SMART TALK

A Community Forum to Explore Issues Surrounding Single IRB Review

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-01S1.

What Is SMART Talk?

An approximately monthly forum with:

- Presentations on topics relevant for single IRB review
- Q&A on topic presented as well as questions submitted when participants register

Open and free to anyone with interest

Upcoming sessions

- TODAY – NIH Proposed Updates to the SMART IRB Agreement & sIRB Considerations in the Context of COVID-19
- May: Resources for Training Study teams in Single IRB
- NIH's Approach to the Implementation of the NIH Single IRB policy

Key SMART IRB Resources at SMARTIRB.ORG

- Master Reliance Agreement
- Implementation Checklist for use of the SMART IRB Agreement
- Online Reliance System (Helps investigators and institutions request, track, and document reliance arrangements for each study)
- SMART IRB SOP Manual
- Communication Plan for Single IRB Review
- Reviewing IRB Instructions for Relying Institution Point(s) of Contact
- Reviewing IRB Instructions for Relying Site Study Teams
- FAQs for Research Teams - Relying on an External IRB
- Overall PI (and Lead Study Team) Checklist
- Relying Site Investigator Checklist
- Grant Applications: Template Description of SMART IRB
- Local Considerations: Institutional Profile
- Local Considerations: Protocol-specific Document

Join us for the next
SMART Talk
May 20, 2020
2:00-3:30 pm EDT

Resources for Training Study Teams in Single IRB

Register at smartirb.org

Sign up for our mailing list to be notified of future offerings

Questions?
Contact help@smartirb.org

NCATS

COLLABORATE. INNOVATE. ACCELERATE.

Transitioning to SMART IRB Master Reliance Agreement 2.0

Valery Gordon, Ph.D., M.P.H.

Project Scientist, SMART IRB

National Center for Advancing Translational Sciences (NCATS)

National Institutes of Health

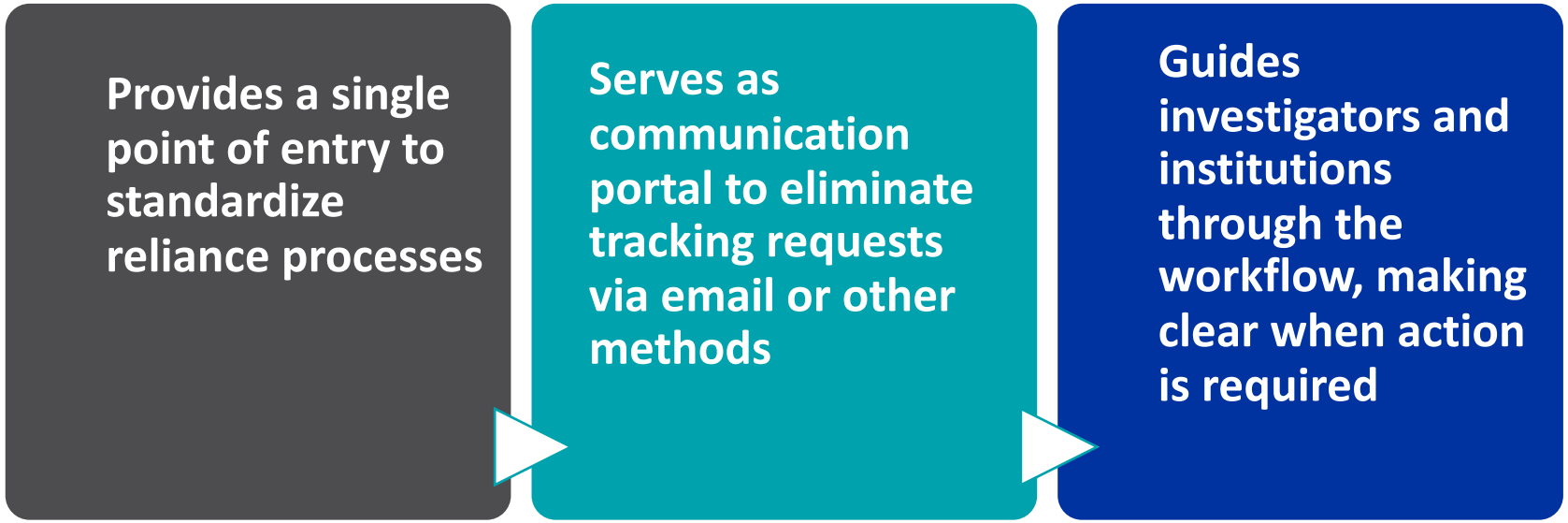
SMART Talk April 15, 2020

NIH National Center for Advancing Translational Sciences

SMART IRB Online Reliance Platform

Introduced in May 2017 as a tool to help institutions request, track, and document reliance arrangements

