

Human Subjects Protection Training: For VA Research Personnel Conducting Expanded Access Program Activities for the Treatment of Patients with COVID-19

December 8, 2020

Training Objectives

By completing the review of this training slide deck, you will gain an understanding of:

- key events in history that influenced the current ethical protections governing research involving human subjects;
- key regulations and requirements that govern VA research involving human subjects;
- key responsibilities of the investigator and the main entities involved in the review and approval of VA research;
- pathways for accessing drugs and biologics through FDA's Expanded Access Program; and
- mechanisms for VA Clinicians at VA Facilities without Research Programs to access Investigational Drugs for the treatment of COVID-19 through the Expanded Access Pathway.

This Training Meets ORD's Training Requirements in Human Subjects Protections for the Following Purposes Related to the COVID-19 Pandemic

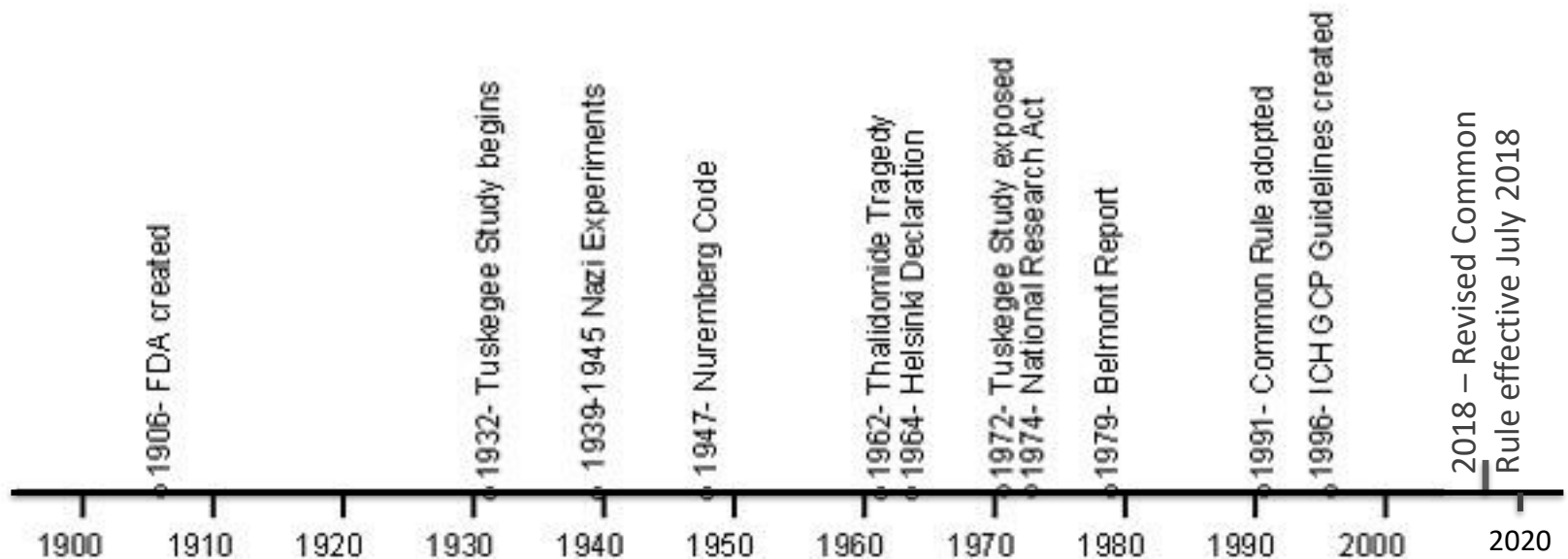
- This training meets the VHA Office of Research and Development's training requirement in VHA Directive 1200.05, Paragraph 26 requiring all individuals involved in conducting VA human subjects research to complete training in ethical principles if the following criterion is met:
- The VA Research Activity is an expanded access program regulated by the U.S. Food and Drug Administration involving investigational drugs, biologics, or medical devices for the treatment of COVID-19.



Historical Perspective on Research Involving Human Subjects

Key Historical Events Impacting Research Involving Human Subjects

From the 1930s to 1970s a number of significant events occurred that have influenced how research is conducted today.



