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A Dialogue With the VA: A Federal Agency's Challenges and Solutions in Working with External IRBs to Facilitate Implementation of the Cooperative Research Provisions

Kristina Borror, Elizabeth Clark, Karen Jeans, and Don Workman

Disclosures:

I have no relevant personal/professional/financial relationship(s) with respect to this educational activity

Kristina Borror, PhD

Elizabeth Clark, RN

Karen Jeans, PhD

Don Workman, PhD

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Learning Objectives

1. Identify commercial institutional review boards (IRBs) currently utilized by the Department of Veterans Affairs (VA)
2. Describe the process utilized by VA to approve commercial IRBs for VA Facilities
3. Describe common issues with resolutions with VA's use of commercial IRBs.
4. Describe the role of local and national compliance oversight with VA's use of commercial IRBs.

Overview of VA Facility Programs Conducting Human Subjects Research

110 VA Facilities are currently approved to conduct human subjects research by the Department of Veterans Affairs (VA)

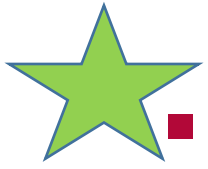
96 IRBs are currently approved for use by the VA for at least one VA Facility by the VHA Office of Research and Development (ORD).

VA's Use of Commercial IRBs is Relatively New

- National VA human subjects policy revised on March 3, 2020 to allow VA Facilities to use commercial IRBs approved by ORD.

Types of IRBs Approved for Use by VA Prior to March 3, 2020

- VA Facilities could rely upon:
  - the facility's IRB(s) of Record (if the VA Facility chooses to have one);
  - VHA Central Office IRB (VA Central IRB);
  - an IRB of another VA facility;
  - the IRB(s) of an affiliated medical or dental school;
  - the IRB of another Federal agency.



- <u>After March 3, 2020</u> – VA Facilities could rely upon ORD-approved commercial IRBs and non-affiliated medical or dental schools.

Regulatory Initiatives: Status of VA's Use of Commercial IRBs

- Amendment to VHA Directive 1200.05: VHA Directive 1200.05 was amended on March 3, 2020 permitting VA Facilities to use commercial IRBs for cooperative (multi-site) research activities as approved by ORD:

> "VA will permit 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."
>
> VHA Directive 1200.05(1), 5.f.(8)(b)

What Process is Used by VA to Approve Commercial IRBs for VA Facilities?

Commercial IRB Review/Vetting Process

- Review process requires approval by both ORD and the VHA Office of Research Oversight (ORO) and negotiations with legal teams by both VA and the commercial IRB.
- Local VA Facilities cannot review/vet commercial IRBs for use by their own or other VA Facilities.
- Master agreements are negotiated between VA and the respective commercial IRB, which includes requirements for:
  - Information security,
  - Agreement to review VA research according to VA requirements and meet VA reporting requirements, and
  - Agreement to not allow VA Facilities to utilize the commercial IRB until the VA Facility has entered into its own IRB reliance agreement.

Commercial IRB Reliance by VA Facilities

- Commercial IRBs: Submit an email request to IRBRelianceandSIRBExceptions@va.gov.
- ORD will send the VA facility the local VA facility IRB reliance agreement for the Director's signature and the facility will return to ORD to send to the commercial IRB.
- ORD will also send an SOP template for the VA facility to customize. The VA facility will send to ORO for review and approval.
- Once each document is approved, ORD will send a formal approval email.
- The approval email will include the executed VA Facility's IRB reliance agreement and ORD approval memo.

Has VA Rejected Any Commercial IRBs Thus Far Seeking a VA Relationship?

Each commercial IRB has worked professionally and collegially with VA to facilitate VA's utilization of their respective commercial IRBs.

Current VA-Approved Commercial IRBs

Different Types of IRBs Approved by ORD for VA Facilities as of November 1, 2022.

Type of IRB	Number
VA Central IRB	1
Commercial IRB	3
Other Federal IRB (National Cancer Institute IRB, All of Us IRB, Department of Energy Oakridge Associated Universities IRB, Centers for Disease Control and Prevention IRB)	4
University affiliate IRBs (with at least one VA facility)	30
VA facility IRB	58
Total Number of IRBs Currently Approved by ORD	**96**