For Investigators and Participating Institutions



SMART IRB Master Reliance Agreement facilitates reliance arrangements for multi-site studies

NCATS' Goals for SMART IRB System

➢ Ensure the sustainability of SMART IRB

Demonstrate a process for periodic updates to Master Reliance Agreement (RA) to enable signatories to sign on to the most current version

- Revisions to RA
- Community outreach
- Technical aspects related to transitioning from one version to another in SMART IRB System

Transitioning between Reliance Agreements

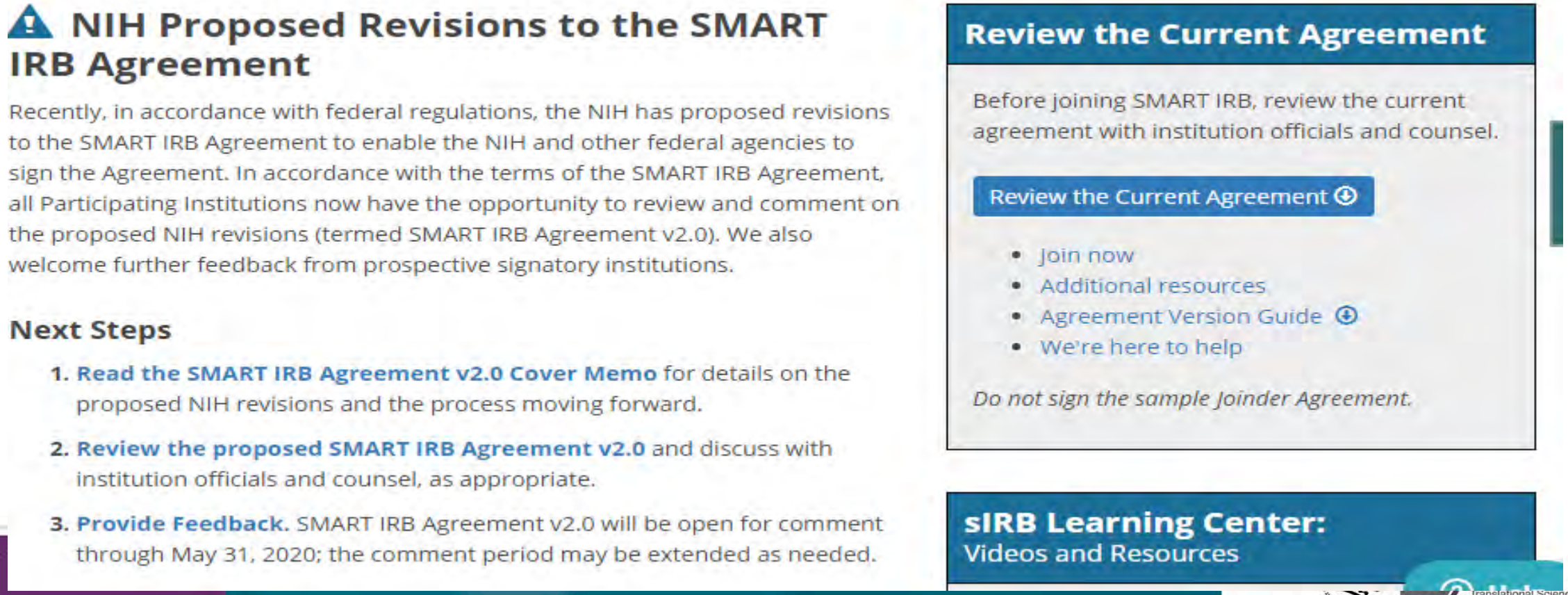
➢ Enable use of SMART IRB RA by NIH Intramural Research Program (IRP)