Historical Perspective on Research Involving Human Subjects

- Nazi war crimes
 - Used unconsenting concentration camp victims as subjects and subjected them to great pain, suffering, disfigurement, and death. These were not therapeutic trials.
 - Led to the development of the Nuremberg Code: a set of ethical principles developed by U.S. military tribunal post WWII (1949)
 - Consent; Right to withdraw; Weighing of risks and benefits
- Thalidomide
 - Use in pregnant women resulted in thousands of babies born with malformed limbs
 - Lead to 1962 Drug Amendments Act – prove efficacy not just safety

Historical Perspective on Research Involving Human Subjects (continued)

- Declaration of Helsinki
 - Issued by the World Medical Association (1964, amended 7x, 2013 most recent)
 - Well-being of the [human subject](#) should take precedence over the interests of science and society
 - Physician's responsibility is to safeguard the health of the people
 - Medical research should be subject to review, approval, and oversight of an independent ethics committee

Historical Perspective on Research Involving Human Subjects (continued)

- Willowbrook Case
 - Injected isolated strains of hepatitis into institutionalized children with intellectual disabilities to understand the natural history of the disease and effects of gamma globulin
- Jewish Chronic Disease Hospital Case
 - Injected live cancer cells into patients without informing them
- US Public Health Service Syphilis Study at Tuskegee
 - 40-year research study designed to gain an understanding of the natural history of untreated latent syphilis
 - During course of study, penicillin was identified to be effective treatment but subjects were denied access to treatment

The Belmont Report: Basic Ethical Principles



- National Research Act
 - Mandated regulations to protect human subjects
 - Created National Commission to examine ethical issues
- National Commission published the Belmont Report in 1979
 - summarizes the ethical principles and guidelines for research involving [human subjects](#)
 - Respect for persons: operationalized by obtaining informed consent
 - Beneficence: minimizing possible harms and maximizing possible benefits
 - Justice: fair or equitable selection of subjects



