Bi-Monthly Updates in Human Research Protection

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July 27, 2022

- ✓ 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

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

- ✓ 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.

- ✓ Experiencing sound issues – you can call in using the number included on the handouts and on your registration confirmation email that you received.

Purpose

- The purpose of this bi-monthly webinar is to update the VA research community on the following July topics:
  - Expanded access use of Tecovirimat for Monkeypox
  - VA issues received from the National Cancer Institute Central IRB (NCI CIRB) for updates to VA Facility Annual Signatory Institution Worksheets
  - Commercial IRB issues and resolutions: Questions received by ORD and Advarra, WCG, and Sterling IRBs from VA Facilities

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

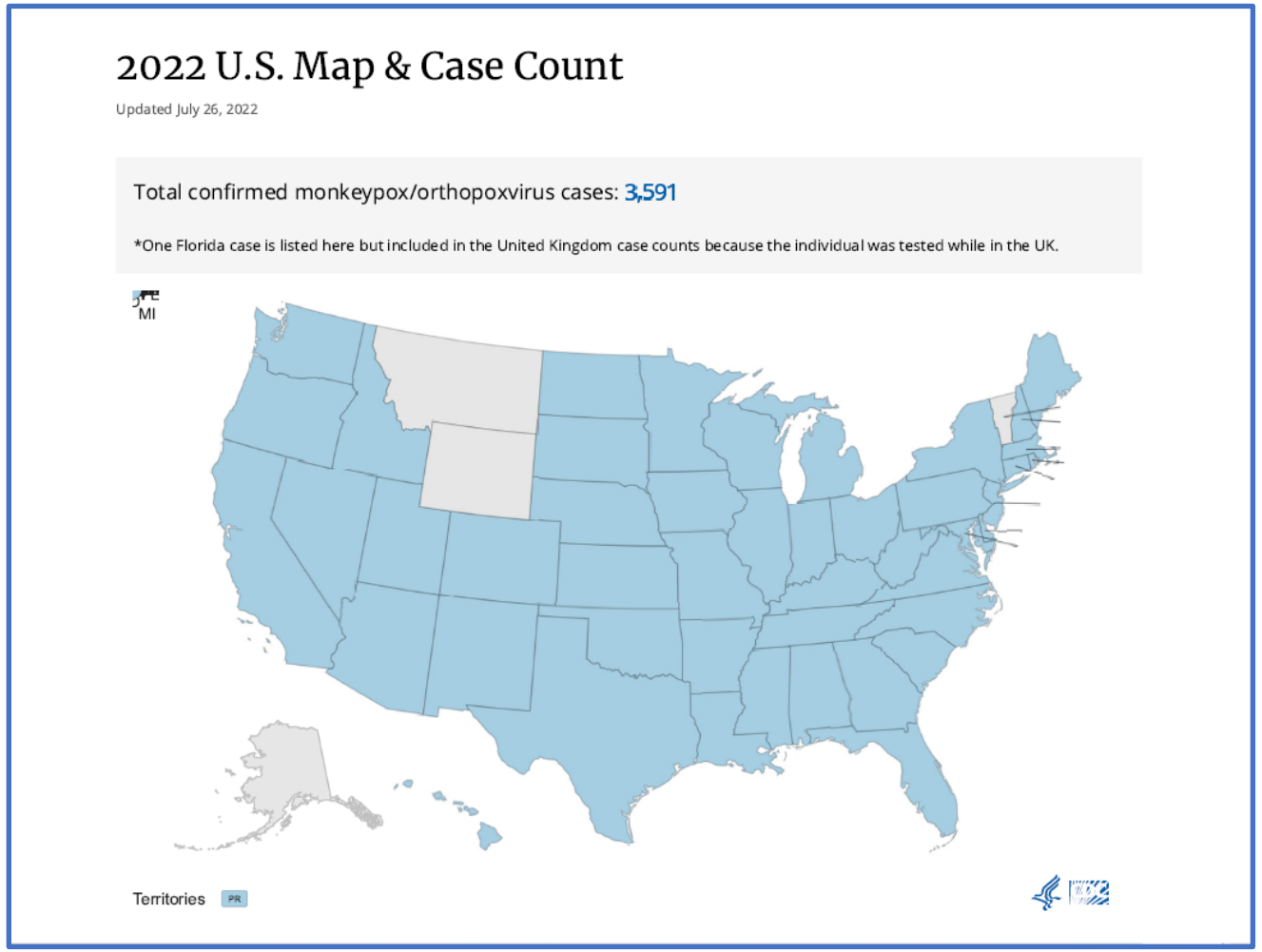
- Monkeypox was discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research.
- Despite being named "monkeypox," the source of the disease remains unknown.
- However, African rodents and non-human primates (like monkeys) might harbor the virus and infect 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 26, 2022



