MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

A USA perspective on diversity and inclusion

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Australian Clinical Trials Alliance

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- We are committed to autonomy in our research and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results and deliverables.
- We have no personal conflicts of interests with regard to the content of this presentation or discussion.

The MRCT Center

- Academic credibility
- Trusted collaborator
- Independent convener

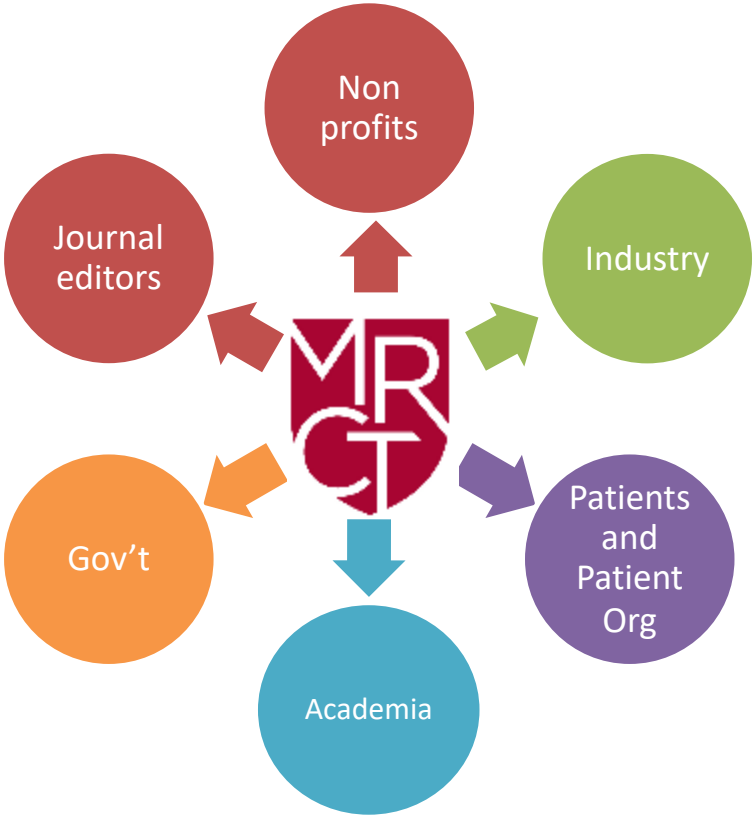
The MRCT Center is a research and policy center focused on addressing the conduct, oversight, ethics and regulatory environment for clinical trials.

Vision

Improve the integrity, safety, and rigor of global clinical trials.

How we work

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.



MRCT Center is affiliated with BWH and Harvard University

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD UNIVERSITY

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Faculty Director, MRCT Center