Regulations and Requirements for Conducting VA Human Subjects Research

Key Regulations and Requirements Governing VA Research Involving Human Subjects

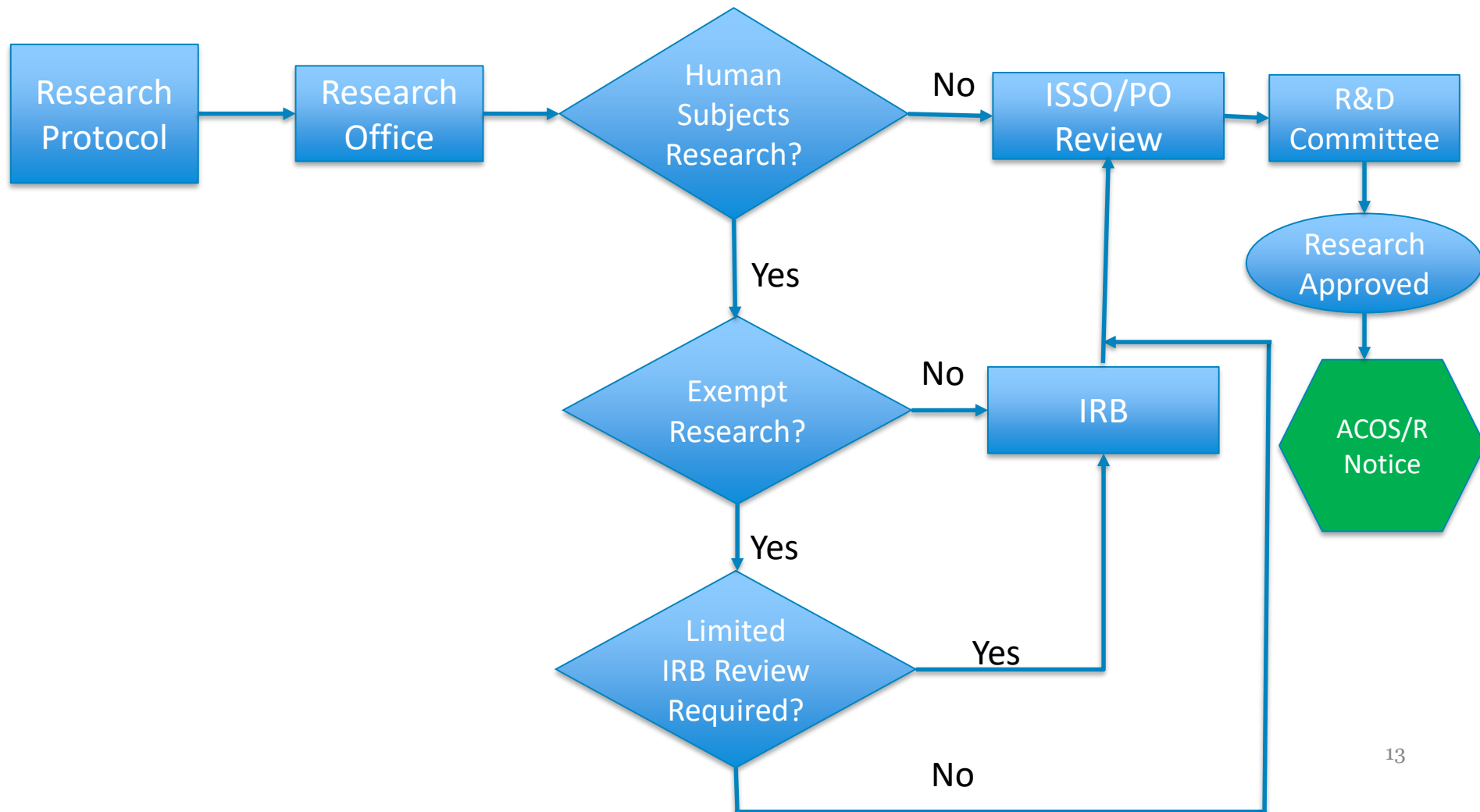
- The Federal Policy for the Protection of Human Subjects (aka The Common Rule)
 - 38 CFR 16
- US Food and Drug Administration (FDA) regulations for research involving human subjects subject to FDA regs
 - 21 CFR 50/56: Protection of Human Subjects/Institutional Review Boards
 - 21 CFR 312: Investigational New Drug Applications
 - 21 CFR 812: Investigational Device Exemptions
- VA Policy governing research involving human subjects:
 - VHA Directive 1200.05: Requirements for the Protection of Human Subjects in Research
 - VHA Directive 1200.01: Research and Development Committee
 - VHA Directive 1058.01: Research Compliance Reporting Requirements

VA Research Program Infrastructure and Federalwide Assurance (FWAs)

VA policy requires any VA Facility conducting [human subjects](#) research to have the following:

- Research Program – Infrastructure that includes at a minimum
 - Its own Institutional Review Board (IRB) or ability to use another institution's IRB
 - Its own Research and Development Committee or ability to use another institution's R&D Committee
 - Key positions – Associate Chief of Staff for Research and Development, Administrative Officer for Research and Development, and Research Compliance Officer
- Federalwide Assurance
 - An institutional commitment signed by the institutional official (VA Medical Center Director) approved by the Office for Human Subjects Protections (OHRP) and the VHA Office of Research Oversight that will follow the federal policy for the protection of human subjects (38 CFR Part 16).

Simplified Overview of Review and Approval: What Normally Occurs for VA Research Programs With Federalwide Assurances



IRB Responsibilities

- The IRB is responsible for the approval and ethical oversight of non-exempt research involving [human subjects](#) and for performing limited IRB review of exempt research requiring limited IRB review as a condition of the exemption.
- The IRB conducts initial and continuing review of research; reviews modifications to approved research; reviews unanticipated problems involving risks to subjects or others; reviews reports of serious or continuing noncompliance; and suspends or terminates research. Findings and actions are reported to the investigator, R&D Committee, and the institution that relies upon it.
- The IRB performs a review of the research and ensures that:
 - all IRB approval criteria specified in 38 CFR 16.111 and VHA Directive 1200.05 are met;
 - Informed consent is obtained, unless the study meets the criteria for a waiver of informed consent;
 - Research involving investigational drugs and devices is reviewed in accordance with applicable FDA regulations.