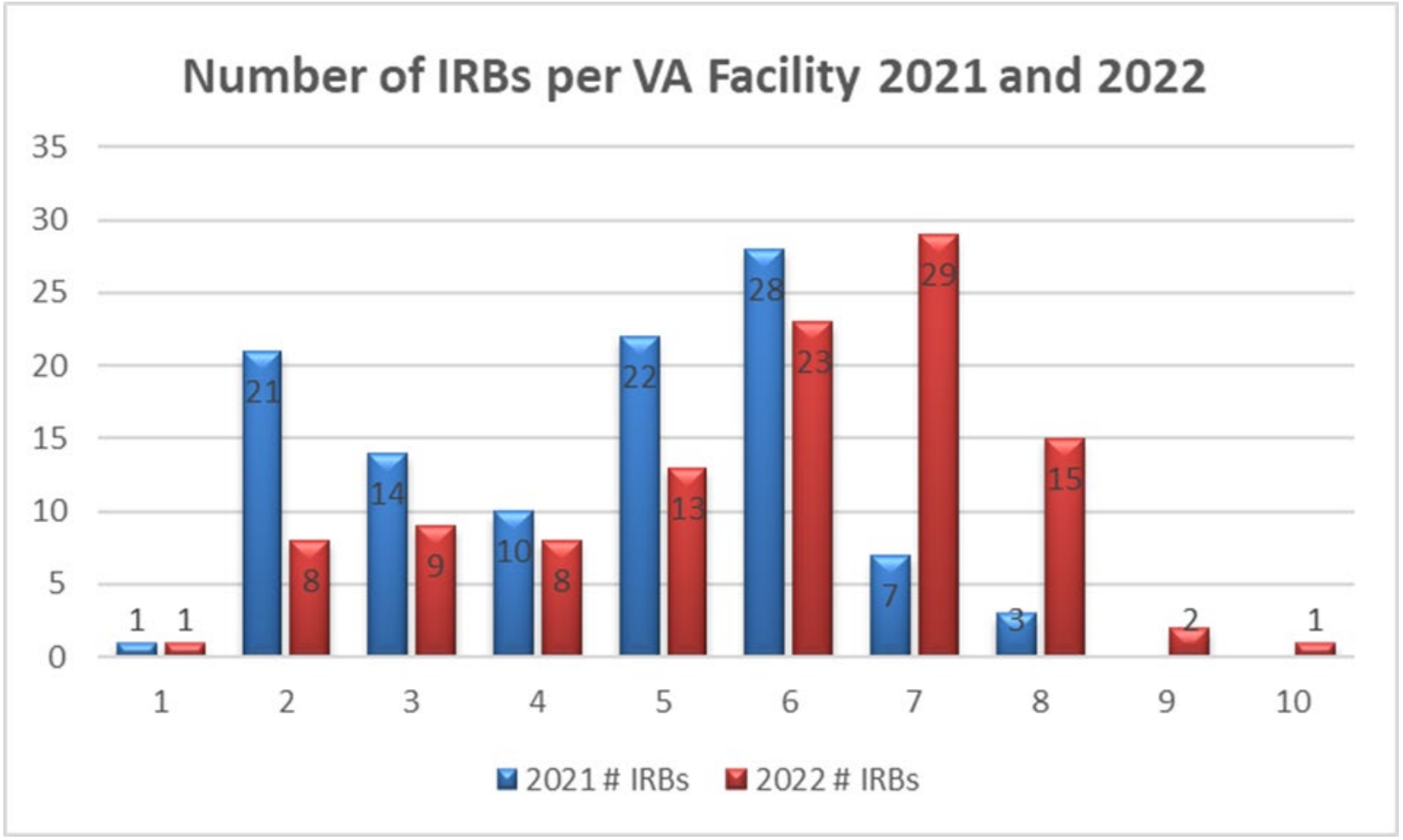
Utilization of Commercial IRBs by VA Facilities

- The majority of VA Facilities have entered into IRB reliance agreements with at least one of the three ORD-approved commercial IRBs.
- Each VA Facility is required to have a liaison (commercial IRB liaison) specifically designated to be the primary point of contact for administrative issues related to the VA Facility's use of the commercial IRB.

Commercial IRBs Approved for Use by VA with Number of IRB Reliance Agreements Facilities as of November 1, 2022

Name of IRB	Date of Executed Master Services Agreement	Number of VA Facilities 2021	Number of VA Facilities 2022
WCG IRB	March 26, 2020	71	76
Advarra IRB	April 6, 2020	71	82
Sterling IRB	September 24, 2020	9	12

Total Number of Different IRBs Used by Individual VA Facilities



VA's Number of Studies Approved by a Commercial IRB Increase Each Year

- For the period between October 31, 2021, and November 1, 2022,
  - VA had a total of 160 VA facility approvals for sponsored clinical trials from the Advarra IRB (44% increase compared to 2021),
  - 105 VA facility approvals for sponsored clinical trials from the WCG IRB (more than 100% increase compared to 2021) and
  - 8 VA facility approvals for sponsored clinical trials from the Sterling IRB (a four-fold increase compared to 2021).