HARVARD CATALYST
THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

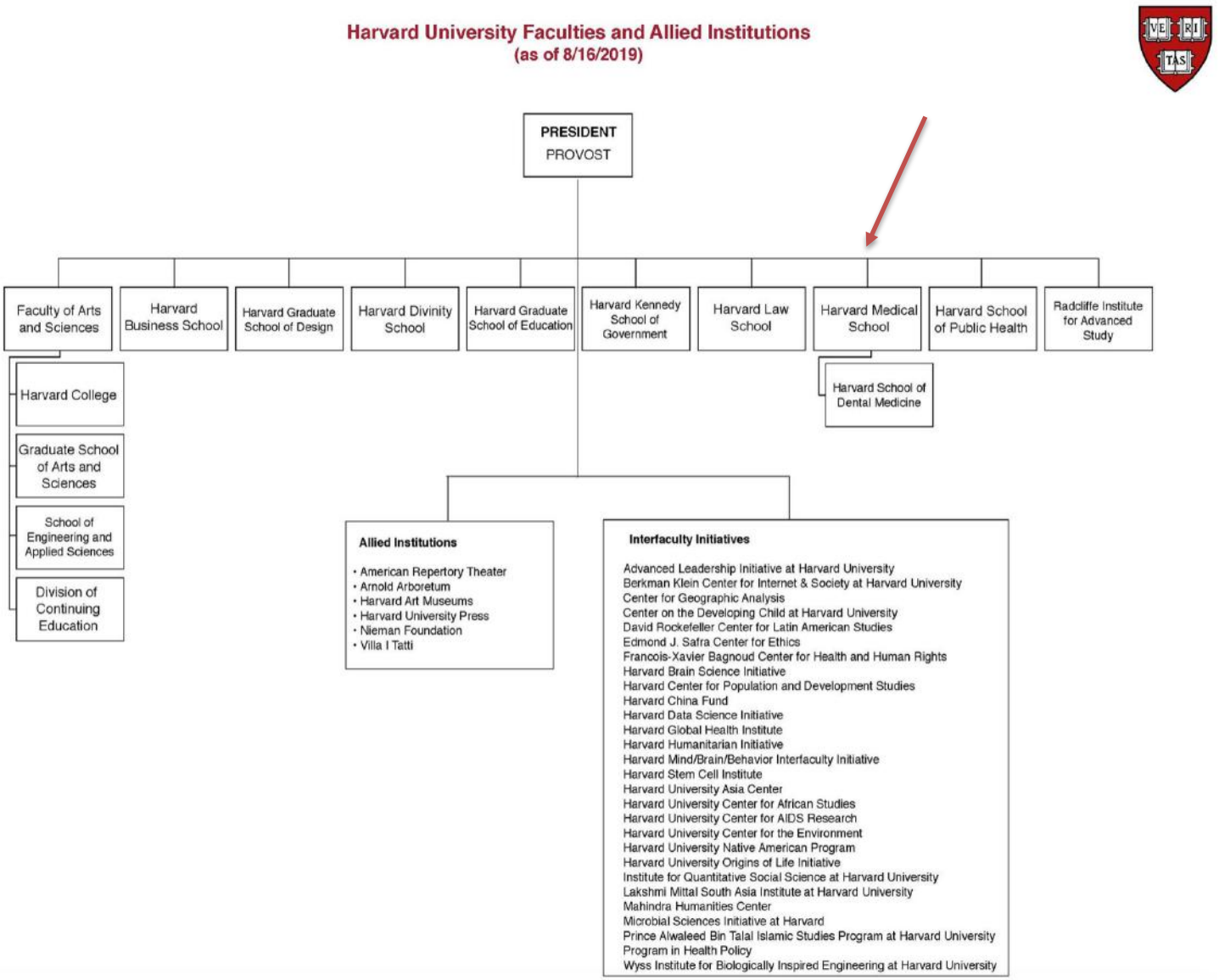
Director, Regulatory Foundations, Law and Ethics Program, Harvard Catalyst