◆ Belmont Principles

➤ Common Rule Approval Criteria (38 CFR 16.111)

Respect for Persons

- ◆ Treat Individuals as Autonomous Agents
 - ◆ Protect those with Diminished Autonomy
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative;
- Informed consent will be appropriately documented or appropriately waived in accordance with 38 CFR 16.117;
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with diminished capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Justice

- ◆ Equal Distribution of Burdens and Benefits
- Selection of subjects is equitable. The IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research involving vulnerable populations.

Beneficence

◆ Do No Harm

- Risks to subjects are minimized: (i) By using procedures consistent with sound research design and that do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonable be expected to result;
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

◆ Maximize Benefits

◆ Minimize Risks

Informed Consent: Obtaining Legally Effective Informed Consent

- Unless informed consent is waived by the IRB, the Common Rule requires that investigators obtain the legally effective informed consent of the subject or the subject's [legally authorized representative](#) (LAR) prior to involving a human being as a subject in research.
- With very few exceptions, FDA regulations require that investigators obtain the legally effective informed consent of the subject or the subject's [legally authorized representative](#) prior to involving a human being as a subject in research.
- Informed consent should only be sought under circumstances that provide the prospective subject or their [LAR](#) sufficient opportunity to discuss and consider whether or not to participate in the research and that minimizes the possibility of coercion or undue influence.
- The information provided must be in language understandable to the subject or the [LAR](#).

Informed Consent: Obtaining Legally Effective Informed Consent (continued)

- The prospective subject must be provided with the information a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.
- The informed consent process must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject in deciding whether they wish to participate in the research or not.
- The informed consent process may not include any exculpatory language through which the subject or the [LAR](#) waives or appears to waive any of their legal rights or releases or appears to release the investigator, sponsor, institution, or its agents from liability for negligence.

Informed Consent: Required Elements

- Common Rule Requirements:
 - Nine basic elements as described in 38 CFR 16.116(b)
 - Nine additional elements as described in 38 CFR 16.116(c)
 - 12 elements for broad consent as described in 38 CFR 16.116(d)

- Additional FDA Requirements:

For clinical trials, the following statement must be provided to each human subject as part of the informed consent process, "A description of this clinical trial will be available on <http://www.clinicaltrials.gov> as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

- Additional VA-specific elements

- A statement that VA will provide treatment for research related injury in accordance with 38 CFR 17.85 (VHA Directive 1200.05 paragraph 17d(10));
- When appropriate, a statement that informs VA research subjects that they or their insurance will not be charged for any costs related to the research (VHA Directive 1200.05 paragraph 17e(10)).

Documentation of Informed Consent in VA Research

- Unless a waiver or alteration is approved by the IRB, the written informed consent form must contain the elements of informed consent described in VHA Directive 1200.05 as approved by the Institutional Review Board (IRB).
- Unless documentation of informed consent is waived by the IRB, the informed consent document must be signed and dated by the Subject or the [LAR](#).
- Use of the VA Form 10-1086 (Research Consent Form template) to document informed consent for VA studies involving human subjects is not required.
- Documentation of consent may be obtained electronically so long as the informed consent process meets all Common rule requirements and VA requirements for use of electronic signatures.

Information System Security Officer and Privacy Officer Responsibilities

- The Information System Security Officer (ISSO) is responsible for ensuring that all proposed research complies with information security requirements for VA sensitive information.
 - ISSO review must occur prior to the IRB submission.
- The Privacy Officer (PO) is responsible for ensuring that all proposed research complies with VA Privacy requirements and the HIPAA Authorization contains all required elements.
 - Investigators must complete and submit the VA Form 10-250, "VHA Research Protocol Privacy Review Checklist" to the research office as part of the initial protocol submission.

R&D Committee Responsibilities

- The R&D Committee is responsible for ensuring that all research in which the facility is engaged is consistent with the VA mission and complies with all applicable statutory and regulatory requirements.
- The R&D Committee approval letter is only issued after the R&D Committee receives documentation from all applicable subcommittees of their review and non-contingent approval.
- The R&D Committee performs a review of the research study and ensures:
 - Proposed research is relevant to VA's mission and the care of Veterans;
 - All research studies have been reviewed and approved for high scientific quality, the protection of human subjects and research staff, the welfare of animal subjects, the safety of all involved in research, the security of research laboratories, and the security of VA data and sensitive information.