1. NIH Intramural Research Program request to sign SMART IRB RA
2. Harvard Catalyst enthusiastic about NIH use of RA
3. NIH IRP unable to sign RA unless specific changes are made

NCATS' decision to use NIH IRP as a model for demonstrating capability of SMART IRB System to transition from one RA to another

SMART IRB Master Reliance Agreement version 2.0 (RA 2.0)

- On April 2, 2020 RA 2.0 was posted for 60-day comment period
  https://smartirb.org/agreement/



NIH Proposed Revisions to the SMART IRB Agreement

Recently, in accordance with federal regulations, the NIH has proposed revisions to the SMART IRB Agreement to enable the NIH and other federal agencies to sign the Agreement. In accordance with the terms of the SMART IRB Agreement, all Participating Institutions now have the opportunity to review and comment on the proposed NIH revisions (termed SMART IRB Agreement v2.0). We also welcome further feedback from prospective signatory institutions.

Next Steps

1. **Read the SMART IRB Agreement v2.0 Cover Memo** for details on the proposed NIH revisions and the process moving forward.
2. **Review the proposed SMART IRB Agreement v2.0** and discuss with institution officials and counsel, as appropriate.
3. **Provide Feedback.** SMART IRB Agreement v2.0 will be open for comment through May 31, 2020; the comment period may be extended as needed.

Review the Current Agreement

Before joining SMART IRB, review the current agreement with institution officials and counsel.

Review the Current Agreement

- Join now
- Additional resources
- Agreement Version Guide
- We're here to help

Do not sign the sample Joinder Agreement.

sIRB Learning Center:
Videos and Resources

Proposed Revisions to SMART IRB RA 1.0

- Insurance/Liability coverage
- IRB Review of grant applications/contract proposals
- Conflict of interest disclosures
- Actions congruent with legal responsibilities

Proposed Revisions to RA: Liability Coverage for Research Activities

- **Adds a footnote indicating that Federal Agencies are not required to maintain liability coverage for all activities under the RA**

  - NIH has liability coverage as offered by federal statutes
    - Federal Tort Claims Act
    - Public Health Service Act

  - NIH employees are generally eligible for liability coverage for negligence claims brought by research participants

SMART IRB MRA, section 4.10

Proposed Revision to RA: IRB Review of Federal Grant Applications/Contract Proposals

- **Revised Common Rule no longer requires IRB approval of grant applications/contract proposals**

  - RA 2.0 deletes text relating to IRB review of grant applications/contract proposals, "when such review is required by federal regulations or oversight agencies"

SMART IRB MRA, former section 5.12

Proposed Revisions to RA: Conflict of Interest (COI) Disclosure to Reviewing IRB

- **NIH must follow statutory and regulatory requirements that prohibit COI disclosure.**
  - NIH investigators can neither
    - provide financial disclosures to a reviewing IRB, nor
    - provide management plans for eliminating or minimizing financial conflicts of interest

- **When Federal Agencies rely on non-federal IRBs, they will provide assurances to reviewing IRB that they have completed COOI analyses under existing policies and that participation of agency personnel is permissible consistent with federal law.**

SMART IRB MRA, Section 6.6.

Proposed Revisions to RA: Withdrawal of Research from Ceded Review

➢ Lack of agreement regarding COI management plans applies only to non-federal institutions

- Federal agencies may not provide COI management plans to non-federal IRBs
  - When Federal agencies rely on non-federal IRBs, they can not be compelled to withdraw from participating in studies due to failure to provide a management plan.
  - However non-federal relying institutions must provide COI management plans when requested by the reviewing IRB.

➢ A non-federal IRB that does not accept federal system for reviewing potential COI can decline to serve as the reviewing IRB for federal agencies

SMART IRB MRA, section 6.6

Proposed Revision to RA: Actions under RA must follow law

- **Addition of section to add:**

  "Nothing in this agreement will be construed to require a Participating Institution to take any action in violation of its legal obligations or responsibilities."