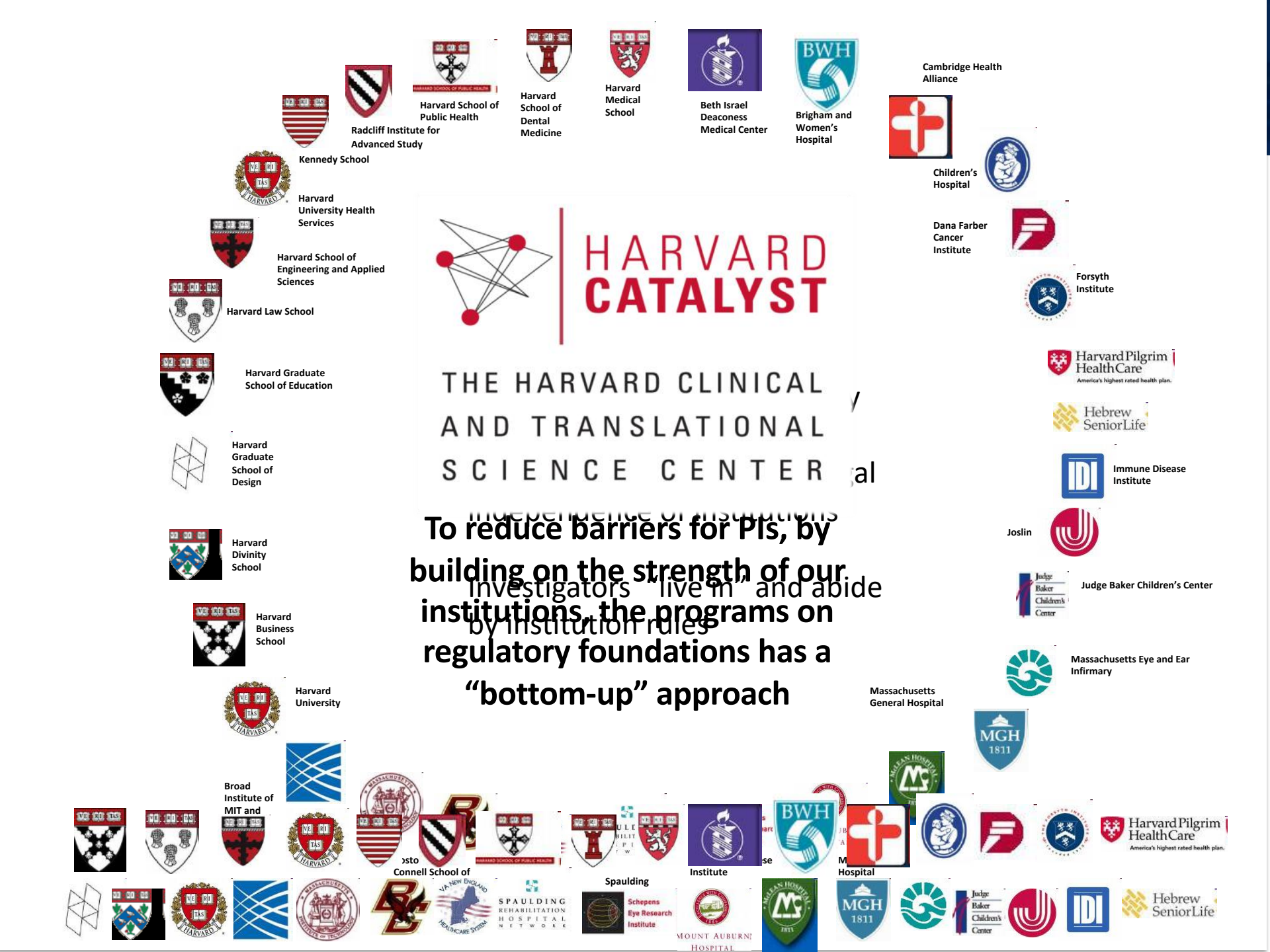
Agenda

- Political complexities
- The task
- Approaches and questions

Harvard Medical School

Harvard University





independence of institutions

Investigators "live in" and abide by institution rules

To reduce barriers for PIs, by building on the strength of our institutions, the programs on regulatory foundations has a "bottom-up" approach

Harvard Catalyst (Harvard Clinical and Translational Center)