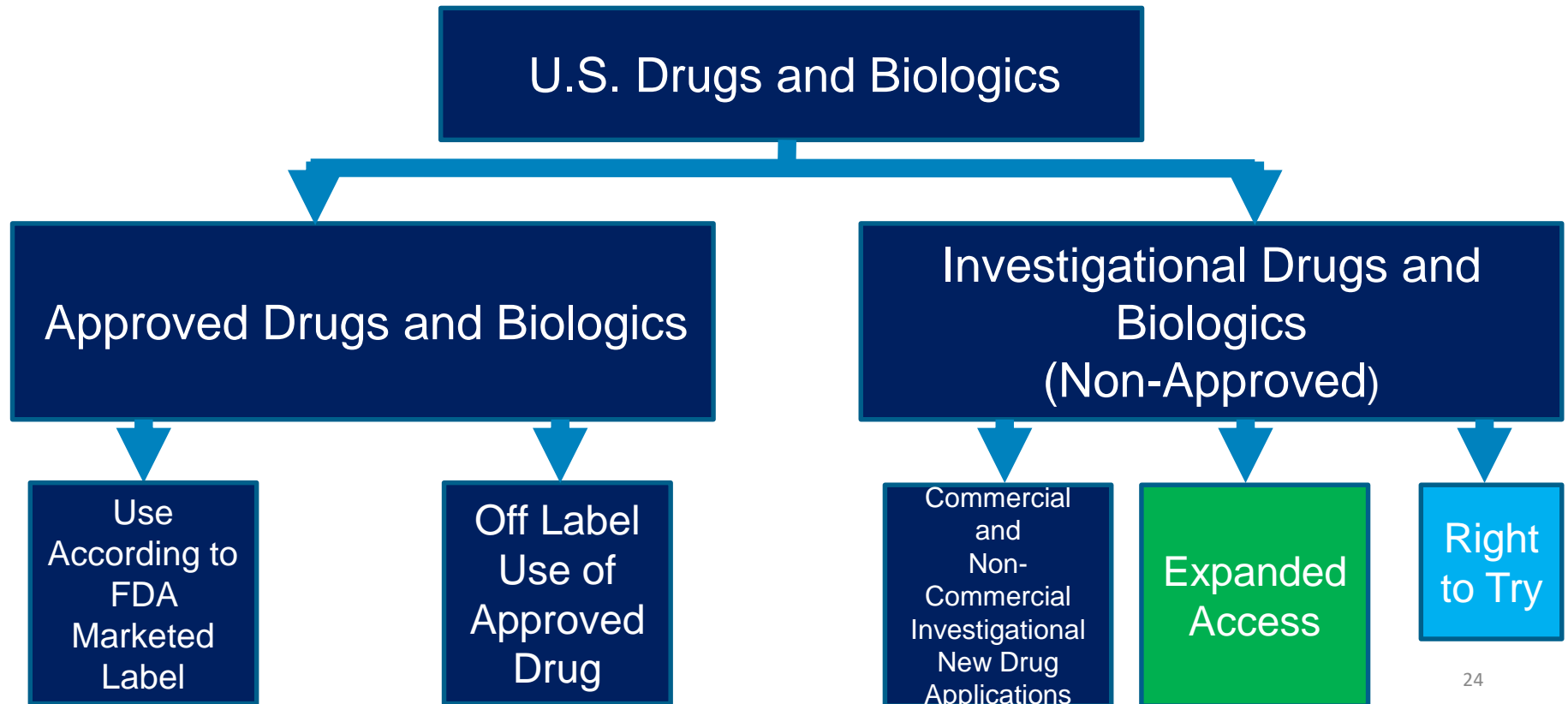
R&D Committee Responsibilities (continued)

- The R&D Committee performs a review of the research study and ensures:
 - Availability of required resources, investigator's time, and appropriate location where the research will be conducted;
 - Availability of qualified research team members, including investigators, who can conduct the approved research, and prove successful completion of all relevant research-related training;
 - Inclusion of Non-Veterans in VA research is justified;
 - Conflicts of interest are reported, reviewed, and managed in accordance with government ethics rules and regulations, and VA ethics policies;
 - ISSO and PO review is complete before the study is given final approval.