- Added for clarity

Section 8.12

Short-Term Plans for Moving Forward

➢ Proposed process

- Publicize availability of SMART RA 2.0
- Incorporate revisions and if necessary, post for final comment
- After consideration and response to comments
  - Educate institutions about goals for SMART IRB
    - Develop FAQs
  - Encourage institutional sign on to RA 2.0

➢ Anticipated outcomes

- SMART IRB RA 2.0 can be signed and used by NIH, which may provide encouragement to other Common Rule Agencies/Offices to participate in efforts to create RA 3.0.
- Greater sign-on and use will further growth of National Reliance Network.

Longer-term Plans for Moving Forward

- SMART IRB Harmonization Steering Committee will build upon RA 2.0
  - Goal: Develop RA 3.0, which can be signed by other Common Rule signatory Agencies/Offices
- Develop process to track how RA is being used
  - Types of institutions
  - Types of studies
- Transfer SMART IRB System to management partner

➢ **Ensure the sustainability of SMART IRB in the future**

Questions and Discussion

NCATS

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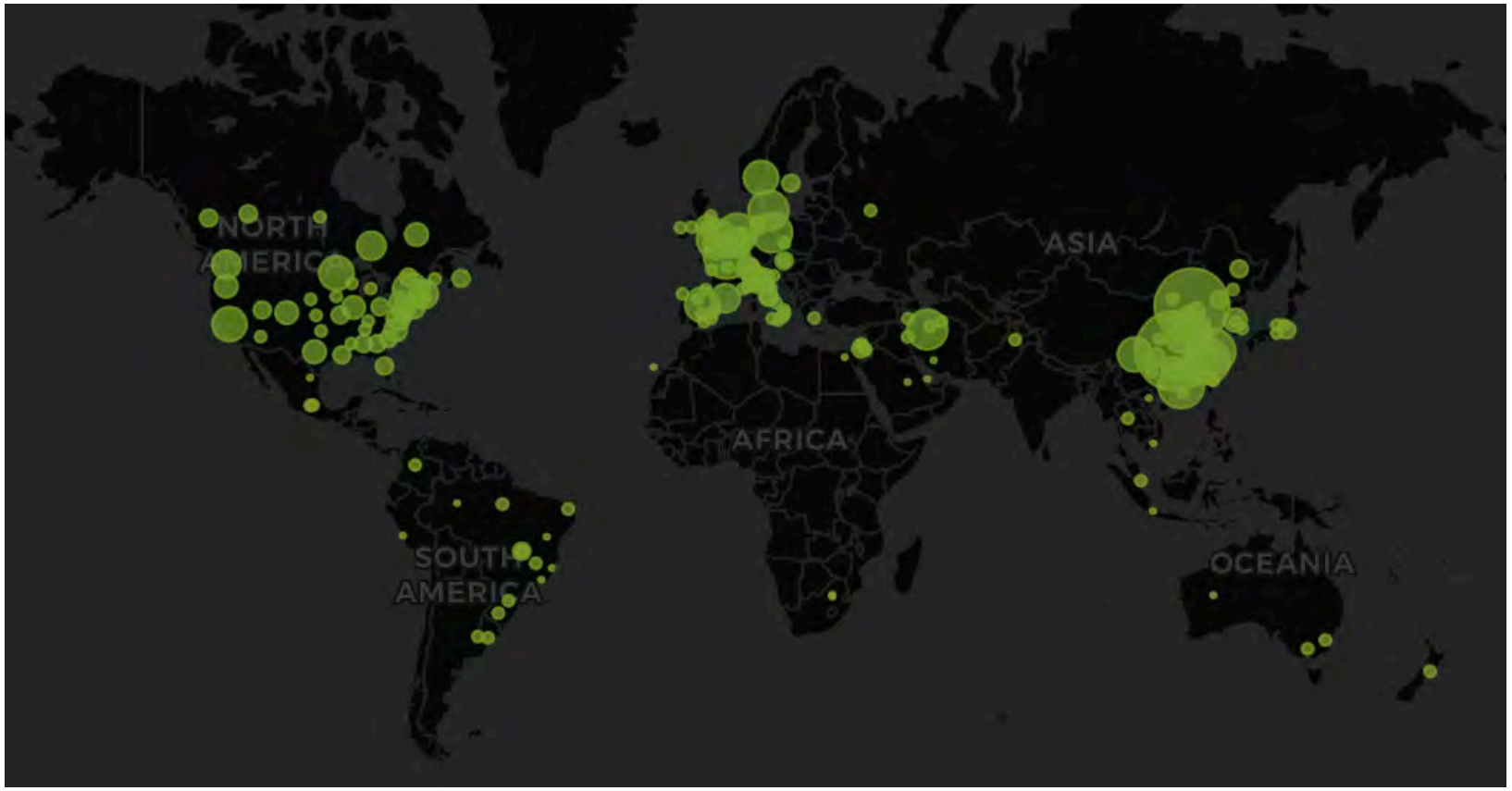
Comparison of version 2.0 vs. 3.0