Decentralized and Large

Decentralized system of legally separate and financially distinct entities

21 separate 501(c) 3 institutions

24 separate Federal wide Assurances

Diverse Faculty

Investigators are faculty of Harvard, Broad, or MIT; not all Harvard employees

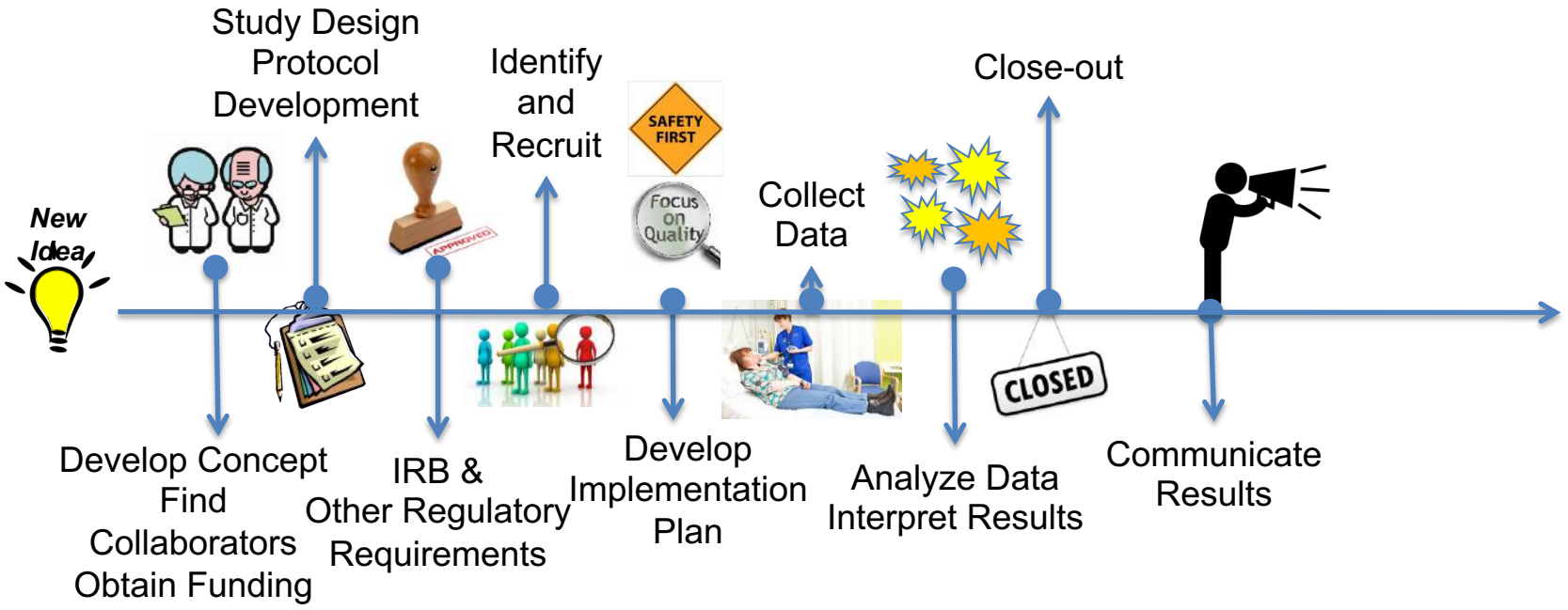
31 institutions and schools

Expertise and Funding

Varying degrees of AAHRPP accreditation

Research revenues from ~$1M to ~$900M

One focus is on the INVESTIGATOR over the ENTIRE LIFESPAN of a given research study



NIH CTSA goals

- Goal 1: Train and Cultivate the Translational Science Workforce
- Goal 2: Engage Patients and Communities in Every Phase of the Translational Process
- Goal 3: Promote the Integration of Special and Underserved Populations in Translational Research across the Human Lifespan
- Goal 4: Innovate Processes to Increase the Quality and Efficiency of Translational Research, Particularly of Multisite Trials
- Goal 5: Advance the Use of Cutting-Edge Informatics

The power of a funder: requirements and accountability

Training: Alignment and harmonization of core competencies

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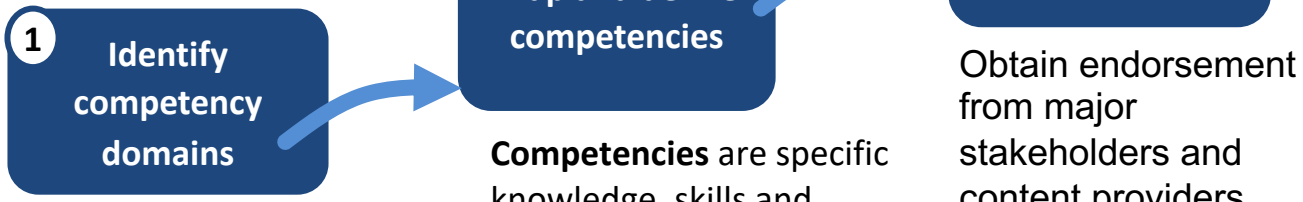