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

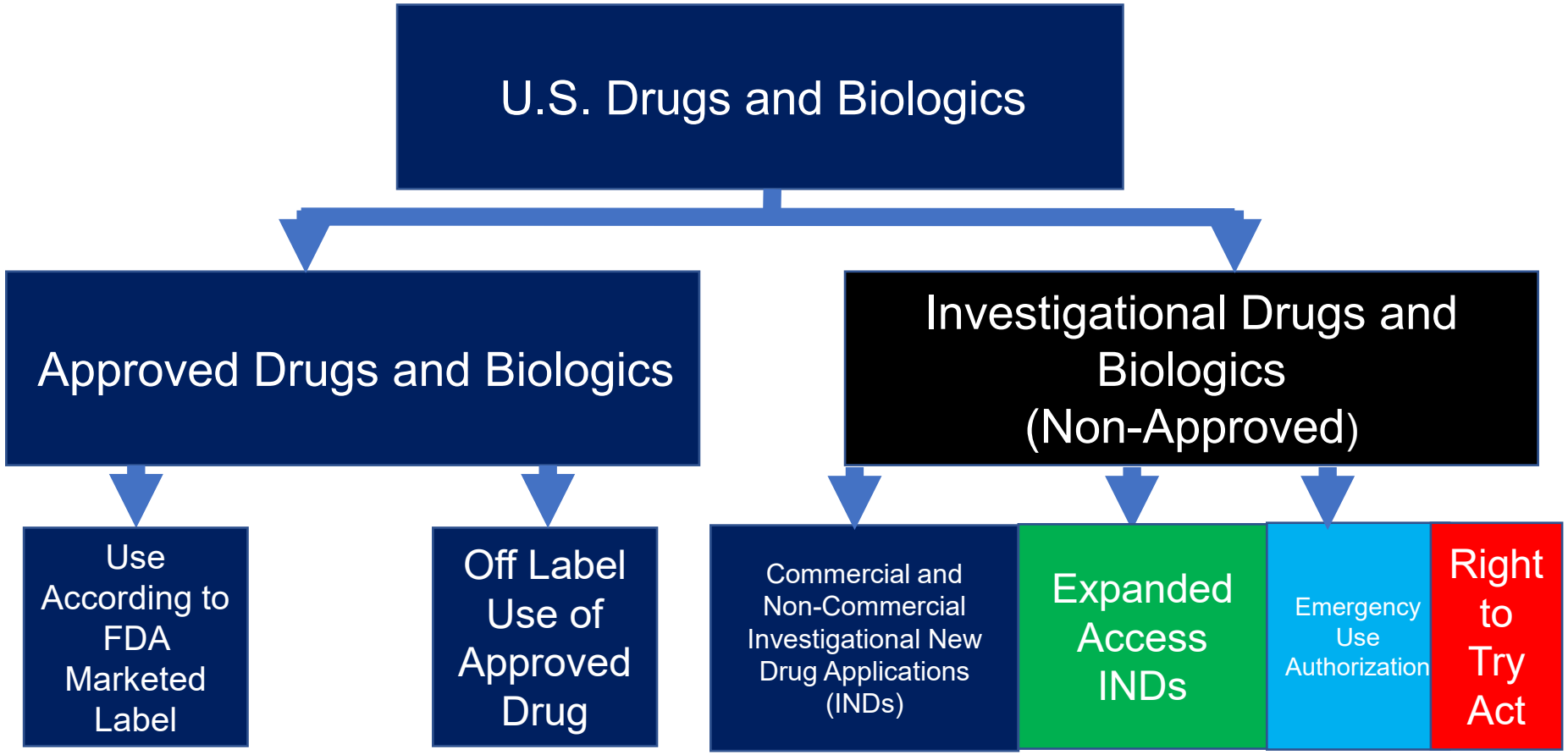
Tecovirimat: Medical Countermeasure for Treatment of Monkeypox

- 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 Tecorivimat 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.