	MRA 2.0	MRA 3.0
Revisions proposed by	NIH	NIH, VA, DoD, HSC, Ambassadors and Current SMART IRB Participating Institutions
Summary of Revisions included	• Insurance Coverage • Conflicts of interest • Grant Congruency • No violation of law statement added	• Insurance Coverage • Conflicts of interest • Grant Congruency • No violation of law statement added • Revised Common Rule – Updates throughout document to avoid confusion with regulatory changes. • Indemnification • HIPAA • Digital Signatures - Allows the use of digital signatures to the joinder agreement. • Statement added to prohibit modification of the agreement by participating institutions • Choice-of-law and venue provision to the Agreement added. • Updates definitions • Other

Covid-19



https://www.covid19-trials.com

Currently 535 trials registered

Most trials are not centrally organized even though many of them are designed to answer similar questions

Covid-19 Collaboration

- Many studies are being run outside of the research environment by hospitals in need of decision-making information for their clinicians
- Local outbreaks may attenuate before institutions are able to enroll their target sample size
- If protocols were public and open for collaboration, an RCT could be accessed in different geographic regions
- Shared protocols would increase data reliability and decrease risk of a Type 1 error
- No platform currently exists for such collaboration on RCTs

COVID-19 Collaboration Platform

https://www.covidcp.org/

> "In the context of public health emergencies… study teams should be encouraged to collaborate on existing, ongoing protocols rather than starting new, independent trials."
>
> Dean et. al, *The New England Journal of Medicine*, April 10, 2020.

Purpose

- To publicize protocols whose PIs are open to various levels of collaboration:
  - Joining forces with other research teams to create a multi-site collaborative protocol
  - Adding new sites under the existing PI and IRB
  - Sharing anonymized interim and/or final data with other sites that choose to independently operate a trial under a similar protocol
- Our goal is to get high-quality evidence to clinicians quickly

https://www.covidcp.org/

How it works

- PIs can submit a protocol or request to use an uploaded protocol
- Protocols are public so that new study teams do not have to reinvent the wheel
- Gives PIs a forum to work together on shared core protocols; brings PIs together to form multi-site studies
- Helps track different research groups working on the same interventions in order to facilitate aggregated analyses
- Provides statistical expertise to aggregate evidence across trials

https://www.covidcp.org/

Submitting a Protocol

To submit a protocol click here. Protocols can be in draft form, enrolling, or completed. To ensure that the authors receive credit, anyone using a protocol will be required to include a citation in any resulting research products. Submissions will be vetted for legitimate scientific value and well-defined interventions and outcomes.

Using a Protocol

To request a protocol, click the link in the description of the protocol. In doing so you agree to appropriately cite the authors of the original protocol in any resulting research products. Requests will be vetted for legitimate scientific value.

Collaborating on a Protocol

We **strongly encourage collaboration**. If a protocol is not yet enrolling subjects at the time of submission, we encourage the submitting study team to accept input from other interested research groups in order to create a shared core protocol. If a protocol is currently enrolling, it may be possible for interested research groups to join the existing study as a second site under the submitting PI and existing IRB. If that is not possible we encourage interested research groups to match eligibility criteria, intervention definitions, and a subset of the six core outcomes (presumed COVID-19 diagnosis, hospitalization, ICU admission, supplemental oxygen use, mechanical ventilation, death) as closely as possible. In all cases, we encourage all researchers to make their data available for aggregated analyses and to make every attempt to include or reference an analysis that combines evidence from all collaborating studies in any resulting reports.

Citing a Protocol

Cite protocols as [Authors] (2020). Protocol for [Study Name]. Retrieved from covidcp.org.