However, Issue Solving Has Been A Component of VA's Management of its Use of Commercial IRBs

Issues Impacting VA Facility's Use of Commercial IRBs

- Prior history of close relationship with an internal VA facility IRB, an academic-affiliated university IRB, and/or the VA Central IRB.
- Utilization of different electronic platforms and application documents.
- Different procedures for communication with different parts of a commercial IRB's administrative and regulatory experts.
- Speed of operation commercial IRBs utilize for reviewing applications and processing reports.

Issues were Addressed and Resolved, but Other Outstanding Issues Required Additional Solutions

ORD-Approved Commercial IRBs – Informed Consent

- ORD-approved commercial IRBs are required to include VA required informed consent language in the IRB-approved informed consent documents.
- VA specific requirements for language in the informed consent (and HIPAA authorization for combined documents) has been supplied at https://www.research.va.gov/programs/orppe/VA-Specific-Requirements-Informed-Consent-HIPAA-Commercial-IRB.pdf
- There is confusion over who inserts the VA-specific required language and what role the commercial IRBs have in ensuring VA requirements are met.

VA Specific Requirements for Informed Consent and HIPAA Authorization When Using A Commercial IRB

Veterans Health Administration
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VA Specific Requirements for Informed Consent and HIPAA Authorizations When Using a Commercial IRB
September 14, 2020

The following instructions with language for VA informed consent and VA HIPAA authorizations have been provided to commercial IRBs approved by the VHA Office of Research and Development to review and approve VA research. VA Facilities are to include VA informed consent language into the commercial IRB informed consent document, where applicable. It is the responsibility of the VA Facilities to include the language prior to uploading their local VA Facility informed consent documents and HIPAA authorizations as part of the application process.

Policy or Law	Citation and Topic	Policy Language	Language Provided to the Commercial IRBs	Comments
VHA Directive 1200.05	Paragraph 17.d.(10) VA Treatment for Research-Related Injuries	A statement that VA will provide treatment for research related injury in accordance with 38 CFR 17.85. **NOTE:** *VA's statutory requirement in 38 CFR 17.85 apply regardless of inclusion of the information as part of the informed consent process.*	If you are a VA study participant, 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***	This ORD policy requirement is a VA-specific element of informed consent. Do not include this language if the VA informed consent document is required to include the VA required language consistent with the PREP Act; the PREP Act informed consent language addresses this policy requirement for COVID-19 related research involving medical countermeasures.

It is the VA Study Team's Responsibility to Initially Insert the Language into the Provided Template

Insertion of VA Language for Informed Consent – Commercial IRB

- Commercial IRBs send the approved sponsor informed consent form template to the VA Investigator/VA Facility.
- The VA Investigator/study team is responsible for inserting the required VA language into the template, including the HIPAA authorization language when the informed consent is combined with the HIPAA authorization.
- If the language is not inserted upon submission, the VA Facility is responsible for informing the applicable commercial IRB that is serving as the IRB of Record for the study.
- Each commercial IRB has a quality improvement process to check that the VA specific language is inserted after submission.

Submission Issues – Commercial IRB

- No submission will be processed unless the submission includes a VA Facility Commercial IRB Endorsement Letter.
  - Initiated in coordination between VA and commercial IRBs after numerous VA study teams were submitting studies to commercial IRBs without the VA Facilities being made aware.
  - This endorsement letter cannot be signed by the PI.
- The VA Facility's commercial IRB liaison is copied if the VA Investigator/study team has issues regarding submission to assist.
- The VA Facility commercial IRB liaison is often requested by the VA study team to describe commercial IRB application processes to help the study team with submission processes.

Commercial IRBs – Central or Local VA Facility PO and ISSO Review

- The commercial IRBs do not perform privacy and information security reviews.
- Some (not many) studies reviewed by an ORD-approved commercial IRB have a central privacy officer (PO) and information system security officer (ISSO) review.
- ORD has worked to ensure communication is submitted to both VA study teams and VA Facility research offices when central privacy officer and central information security reviews are done.
- No local ISSO or PO review is to be conducted when central reviews have been provided.