Expanded Access: One of the Pathway for Use of Drugs and Biologics

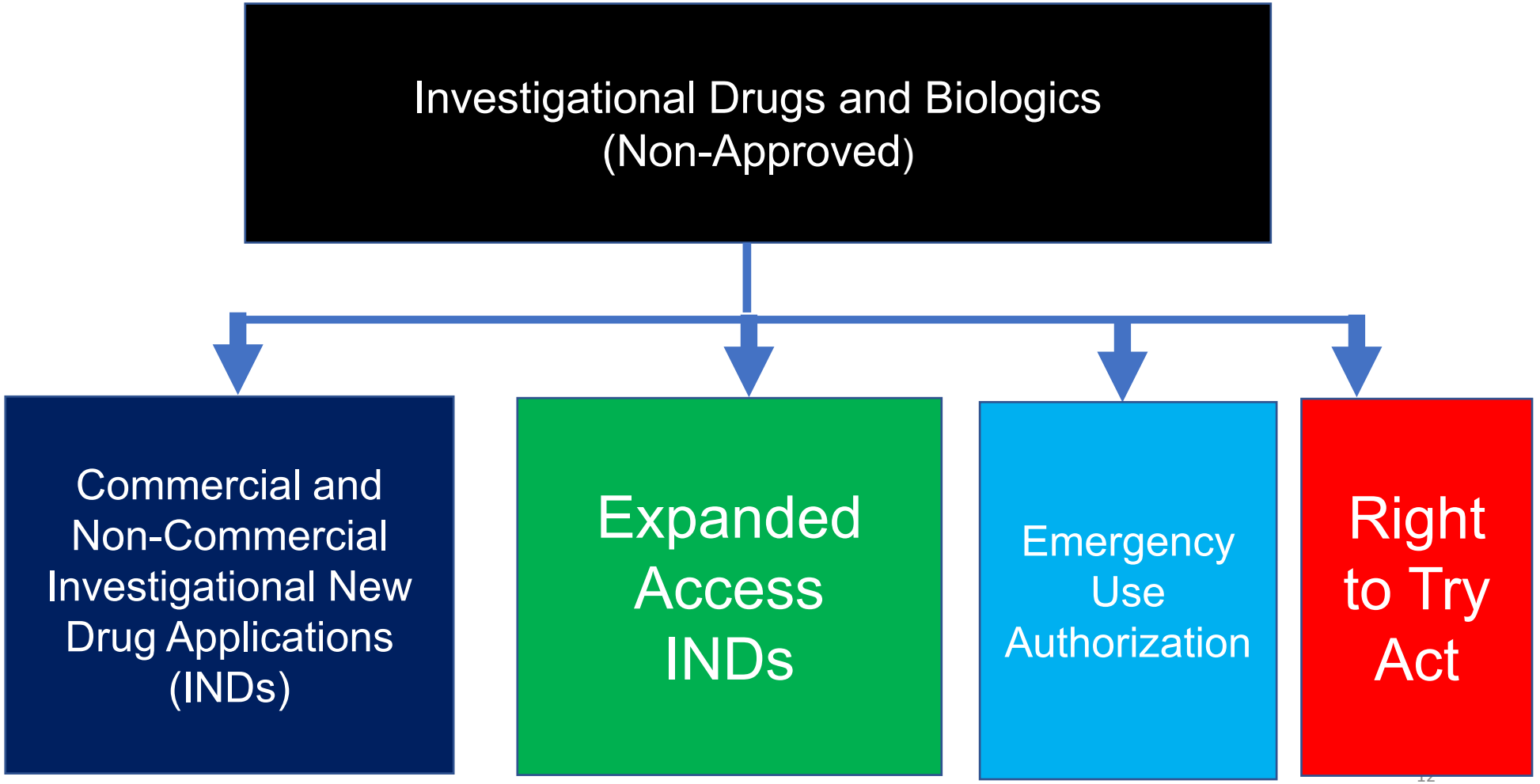


When Investigational Drugs or Biologics Are Used Under FDA's Expanded Access Regulations