Aggregated Data Analysis

Statisticians from top (bio)statistics departments will volunteer time to run or advise on aggregated analyses, including working with study-specific Data Monitoring Committees to ensure that any interim analyses are grounded in best statistical practice, ethical, and maximally informative. Resources to anonymize and house interim and final data provided free of charge by Vivli.

https://www.covidcp.org/

For help, email contact@covidcp.org.

OHRP Guidance on COVID-19

SMART IRB Talk

April 15, 2020

Julie Kaneshiro
Office for Human Research Protections

OHRP's Guidance on COVID-19: Issued April 9, 2020

- OHRP's COVID-19 guidance: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html

- Covered topics:
  - Public Health and Clinical Activities
  - Excluded Public Health Surveillance Activities
  - Legally Required Reporting
  - Research Changes to Eliminate Apparent Immediate Hazards
  - Proposing and Reviewing Study Changes
  - Whether Suspensions of Research Must be Reported

Key Message

- OHRP understands that institutions and investigators have needed to quickly implement actions necessary to protect public health, and appropriately protect human subjects.

- We will take into account the specific circumstances that institutions and investigators are experiencing, and will use available flexibility in our decision making.

Public Health and Clinical Activities

- **Key point:** Actions taken for public health or clinical purposes (and not for research) are not research activities. No institutional review board (IRB) approval required before implementation. For example:
  - Mandatory clinical screening for COVID-19 for all who come to an institution, including research subjects.
  - Sharing such clinical screening results with a public health authority or with the research subjects.

    *Note that other permissions or notice may be necessary under applicable law or policy.

Excluded Public Health Surveillance Activities

- **Key point:** Certain public health surveillance activities are excluded from the definition of “research,” even if they might otherwise meet the definition.

  *Note that FDA regulations may apply if this involves use of an investigational in vitro diagnostic device.

Excluded Public Health Surveillance Activities

- Public health surveillance exclusion at 45 CFR 46.102(l)(2) of the revised Common Rule:

  "**Public health surveillance activities**, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a ***public health authority***. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters)."

Excluded Public Health Surveillance Activities

- ***Public health authority*** means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate. (45 CFR 46.102(k) of the revised Common Rule)

Excluded Public Health Surveillance Activities

- Example: If a public health authority authorizes general screening for COVID-19 for public health surveillance purposes, and requests that test results be shared as necessary with a public health authority to allow the public health authority to identify, monitor, assess or investigate the COVID-19 outbreak, an investigator may incorporate these activities into an existing research study visit without prior IRB review and approval.

Legally Required Reporting

- **Key Point:** When required by law, information (including individually identifiable information) related to a research subject's COVID-19 tests results may be reported to a public health authority. This is the case even when:
  - Such reporting would be inconsistent with statements made in the study's consent form.
  - The research is covered by a Certificate of Confidentiality.

*In such circumstances, investigators should inform the participant of the required reporting of results.

Research Changes to Eliminate Apparent Immediate Hazards

- **Key point:** Investigators may implement changes to approved research prior to IRB review and approval, if the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.108(a)(3)(iii) under the revised Common Rule and 45 CFR 46.103(b)(4)(iii) under the pre-2018 Requirements).
- We expect that investigators are cancelling or postponing non-essential study visits or conducting phone visits instead of in-person visits to reduce COVID-19 transmission risks.
- In these situations, investigators may make such changes to the research to reduce risks without prior IRB approval, but they should report those changes to the IRB when possible.

Proposing and Reviewing Study Changes

- **Key point:** Investigators may submit any proposed changes to previously approved research to the IRB at any time.
- The IRB may use an expedited review procedure to review and approve those changes if the changes are minor (45 CFR 46.110(b)(1)(ii) under the 2018 Requirements and 45 CFR 46.110(b)(2) under the pre-2018 Requirements).

Whether Suspensions of Research Must be Reported

- **Key point:** Only IRB suspensions or terminations of approved research are required to be reported to OHRP.
- If an investigator or an institutional official suspends or terminates approved research, such actions are not required to be reported to OHRP under 45 CFR 46.113.