FDA's Expanded Access Program for Investigational Drugs and Biologics

FDA Regulated Research Studies: Common Pathways for Use of Drugs and Biologics



Expanded Access Program: Accessing Investigational Treatments Outside of Clinical Trials

- Regulated by the U.S. Food and Drug Administration
- 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
 - when no comparable or satisfactory alternative therapy options are available
 - with an immediately life-threatening condition or serious disease or condition

Expanded Access Uses of Investigational Drugs or Biologics

- Expanded access uses are not designed to replace clinical trials.
- Industry/sponsors are not required to supply investigational drugs or biologics for expanded access uses; FDA does not make the decision.
- The industry/sponsor decides what type of expanded access will be used for the investigational drug or biologic supplied.
- All expanded access uses of investigational drugs or biologics either require IRB prospective approval or retrospective IRB notification and informed consent from the subject or subject's legally authorized representative, except in emergency use if specific federal regulations are met.
 - Non-emergency use (prospective IRB approval)
 - Emergency use (IRB notification 5 working days after the initial use of the investigational drug or biologic)

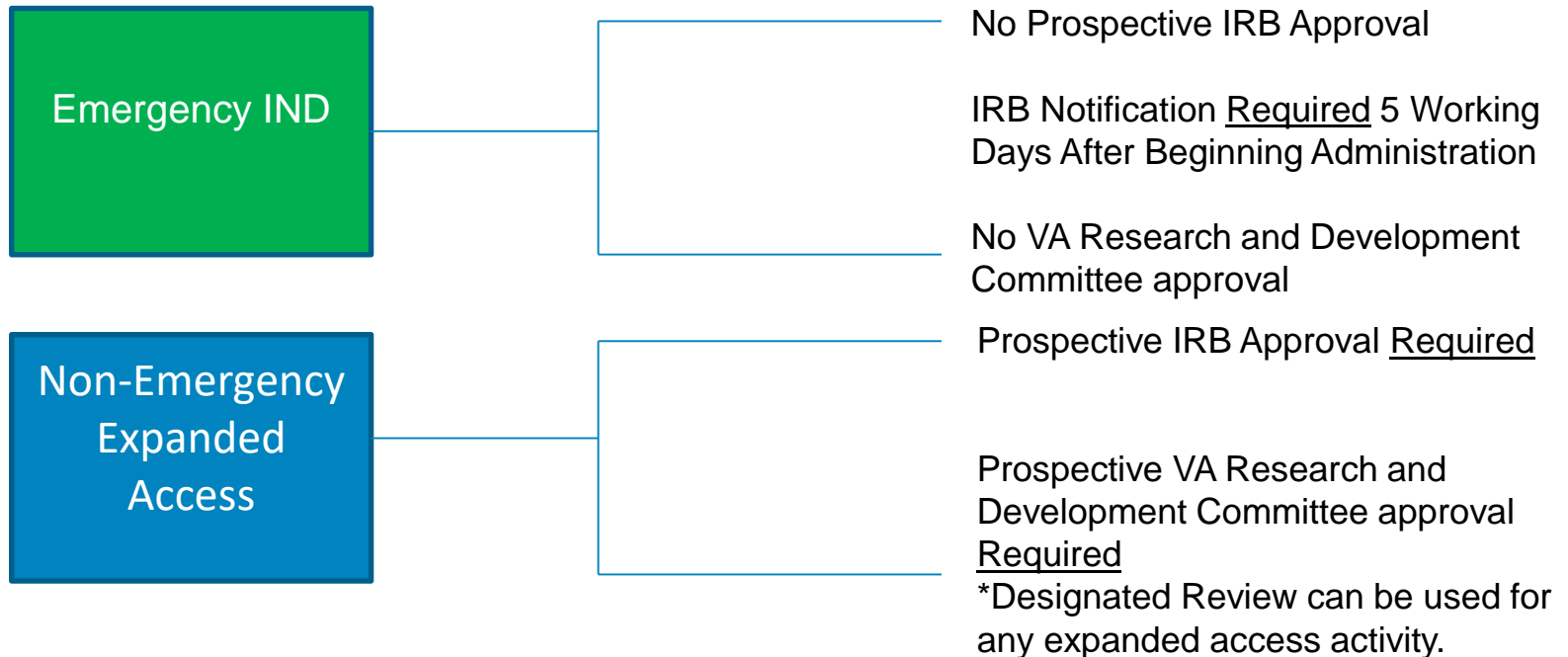
Summary of Different Types of Expanded Access: Drugs and Biologics