- 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

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

Pathways for Use of Investigational Drugs and Biologics



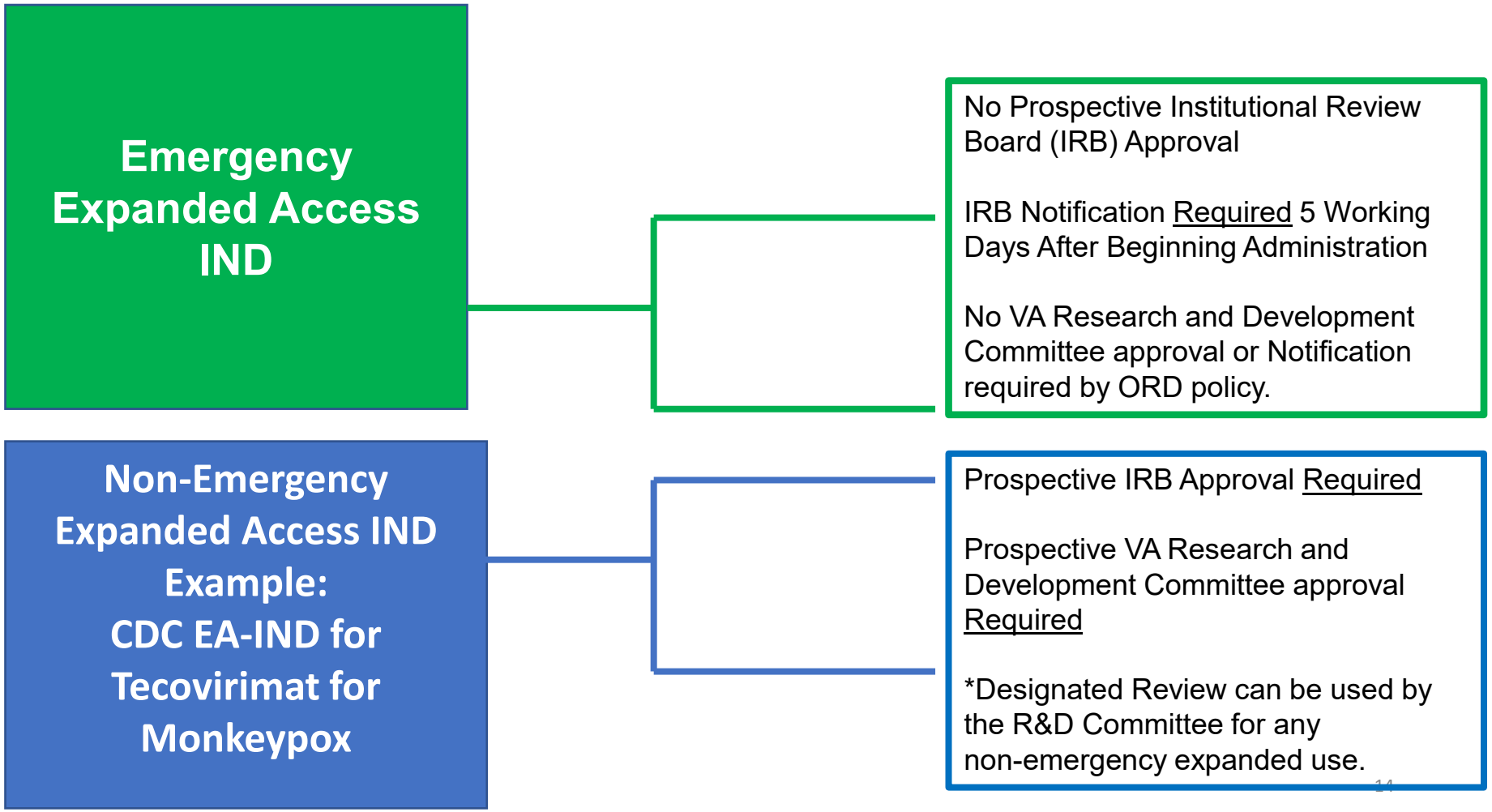
Summary of Different Types of Expanded Access: Drugs and Biologics

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

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?



CDC EA-IND Tecovirimat Program for MonkeyPox

- ORD and the Office of Research Oversight (ORO) has established mechanism for VHA Facilities to rely upon the CDC Institutional Review Board (IRB) to participate in the expanded access program.
- The CDC's EA-IND Tecovirimat Program for Monkeypox does not meet the definition of research under the Common Rule.
  - The activity is not a systematic investigation designed to develop or contribute to generalizable knowledge.
  - It is treatment with an investigational drug.
- However, this program requires prospective IRB review and approval under FDA regulations and IRB-approved informed consent as required by the CDC IRB.

CDC EA-IND Tecovirimat Program for MonkeyPox (cont.)