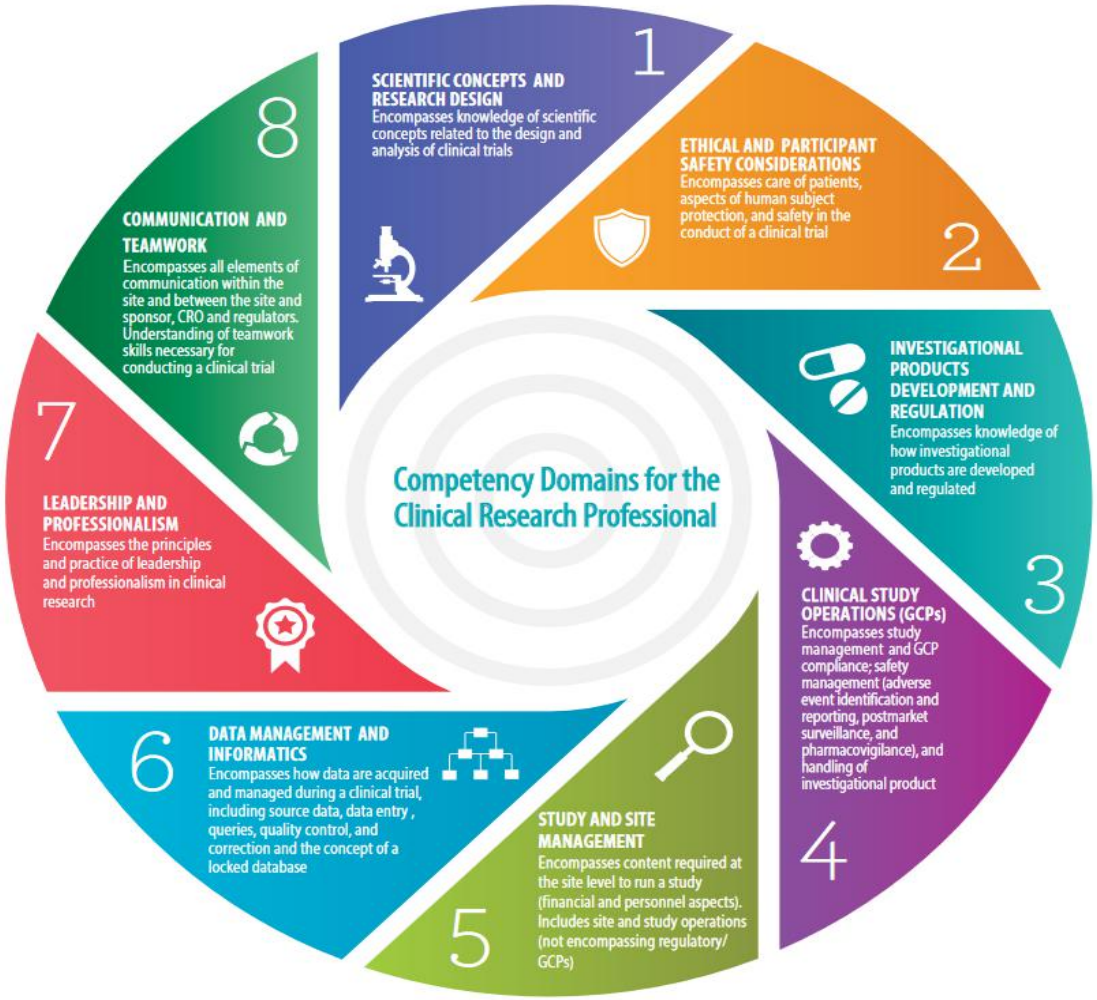
Competency Domains are broad categories of knowledge, skills and attitudes which are necessary to successfully function within a field of expertise

Competencies are specific knowledge, skills and attitudes which comprise Competency Domains

- Categorize competencies, learning objectives and statements from published efforts
- Define harmonized competency statements for each category

Obtain endorsement from major stakeholders and content providers

JTF Framework – Competency Domains for the Clinical Research Professional



- Standardized role descriptions
- Competency-based training/education
- Level of competency vs level of job
  - Promotion and upward mobility
- Self-assessment & competence
  - Recognize personal training needs
  - Personal portfolio of competencies
- Competence & career development
  - Academic program accreditation
- Continuous process (competence not static, jobs change, gaps appear); lifelong learning

- Sonstein, S.A., Seltzer, J., Li, R., Jones, C.T., Silva, H., Daemen, E. (2014, June). **Moving from compliance to competency: A harmonized core competency framework for the clinical research professional**. *Clinical Researcher*. 28(3); 17-23

Leveling of the JTF Core Competency Framework (2018)

SKILL LEVELS

- **Fundamental level**: can perform with coaching/explain
- **Skilled level**: can perform independently/demonstrate
- **Advanced level**: can teach/develop

Translating the MRCT Center JTF Framework

We are committed to providing the JTF Core Competency Framework in as many languages as possible. If you are interested in helping with translations, please contact

mrct@bwh.harvard.edu.

The following translations are currently available:

- Spanish
- French (in process)
- Japanese (in process)
- Portuguese (in process)

Spanish

Home > Framework > Translations > Spanish

El Joint Task Force for Clinical Trial Competency (JTF)

El Joint Task Force for Clinical Trial Competency (JTF) es un equipo internacional de investigadores, educadores y profesionales de la investigación clínica que están comprometidos a proveer investigadores con la dirección y herramientas para asegurar la competencia profesional de todos miembros del equipo de la investigación. El diagrama de la "rueda" representa el JTF Marco de Competencias que consiste en 8 Dominios de Competencia.