Time for Questions

Contact OHRP

Web Site: http://www.hhs.gov/ohrp

Email (policies/regulations)**:** OHRP@hhs.gov

Email (education activities)**:** OHRP-Edu@hhs.gov

Phone: Toll Free within the U.S. (866) 447-4777

Join our ListServ: http://www.hhs.gov/ohrp/news/sign-up-for-announcements/index.html

OHRP's disaster guidance: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/effects-of-disasters-on-human-research-protections-programs-guidance/index.html

Bookmark this page for quick reference to OHRP resources on the revised Common Rule: www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html

Single IRB Considerations in the Context of COVID-19

Barbara Bierer, **Harvard Medical School, Brigham and Women's Hospital,** & SMART IRB

Stacey Goretzka, Medical University of South Carolina & SMART IRB

Julie Kaneshiro, Office for Human Subjects Protection

Adrienne Meyer, University of Washington & SMART IRB

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-01S1.

Rationale for Single IRB

- Single IRB review part of NIH's vision of streamlining multi-site research review to accelerate "clinical research studies benefits researchers, research participants, and all who stand to gain from research results."

-Francis Collins, 2016

Single IRB & COVID-19

- Single IRB can be leveraged during the COVID-19 pandemic for multisite studies that require fast activation, rapid addition of sites, less burdensome review of amendments, efficient review of expanded access protocols, and when institutional IRB resources are strained
  - Useful for new studies and for the transition of already approved multisite studies to a single IRB
- Research suspensions and terminations
  - If an institution suspends or terminates ceded studies (e.g., because of changes in priorities or the inability for the study to be completed), they must inform the Reviewing IRB
  - OHRP clarified that institutional suspension or termination of research does not require reporting to that agency

Single IRB & COVID-19

- In a federally-supported research study, if a single IRB suspends or terminates research due to exigent circumstances, not-for-cause related to the research must the suspension or termination be reported?
  - Can occur as an institutional activity
  - Yes, any IRB suspension or termination of research should be reported
- If a collaborating research site is unaffected by the exigent circumstances, can the IRB oversight responsibilities be transferred to another IRB of record?
  - Yes, there is no requirement by the regulations that the single IRB of record be one IRB
  - Optimally, the transfer of responsibilities would occur prior to the suspension or termination of the research
  - OHRP will exercise available flexibility under COVID-19 circumstances

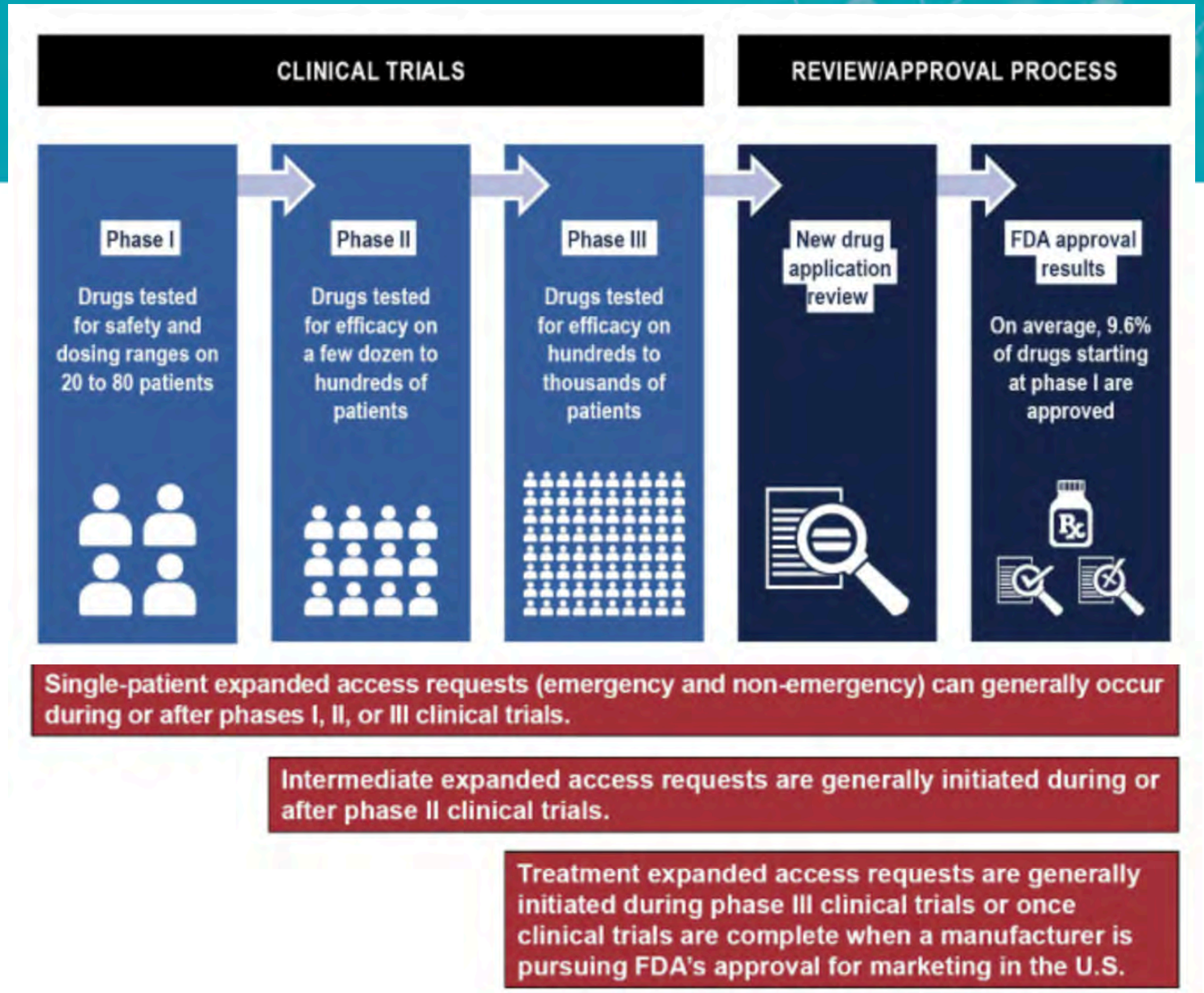
Single IRB & Expanded Access for Investigational Drugs