- 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

- ORD will be holding a webinar on the CDC IRB reliance process and related human subject protection issues related to this program on July 29th from 2:00 p.m. to 3:00 p.m. EST; the registration link is located at https://veteransaffairs.webex.com/veteransaffairs/onstage/g.php?MTID=ef17b15757205edc29d705d4dc67ed3da

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

VA Issues Received from the National Cancer Institute Central IRB (NCI CIRB)

Issues with Completion of the Annual Signatory Institution Worksheets

Annual Signatory Institution Worksheet

Reason for submission:

- ☐ First submission to the CIRB of an Annual Signatory Institution Worksheet
- ☐ Revised submission of the Annual Signatory Institution Worksheet

Signatory Institution Information

Submitting User Information (auto-populated)

Name of Signatory Institution (auto-populated)

If there are any changes to the Submitting User Information please update within user's Identity and Access Management (IAM) account.

1. What type of studies does this Signatory Institution intend to open with the CIRB?

   - ☐ Phase 2/3 and Large Phase 2 Adult Studies
   - ☐ ETCTN and Group Phase 1 and 2 Adult Studies
   - ☐ Cancer Prevention and Control Studies
   - ☐ Pediatric Studies

Comments: Issues with Completion of the Annual Signatory Institution Worksheets (cont.)

- Numerous VA worksheets are being rejected by the NCI CIRB for either content and/or technical reasons, requiring resubmission.
  - Questions requiring a response must be completed.
  - Responses must be relevant to the question.
  - NCI CIRB reviewer's notes are not being reviewed and/or may be inadvertently being overlooked, causing the worksheet to be rejected repeatedly. These notes are also sent to them via an email when the worksheet is rejected.
  - If the NCI CIRB reviewer rejects the worksheet with notes requesting additional information or corrections, responses are being added to "Add note". VA Facilities should be updating their response in the text box where their original response was entered and not in "Add note".

Examples of VA Facility Responses (Rejected) – Question #6 Annual Signatory Worksheet Responses (cont.)

Question #6: What is the age of majority in your state?

Example Responses:

1. **Please refer to VHA Publications.**
2. **We are a federal institution.**
3. **Will be determined by the NCI CIRB.**

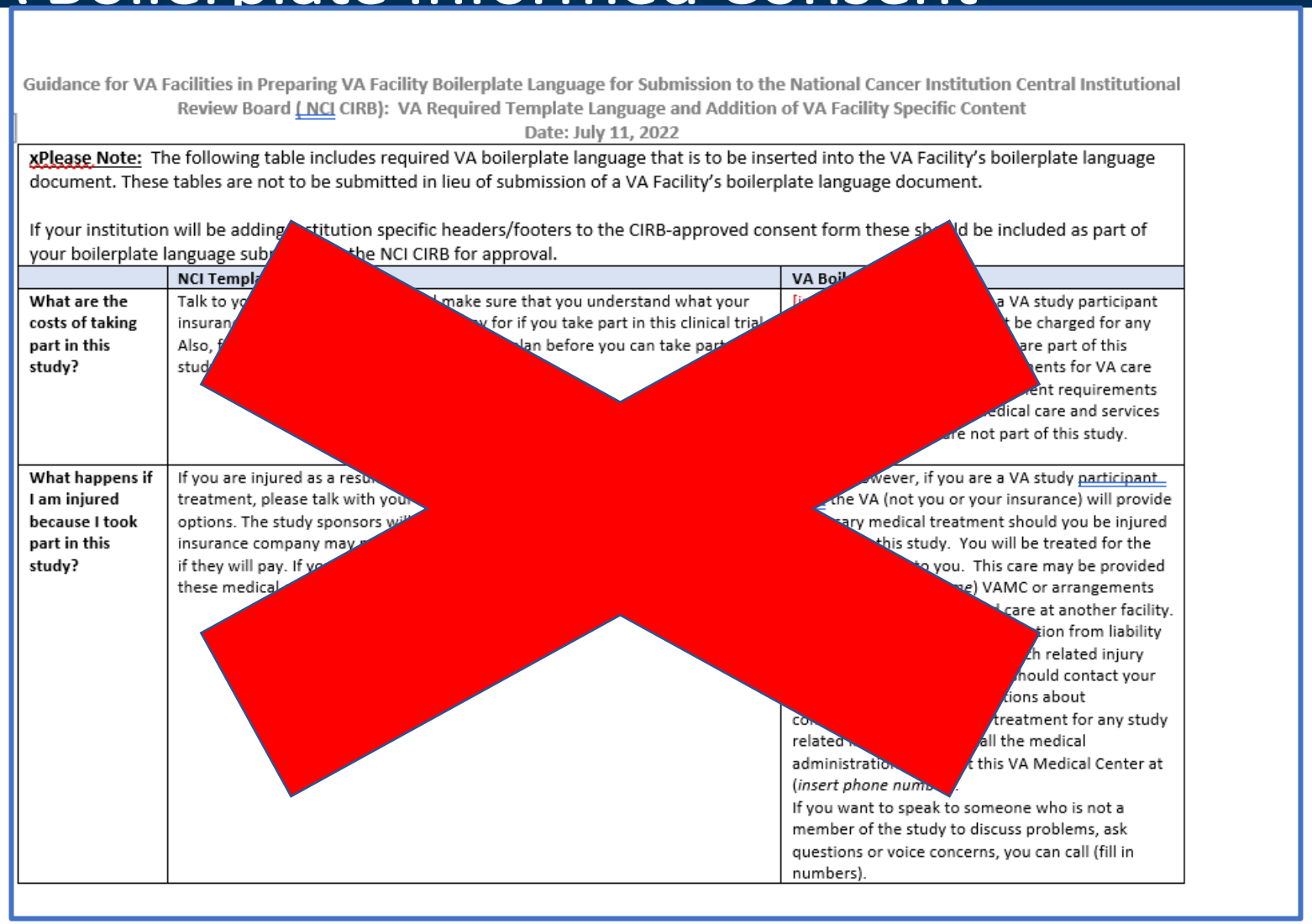
Issues: None of these responses address the question.