JOINT TASK FORCE FOR CLINICAL TRIAL COMPETENCY
www.clinicaltrialcompetency.org

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APEIC
www.apeic.org

Training materials

DIAMOND Portal Offers Research Training for All

Staff who work on clinical studies can improve their skills with high-quality training materials on the **DIAMOND portal**. The goal of the DIAMOND project is to create well-run clinical trials through well-trained staff.

https://ncats.nih.gov/ctsa/training/resources

PRAXIS AUSTRALIA

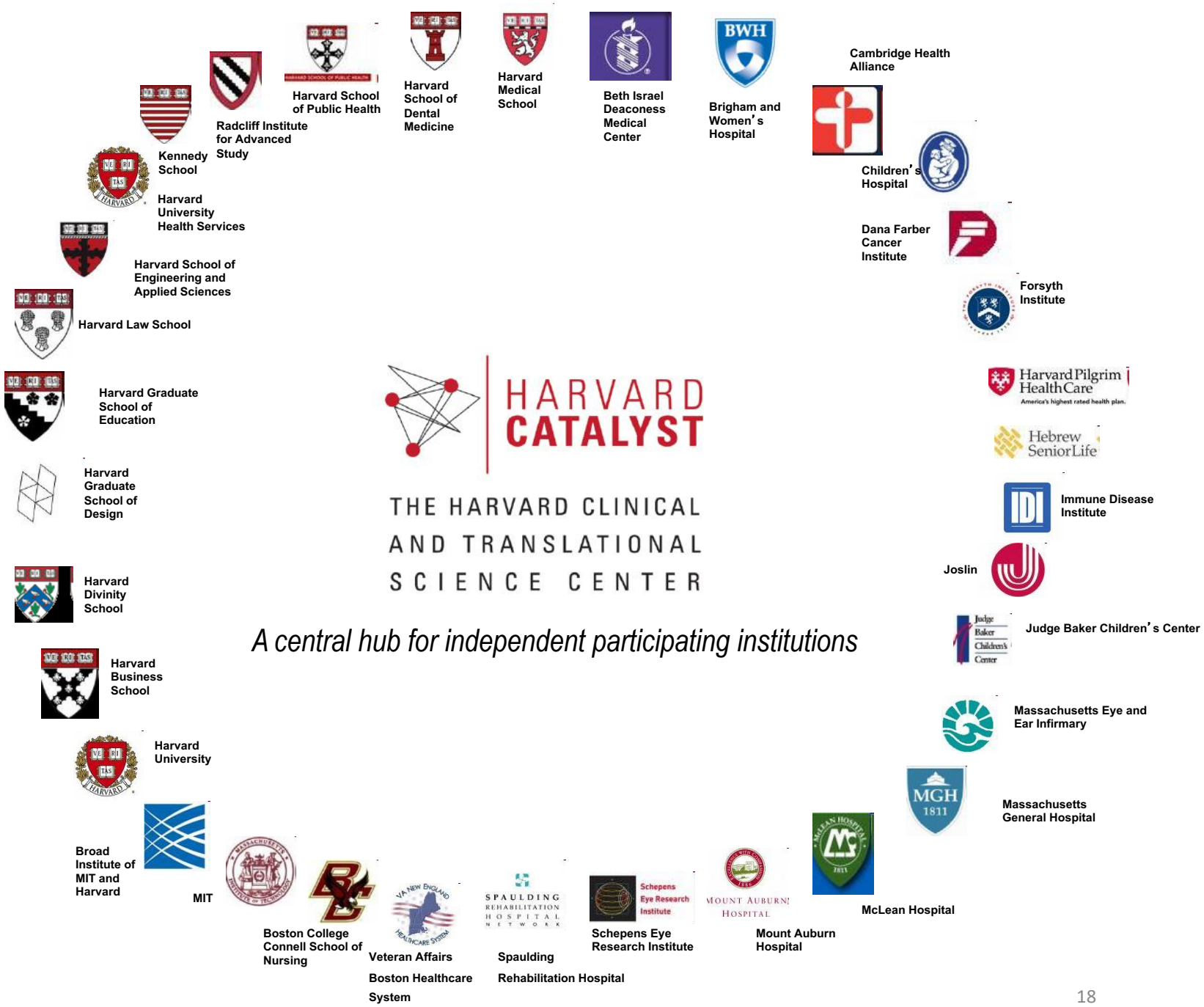
Promoting Ethics and Education in Research

About Us | Our Services

What is Research Essentials?