Commercial IRBs – Central or Local VA Facility PO and ISSO Review

- The Partnered Research Program (PRP) is a program office within ORD that facilitates sponsors conducting multi-site clinical trial within VHA and often communicates with the commercial IRBs to facilitate VA Facility submissions.
- If the study if being managed by PRP, the PRP consults with ORD and the Research and Operational Technology Cybersecurity Division (ROTC-D) regarding the feasibility of conducting a central PO and ISSO review.
- If a central PO and ISSO review is to be done for the applicable study, the PRP will inform the VA study site.

Commercial IRB Issues: When does a VA Facility Need to Contact ORD?

- If a VA Facility has questions regarding information being provided before or following the applicable commercial IRB's review, contact ORD at irbrelianceandsirbexceptions@va.gov.

- Please always include the VA Facility's commercial IRB liaison on communications.

The Role of Compliance in VA Studies Approved by a Commercial IRB

- A common misconception when VA began using commercial IRBs was the following:
  - **Commercial IRBs are not required to follow VA requirements when reviewing VA research – this is FALSE.**
- Both ORD and ORO have reinforced to the VA research community that commercial IRBs follow VA requirements when reviewing VA research.
- VA approved commercial IRBs communicate with ORD and ORO whenever there are issues involving VA requirements.
- VA Facility Research Compliance Officers (RCOs) have a critical role in conducting auditing functions for VA studies reviewed by a commercial IRB.
  - Commercial IRBs are external IRBs in accordance with ORD policy.

Internal vs. External IRBs

- Internal IRB: IRB operated by the VA medical facility where the study team is located.
- External IRB: IRB operated by another VA medical facility, the academic affiliate or other entity.
  - This can be the IRB of another VA facility, the IRB(s) of a medical or dental school, or the IRB of another Federal agency.
  - A facility may also use an IRB for multi-site protocols that has been specifically designated by ORD as an IRB that may serve as a multi-site IRB for VA facilities.
  - **Requires an IRB authorization agreement or Memorandum of Understanding (MOU) with the external IRB.**

Process for Requesting Reliance on an External IRB

- ORD policy requires ORD approval of all reliance arrangements prior to implementation.
- Other than for a Commercial IRB, a VA Facility cannot submit the IRB Reliance request form to rely upon another institution's IRB without asking the other institution.
- For any other IRB other than a commercial IRB or the VA Central IRB, a VA Facility must submit an application, "The Institutional Review Board Request Form" to ORD and ORO prior to any negotiations.
  - The Institutional Review Board Request is an application form. It is not a Memorandum of Understanding or IRB reliance agreement.

Details about Reliance SOPs

- Facilities that rely on any external IRB must have a supplemental SOP.
- The SOP should describe:
  - Communication with the IRB.
  - Responsibilities of all the parties involved in the research.
- The VA facility must have access to the external IRB's SOPs (some commercial IRBs have an investigator handbook in lieu of SOPs).

RCO Access for Conducting Audits

- Academic IRBs: Access by the RCO is negotiated for each reliance.
- Commercial IRBs: RCO may get an account to the electronic IRB platform but may not have access to all documents (e.g., IRB meeting minutes, documents not submitted by the local PI).

Confirming Audit Findings

- RCO should exercise due diligence to ensure that it is reasonable to conclude that the result or event in question represents apparent serious or continuing noncompliance or an apparent Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO).
- Such due diligence may involve consulting with the research team or RRC to seek clarification and/or confirm the results.

Local vs. National Consent Requirements

During the audit process, commercial IRBs will not review informed consent documents or other submission documents for compliance with **local** VA facility policy. The commercial IRBs are only required by the Master Service Agreement to review for **national** VA policy requirements.

Reporting Audit Results

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Audit Reporting: General

- RCOs must report all audit results (regardless of findings) to the R&DC and other appropriate Research Review Committees (RRCs), whether operated by a VA medical facility or another entity.
- Report results using methods and pathways mutually agreed upon by the RCO and RRCs.
- This must be done within the timeframes specified in VHA Directive 1058.01 or local policy.
- Your SOPs or Audit Plan must describe the methods for submitting audit results to each RRC and verifying that the RRC received the reports.

Options for Reporting Audit Results

- RCOs may provide audit results directly to the appropriate RRC in writing through an electronic platform account or other secure system.
- Alternatively, RCOs may provide the audit results to a PI for upload to the electronic platform, for example, if the RCO does not have access to that platform. When using this reporting pathway, the RCO must verify that the report has been submitted by the PI and received by the applicable RRC within the timeframes required.

