecovirimat provided that the treating physician and an independent physician certifies to the following within 3 working days of initiating treatment with tecovirimat:

1. Patient is confronted by a life-threatening situation necessitating the use of tecovirimat.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.
4. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

☐ Document as such in the patient's medical record and ensure the patient or patient's legally authorized representative is made aware that tecovirimat was administered for uses for which it is not FDA-approved.

☐ Name & signature of treating physician who made the determination to administer tecovirimat to patient when informed consent could not be obtained:

Name _____ Signature _____ Date _____

☐ Name & signature of second physician, who is not otherwise participating in this treatment protocol, reviewing and evaluating decision to administer tecovirimat to patient:

Name _____ Signature _____ Date _____

Written HIPAA Authorization

- The CDC IRB-approved informed consent form does not contain HIPAA authorization language.
- The patients are to sign a VA Form 10-5345: “Request for and Authorization to Release Health Information”.
- The VA Form 10-5345 is already present in iMED.
- A sample VA Form 10-5345 completed for this CDC expanded access program will be made available on the ORD website for the CDC Expanded Access Tecorivimat Program for Monkeypox located at https://www.research.va.gov/programs/orppe/CDC-IRB-TPOXX-EAIND-Program.cfm.

Other Related Information

- Research Compliance Audits:
  - Research Compliance officers are not required and do not audit expanded access programs, which includes this CDC expanded access program for Tecovirimat.
- iMED and DocuSign
  - ORD has already requested CDC IRB approval for electronic versation of the IRB-approved informed consent forms for both DocuSign and iMED and their use.
  - ORD has already initiated the process for iMED and DocuSign.
  - ORD will provide notification when these documents are ready for use and how to access them following CDC IRB approval.

Other Related Information

- Form FDA 1572:
  - Only one Form FDA 1572 is to be completed per VA Facility participating in the program.
- Correspondence with the CDC IRB (not reporting)
  - Send to huma@cdc.gov

Availability of Recording

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- An archive of all ORPP&E webinars can be found here: https://www.research.va.gov/programs/orppe/education/webinars/archives.cfm.

Contact Information

- C. Karen Jeans, PhD, CCRN, CIP
  Director of Regulatory Affairs, ORPP&E
  VHA Office of Research and Development
  c.karen.jeans@va.gov

- ORD Regulatory Box: VHACOORDREGULATORY@VA.GOV

References

- ORD webpage: Institutional Review Board (IRB) Oversight for CDC Tecovirimat (TPOXX) IND Expanded Access Program for Monkeypox: Instructions for CDC IRB Reliance For VA Facilities with Research Programs and Related Support of the CDC Tecovirimat Expanded Access Program
- CDC webpage: Information for Healthcare Providers on Obtaining and Using TPOXX (Tecovirimat) for Treatment of Monkeypox | Monkeypox | Poxvirus | CDC
- VHA Directive 1200.01(1): Research and Development Committee at imbed VHA Publications
- VHA Directive 1200.05(2): Requirements for the Protection of Human Subjects in Research at VHA Publications