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>

Research Committees or Subcommittees Involved in the Review or Approval of VA Physician Requests for Investigational Drug or Biologics Through Expanded Access





ORD's Support Program for VA Facilities without
Research Programs to Gain Access to Investigational
Drugs and Biologics Related to COVID-19

Mechanism for VA Clinicians from VA Facilities without Research Programs to use Expanded Access for Investigational Drugs and Biologics Related to COVID-19

- All expanded access uses of investigational drugs or biologics require an IRB.
- VHA has 31 Medical Centers that do not have research programs.
- ORD and the Office of Research Oversight (ORO) have developed a mechanism that will permit VA Medical Centers without Research Programs to be able to use expanded access for investigational drugs and biologics related to COVID-19 for their patients.

If Your VA Facility is Part of a Special Program for VA Facilities without Federalwide Assurance (FWAs)

For purposes of the COVID-19 Pandemic, your VA facility will have the following Research Infrastructure to enable VA Physicians (not contract or fee-basis) to administer investigational drugs or biologics specifically related to COVID-19 as part of an expanded access program:

- Research Program Instructure
 - VA Central IRB or another IRB, if permitted by ORD
 - Baltimore VA Research and Development Committee
 - No requirement for Associate Chief of Staff for Research and Development, Administrative Officer for Research and Development, or Research Compliance Officer
- Federalwide Assurance
 - A VA Special Assurance signed by the Medical Center Director and approved by the VHA Office of Research Oversight is required

VA Special Assurance (VSA)

VA Special Assurance (VSA) for Providing Expanded Access to COVID-19 Investigational Products by VA Facilities that Do Not Hold a Federalwide Assurance (FWA)

This VA Special Assurance (VSA) is authorized by VHA Handbook 1058.03 §5.a(11) under which the VHA Office of Research Oversight (ORO) may negotiate "special Assurances," with concurrence by the VHA Office of Research and Development (ORD), in lieu of a Federalwide Assurance (FWA) for the protection of human subjects.

1. Institution Filing VSA

Legal Name: _____ ("Institution")

City: _____

State/Province: _____

2. Institutional Components

This VSA covers all components over which the Institution has legal authority including those that may operate under a different name.

NOTE: The Signatory Official signing this VSA must be legally authorized to represent the Institution providing this Assurance and all components covered by the Assurance.

3. Applicability

(a) This VSA applies whenever this Institution provides an investigational drug or biologic or approved drugs that have limited availability due to a risk evaluation and mitigation strategy (REMS) to a patient with a confirmed or presumptive diagnosis of Coronavirus Disease 2019 (COVID-19) for treatment under the following types of expanded access program:

- Individual Patient Expanded Access
 - 1) Individual patient expanded access Investigational New Drug (IND)
 - 1a) Individual patient expanded access IND for emergency use
 - 1b) Individual patient expanded access IND for non-emergency use
 - 2) Individual patient expanded access protocol
 - 2a) Individual patient expanded access protocol for emergency use
 - 2b) Individual patient expanded access protocol for non-emergency use
- Intermediate-Size Patient Populations
 - 1) Intermediate-size patient population expanded access IND
 - 2) Intermediate-size patient population expanded access protocol
- Treatment IND or Treatment Protocol (expanded access for widespread use)
 - 1) Treatment IND

VA Special Assurance (VSA) for VA Facilities without FWAs

- **Your VA Facility's VSA is a Limited Assurance: It only applies for treatments related to COVID-19**
- The terms require the VA Facility to:
 - Comply with all applicable FDA regulations applicable to the expanded use;
 - Comply with all applicable VA and VHA policies applicable to the use;
 - Adopt and implement written procedures developed by ORD for providing expanded access to COVID-19 investigational products;
 - Rely upon the VHA Central Office IRB or IRB approved by ORD for review and prior approval of any non-emergency expanded access, and review of any expanded access under this VA Special Assurance. An IRB Reliance Agreement for this VHA Central Office review has been established by ORD; and
 - Rely upon the Research & Development Committee designated by ORD for review and prior approval of non-emergency expanded access under this VA Special Assurance.