Issues with Boilerplate Language in NCI CIRB Consent Forms

- Some VA Sites continue to upload the guidance document rather than changing the language in their VA site specific boilerplate.
- Required fields are not completed.
- Example:

"Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs." [Insert] However, if you are a VA study participant then the VA (not you or your insurance) will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the (insert local name) VAMC or arrangements may be made for contracted care at another facility. You have not released this institution from liability for negligence. In case of research related injury resulting from this study, you should contact your study team. If you have questions about compensation and medical treatment for any study related injuries, you can call the medical administration service at this VA Medical Center at (insert phone number).

Please Do Not Upload the Guidance Document as your NCI CIRB VA Boilerplate Informed Consent



Guidance for VA Facilities in Preparing VA Facility Boilerplate Language for Submission to the National Cancer Institution Central Institutional Review Board (NCI CIRB): VA Required Template Language and Addition of VA Facility Specific Content

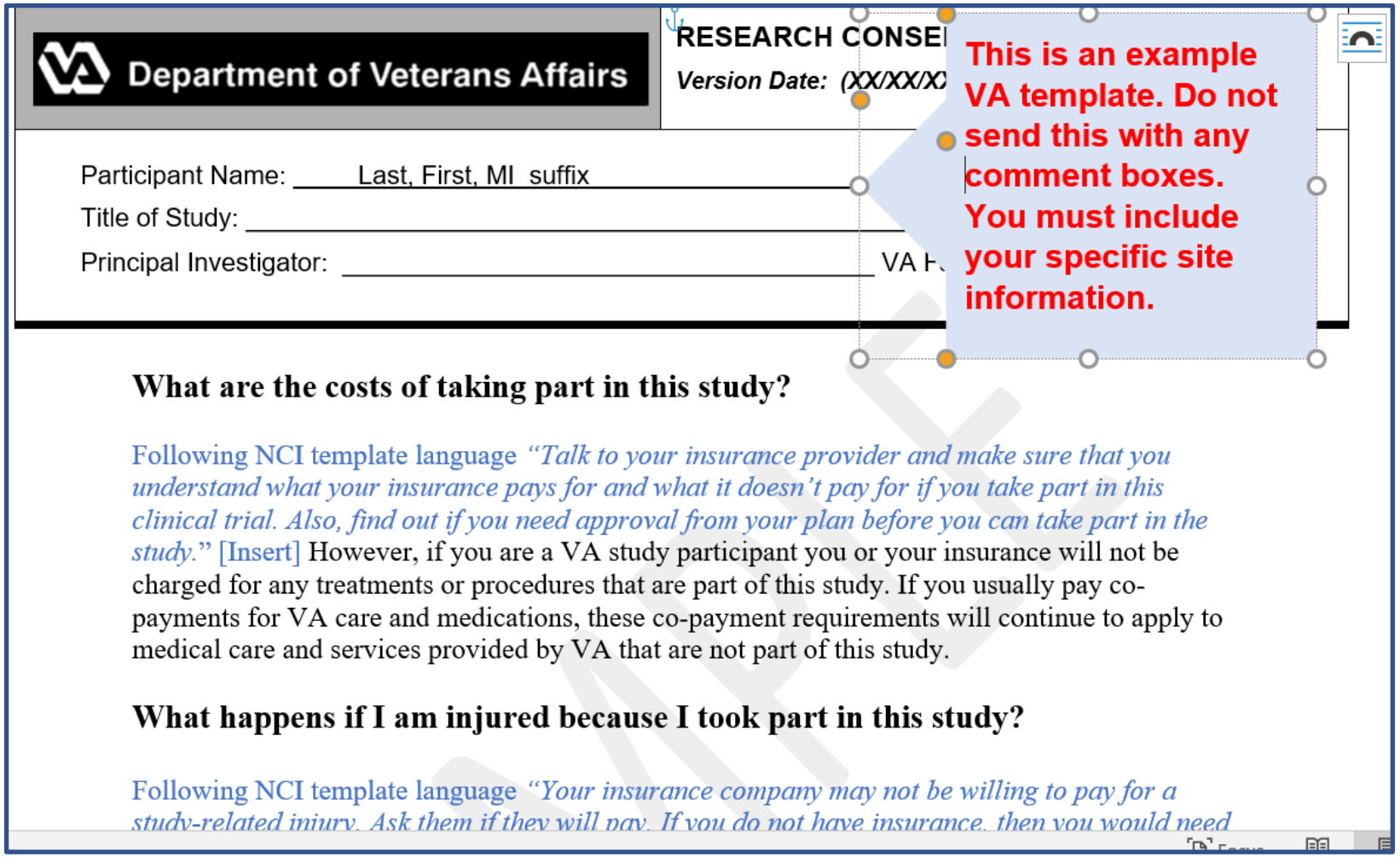
Date: July 11, 2022

xPlease Note: The following table includes required VA boilerplate language that is to be inserted into the VA Facility's boilerplate language document. These tables are not to be submitted in lieu of submission of a VA Facility's boilerplate language document.

If your institution will be adding ...stitution specific headers/footers to the CIRB-approved consent form these sh...ld be included as part of your boilerplate language sub... ...the NCI CIRB for approval.

	NCI Templa...	VA Boil...