Expanded Access ("Compassionate Use")

Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials.

FDA uses this mechanism to facilitate expanded access to investigational drugs for treatment use for patients with serious or immediately life- threatening diseases or conditions

Expanded access to an investigational drug can be provided under a treatment IND or protocol if the sponsor is actively pursuing, with due diligence, marketing approval of the drug for the expanded access use



- Single-patient EA
  - Emergency and non-emergency
- Intermediate EA
- Treatment EA

Source: https://www.gao.gov/products/GAO-17-564

Categories of Expanded Access

Individual patients, including emergency use	• involves a “treatment-use” IND for each individual patient
Intermediate-size populations	• treated under a protocol submitted by the sponsor of an existing IND
Widespread treatment designed for use in a larger population	• through a treatment IND or treatment protocol

Other than emergency-use single patient EA, each involves prospective IRB review and approval

Scope of Expanded Access[1]

Expanded access, access, and treatment use may also refer to use:

- In situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks;
- Of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage of the approved drug;
- Of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug under the REMS; or
- For other reasons.

IRB review and approval is required

1. https://www.fda.gov/media/85675/download

Why Single IRB?

Intermediate-size patient population expanded access INDs and protocols are suited to single IRB review to facilitate faster access to treatments for patients with serious or immediately life-threatening diseases or conditions

Single patient INDs may be submitted to a single IRB for review when feasible and practical, at the request of the sponsor or the FDA

How SMART IRB Can Help

SMART IRB in COVID-19

- Rapid deployment in expanded access protocols (all 3 types)
- Rapid determinations of reviewing IRB in multi-site research
- Required regulatory documentation of reliance in place or effectuated
- SMART IRB team with ambassadors will prioritize all COVID-19 protocols

Joining SMART IRB

- Learn more about joining at https://smartirb.org/join/
- Contact us if you need use to prioritize a SMART IRB joinder application at help@smartirb.org
- The Single IRB Learning Center for Investigators and Study Teams at https://smartirb.org/study-teams/ provides education and training resources to help make the reliance process go smoothly

On the Ground Experiences: Adrienne Meyer & Stacey Goretzka

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Resources for Training Study Teams in Single IRB

Register at smartirb.org

Sign up for our mailing list to be notified of future offerings

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