Reporting Audit Results without Findings

- The timeframe and process for reporting audit results with no findings or findings not required to be reported within a specified timeframe by VHA policy should be described in local SOPs, as agreed upon with the Research Review Committee(s).
- Current commercial IRBs will accept a summary of audit reports with no findings annually uploaded by study.
- Timeframes, methods, and pathways for reporting to each research review committee should be described in the RCO audit plan.

Reporting Audit Results without Findings (continued)

- There are two exceptions to reporting all audit results to the external IRB: If your Facility relies upon the National Cancer Institute Central IRB for oversight of cancer trials, or the NIH All of Us IRB, the RCO will only report audit results with **no findings** to the R&DC and Local Site Investigator.
- RCOs should review the VA facility supplemental NCI CIRB reliance SOP.

Submitting Reports to Advarra

- RCO audit reports should be reported via the Advarra electronic platform CIRBI.
  - Facility Liaisons and RCOs can request access to the platform.
  - Submit access requests via cirbi.net.
  - CIRBI also contains helpful resource materials and submission instructions.
- Audits can be submitted by the PI, the IRB liaison or directly by the RCO.
- Within the platform a list of submission forms includes Audit report.

Submitting Reports to Advarra (cont.)

- Advarra does not require audits with no findings to be submitted but will accept them from the RCOs to comply with VHA Directive 1058.01.
  - There is no method for a summary report.
  - Audits must be submitted on a study-by-study basis.
- Detailed information regarding Advarra can be found on the ORD Single IRB Exceptions and IRB Reliance - Training- Advarra “CIRB” - All Documents (sharepoint.com).

Submitting Reports to WCG

- RCO audit reports should be reported through the IRBNet platform.
- Audits can be submitted by the PI, the IRB liaison or directly by the RCO.
- WCG will now accept audits without findings.
- If an event report is submitted that WCG deems to be non-reportable they may not send a response to the facility.

Commercial IRBs and Responses to Reported Events or Noncompliance

- MOUs with Commercial IRBs require the IRB to review research in accordance with National VA requirements.
- If the R&DC needs clarification on the IRB's response to the event report, the R&DC (through the POC) should request clarification.
- If, after requesting clarification, the R&DC still needs clarification, the R&DC should contact ORD at IRBRelianceandSIRBExceptions@va.gov

Flexibility for External IRBs

- If the procedures of a non-VA operated committee differ from, or the timeframes exceed those of, VHA Directive 1058.01, the medical facility Director must consult with ORD and ORO as to the adequacy of those procedures.
- Consultation with ORO and ORD should occur when requesting formal permission to rely upon the non-VA RRC, or upon learning that a non-VA RRC's SOPs have changed such that the procedures and/or timeframes no longer comport with VHA Directive 1058.01.
- For example, the NCI Central IRB and the NIH All of Us IRBs do not accept RCO audit reports with no findings.

Follow-up of Audit and Other Findings

- Research Review Committees (RRCs) must report to the RCO, Medical Center Director, and Associate Chief of Reserach and Development (ACOS/R&D) determinations related to serious/continuing noncompliance, UPIRTSOs, and other reportable events under VHA Directive 1058.01 within 5 business days.
- The Medical Center Director or designee, must report the RRC's determinations to the appropriate ORO workgroup within five (5) business days after receiving the RRC's written notification. Facility SOPs should outline this procedure.

Summary

- In less then three (3) years, the majority of VA Facilities have successfully utilized at least one ORD-approved commercial IRB for industry-sponsored clinical trials conducted at the VA Facility.
- Communication between all parties at the local and national level has been critical in VA's successful use of commercial IRBs.
- VA continues to expect progressive growth in both the number of commercial IRBs utilized by VA and number of clinical trials approved by commercial IRBs for VA Facilities.

References

- ORD's Policies and Guidance Documents webpage at https://www.research.va.gov/resources/policies/
- ORD's Searchable FAQ database at https://www.research.va.gov/resources/policies/faq-search.cfm
- ORO Home webpage at https://www.va.gov/oro/
- ORO's Policy and Guidance webpage at https://www.va.gov/ORO/oropubs.asp
- VA Specific Requirements for Informed Consent and HIPAA Authorizations When Using a Commercial IRB (September 14, 2020)
- VHA Directive 1058.01: Research Compliance Reporting Requirements (October 22, 2020) at VHA_Directive_1058_01_Research_Compliance_Reporting_Requirements.pdf (va.gov)
- VHA Directive 1200.05(2): Requirements for the Protection of Human Subjects in Research (January 7, 2019, amended March 3, 2020 and January 8, 2021) at VHA Publications

Questions?

Thank You