What are the costs of taking part in this study?	Talk to yo... ...l make sure that you understand what your insuran... ...w for if you take part in this clinical trial. Also, f... ...lan before you can take part... stud...	[i... ...a VA study participant ...t be charged for any ...are part of this ...ents for VA care ...ent requirements ...edical care and services ...are not part of this study.
What happens if I am injured because I took part in this study?	If you are injured as a resu... treatment, please talk with you... options. The study sponsors wi... insurance company may ... if they will pay. If yo... these medical...	...owever, if you are a VA study participant ...the VA (not you or your insurance) will provide ...sary medical treatment should you be injured ...this study. You will be treated for the ...to you. This care may be provided ...me) VAMC or arrangements ...l care at another facility. ...tion from liability ...h related injury ...hould contact your ...tions about co... ...treatment for any study related ... ...all the medical administrati... ...t this VA Medical Center at (*insert phone numb...*. If you want to speak to someone who is not a member of the study to discuss problems, ask questions or voice concerns, you can call (fill in numbers).

New Document Provided by NCI CIRB for VA Facilities: VA Boilerplate Language Sample Template (July 27, 2022)



Department of Veterans Affairs

RESEARCH CONSE

Version Date: (XX/XX/X

This is an example VA template. Do not send this with any comment boxes. You must include your specific site information.

Participant Name: Last, First, MI suffix

Title of Study:

Principal Investigator: VA F

What are the costs of taking part in this study?

Following NCI template language *"Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study."* [Insert] However, if you are a VA study participant you or your insurance will not be charged for any treatments or procedures that are part of this study. If you usually pay 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 study.

What happens if I am injured because I took part in this study?