Research Essentials is a unique research training resource that has been designed to deliver a world class program to meet the specific needs of all those involved in research while also enabling learners to pick and choose from a diverse range of subjects so that they can design a training program that best meets their needs.

https://praxisaustralia.com.au


Harvard School of Public Health
Harvard School of Dental Medicine
Harvard Medical School
Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Cambridge Health Alliance
Radcliff Institute for Advanced Study
Kennedy School
Harvard University Health Services
Children's Hospital
Dana Farber Cancer Institute
Harvard School of Engineering and Applied Sciences
Forsyth Institute
Harvard Law School
Harvard Graduate School of Education
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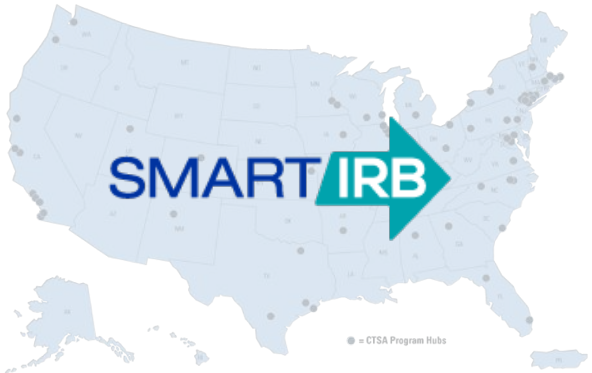
Harvard Pilgrim Health Care
America's highest rated health plan.
Hebrew SeniorLife
Harvard Graduate School of Design
Immune Disease Institute
Joslin
Harvard Divinity School
Judge Baker Children's Center
A central hub for independent participating institutions
Harvard Business School
Massachusetts Eye and Ear Infirmary
Harvard University
Massachusetts General Hospital
Broad Institute of MIT and Harvard
MIT
Boston College Connell School of Nursing
Veteran Affairs Boston Healthcare System
Spaulding Rehabilitation Hospital
Schepens Eye Research Institute
Mount Auburn Hospital
McLean Hospital

Supporting the implementation of single IRB review



A Roadmap to Single IRB Review

Funded by NCATS beginning in July 2016

As of July 2018, led by Harvard University and University of Wisconsin-Madison, along with a team of Ambassadors from across the U.S.

GROW
A national IRB reliance network

SUPPORT
Use of SMART IRB

EDUCATE & TRAIN
Institutions & Investigators

HARMONIZE
sIRB review processes across the nation

A Platform for Single IRB Review

Informatics

SMARTIRB.org
Resources and supportive services freely available to support sIRB review

Joinder platform
Allows institutions to join the SMART IRB Agreement

Online Reliance System
Provides a central system and process to request, track, and document reliance arrangements for each study

SMART IRB Agreement

Single IRB Authorization Agreement

Sign once and implement

SOPs

Clear roles and responsibilities for investigators and institutions

Flexibility to use other SOPs as agreed upon or required

Expertise Across the Nation

Ambassadors
Help institutions join and implement SMART IRB

Education & Training
Tools, templates, FAQs, checklists, guidance, peer consultations, and webinars support adoption of SMART IRB

Harmonization Steering Committee
Leaders in the field promote best practice

Request, Track, and Document Arrangements

SMART IRB Online Reliance System

Launched in May 2017

Single point of entry standardizes reliance processes

Communication portal eliminates tracking via email or other methods

Guided workflow makes clear when action is required

The system works for institutions:

1. With and without significant reliance experience
2. Familiar or unfamiliar with one another
3. With limited or substantial infrastructure to support single IRB review