Steps for VA Facilities without Research Programs to use Expanded Access for Investigational Drugs and Biologics Related to COVID-19

- The Medical Center Director is required to sign and return to ORD:
 - VA Special Assurance (VSA) for Providing Expanded Access to COVID-19 Investigational Products by VA Facilities that Do Not Hold a Federalwide Assurance (FWA);
 - Memorandum of Understanding (MOU) with the VHA Central Office Human Research Protection Program for use of the VA Central IRB; and
 - MOU with the Baltimore VA for use of the Baltimore Research and Development Committee
- ORD will assist the VA Facility with implementing the standardized written procedures for use of the VHA Central IRB or IRB approved by ORD and the Baltimore VA Research and Development Committee.

Expanded Access Support for VA Facilities without Research Programs

- There are multiple regulatory and process requirements when using expanded access. Delays occur when it is unclear what to do to meet the requirements for expanded access.
 - IRB
 - R&D Committee (for non-emergency)
 - Agreements
 - Pharmacy coordination
 - Industry/sponsor coordination
- To support VA Facilities without FWAs, ORD will be assigning a coordinator to assist when a VA physician from a VA Facility without a research program is planning to use expanded access for a COVID-19 related investigational drug or biologic.

Key Investigator Responsibilities for VA Facilities without FWAs

Pre-approval Requirements

- Notify first: Contact the VA ORD Expanded Access Coordinators prior to any use of an investigational drug or biologic in this program.
- Complete application for emergency use
 - Complete the application for IRB notification for any emergency use of an investigational drug or biologic.
 - Obtain informed consent
- Complete application for non-emergency use
 - Submit protocols requiring IRB review to the IRB for initial review; obtain approvals from the IRB, other applicable committees, and from the R&D Committee; and do not initiate research until written notice is received from the ACOS/R&D at the Baltimore VA

Key Investigator Responsibilities for VA Facilities without FWAs

Post-approval Requirements

- Report problems, adverse events, local research deaths, and apparent serious or continuing noncompliance to the VA Central IRB or the IRB of Record and the Baltimore Research and Development Committee.
- Ensure research records include all information made or received by a VA investigator over the entire lifecycle of a research activity.
- Create or update a VHA health record and create a progress note for all research subjects receiving research procedures or interventions as inpatients or outpatients at VA medical facilities.
- Ensure research requiring continuing review undergoes re-approval on or before the date when IRB approval expires.



Resources

Definitions

- (1) **Human Subject** means a living individual about whom an investigator (whether professional or student) conducting research:
 - (i) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
 - (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
- (2) **Intervention** includes both physical procedures by which information or biospecimens are gathered (e.g. venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- (3) **Interaction** includes communication or interpersonal contact between investigator and subject.
- (4) **Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonable expect will not be made public (e.g., a medical record).
- (5) **Identifiable private information** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
- (6) **An identifiable biospecimen** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Definitions (continued)

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Important Links

- ORD Covid-19 SharePoint site (internal to VHA):
<https://dvagov.sharepoint.com/sites/vacovhacomm/admin/projects/covid19>
- Mayo Clinic Convalescent Plasma Expanded Access Website:
<https://www.uscovidplasma.org/>
- [ORD Policies and Guidance Documents](#)
- [ORPP&E Cyberseminars](#)

YOU HAVE COMPLETED THIS TRAINING COURSE

1. No test is associated with this training.
2. Please enter your name and the date you have completed reviewing this course on the certificate following this slide.
3. Send a copy of your training certificate to the applicable individuals at your VA Facility.
4. For VA personnel at VA Facilities without FWAs, please send a copy of your training certificate to covidexpandedcoord@va.gov.



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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
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