Following NCI template language *"Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need*

New Documents Uploaded to ORD-ORO NCI SharePoint Site

- Guidance for VA Facilities in Preparing VA Facility Boilerplate Language for Submission to the National Cancer Institution Central Institutional Review Board (NCI CIRB): VA Required Template Language and Addition of VA Facility Specific Content (July 11, 2022)

- VA Site Boilerplate Language Sample Template (July 27, 2022)

ORD-ORO NCI CIRB SharePoint Site: Home - NCI Central IRB (sharepoint.com) accessible on ORD's NCI CIRB webpage at https://www.research.va.gov/programs/orppe/nci_irb.cfm.

Commercial (Independent) IRBs Questions Received by ORD and ORD-Approved Commercial IRBs

Question #1 : Informed Consent

1. Are the VA Consent Forms approved by the commercial IRBs required to be on the VA Form 10-1086?

ORD's response: No. There is no ORD policy requirement mandating the use of a VA Form 10-1086. In addition, commercial IRBs are not required to follow VA local facility specific policy requirements unless national VA or VHA policy requires it.

Question #2 : Applicability of IRB Approval for VA Nonprofit Corporations (VA NPCs)

2. Our VA Facility is conducting an industry-sponsored clinical trial with funds administered by the VA NPC. The IRB is an ORD-approved commercial IRB. Is the VA NPC required to obtain IRB approval?

ORD's response: No. The only time that IRB approval is required for a VA NPC is when the VA Facility that they are associated with is also conducting non-exempt human subjects research with the VA Nonprofit Corporation administering the federal funds. In the Common Rule, an institution is engaged requiring IRB approval if it administers federal funds associated with non-exempt humans subjects research. VA NPCs do not conduct research, but they support VA Facilities conducting the research.

Question #3 : Amending Master Protocols

3. Our VA Facility would like to amend the protocol for a multi-site industry-sponsored study to reflect our recruiting plan which differs from the protocol approved by the commercial IRB. Can we amend the protocol to reflect our site-specific requests for recruitment?

ORD's response: No. A multi-site protocol from industry, such as clinical trial, does not include every participating sites' specific information. However, site-specific amendments may be permitted as approved by the IRB of Record for the study.

Question #4 : Applicability of IRB Approval - Subparts B and D

4. A commercial IRB has approved a multi-site clinical trial and conducted Subparts B and D determinations when pregnant subjects are followed for pregnancy outcomes; even if they are not being enrolled. A VA site that is participating in the study has requested that the Subpart B and D determinations be removed from the VA site's IRB approval letter. Is the commercial IRB required to remove the content from the VA site's letter?

ORD's response: No. The IRB determination is at the protocol level and not the specific site level. It is appropriate to keep the approval letter content with the determinations regarding Subparts D and D.

Question #5 : Use of Commercial IRB as Primary IRB of Record

5. Can a VA Facility rely upon one of the ORD-approved commercial IRBs as its primary IRB of Record and cover all non-exempt human subjects studies?

ORD's response: No. ORD policy in VHA Directive 1200.05, Paragraph 5.f.(8)(b) permits use of a commercial IRB as an IRB of Record for VA facilities if it has been specifically designated by ORD as a commercial IRB that may serve as an IRB for cooperative research.

Question #6 : Querying the Commercial IRB

6. A clinical trial at our VA Facility recently received approval from an ORD-approved commercial IRB. Our Investigator has questions regarding the IRB approval letter because he/she cannot find the approval of the VA informed consent document. Can he/she query the commercial IRB or should he/she just assume it is approved because it is a commercial IRB?

ORD's response: Yes, the VA Investigator can query the commercial IRB. One does not assume a document is IRB-approved when there is no documentation to support it based on the type of IRB.

August Summary

- Anticipate more updates on the CDC EA-IND Tecorivimat program for Monkeypox.
- ORD continues to work with the commercial IRB and NCI IRB to improve communication and publish tools and guidance documents.

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Contact Information

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- 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
- ORD's NCI CIRB webpage: https://www.research.va.gov/programs/orppe/nci_irb.cfm
- VA's NCI CIRB SharePoint site: https://dvagov.sharepoint.com/sites/vacovhacomm/admin/projects/ncicirb/default.aspx
- VA Specific Requirements for Informed Consent and HIPAA Authorizations When Using a Commercial IRB (September 14, 2020)
- VHA Directive 1200.05(2): Research and Development Committee (January 7, 2019) at VHA Publications
- ORD's Policies and Guidance Documents webpage at https://www.research.va.gov/resources/policies/