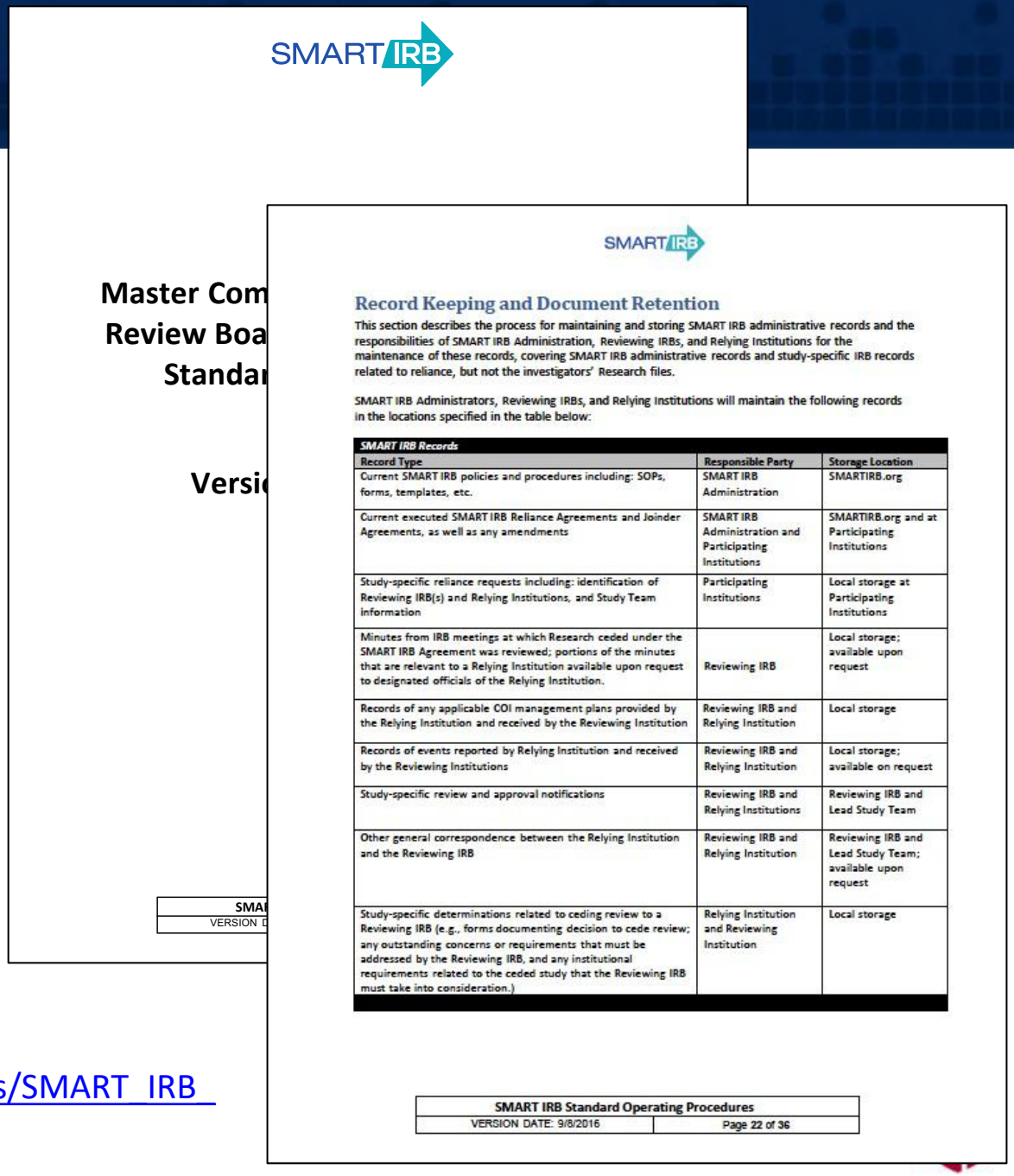
Allows SMART IRB Participating Institutions to work together to establish reliance arrangements on a study-by-study basis

Get started at smartirb.org/reliance.

SMART IRB SOPs

Standard operating procedures (SOPs) for establishing and implementing reliance provide clarity during the review and conduct of research using the SMART IRB Agreement.

- Provide clarity on key roles and responsibilities
- Use of SMART IRB SOPs is not mandated
- SMART IRB supports networks with existing SOPs
- Institutions communicate whether other policies or procedures apply



SMART IRB

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SMART IRB

Record Keeping and Document Retention

This section describes the process for maintaining and storing SMART IRB administrative records and the responsibilities of SMART IRB Administration, Reviewing IRBs, and Relying Institutions for the maintenance of these records, covering SMART IRB administrative records and study-specific IRB records related to reliance, but not the investigators' Research files.

SMART IRB Administrators, Reviewing IRBs, and Relying Institutions will maintain the following records in the locations specified in the table below:

SMART IRB Records		
Record Type	**Responsible Party**	**Storage Location**
Current SMART IRB policies and procedures including: SOPs, forms, templates, etc.	SMART IRB Administration	SMARTIRB.org
Current executed SMART IRB Reliance Agreements and Joinder Agreements, as well as any amendments	SMART IRB Administration and Participating Institutions	SMARTIRB.org and at Participating Institutions
Study-specific reliance requests including: identification of Reviewing IRB(s) and Relying Institutions, and Study Team information	Participating Institutions	Local storage at Participating Institutions
Minutes from IRB meetings at which Research ceded under the SMART IRB Agreement was reviewed; portions of the minutes that are relevant to a Relying Institution available upon request to designated officials of the Relying Institution.	Reviewing IRB	Local storage; available upon request
Records of any applicable COI management plans provided by the Relying Institution and received by the Reviewing Institution	Reviewing IRB and Relying Institution	Local storage
Records of events reported by Relying Institution and received by the Reviewing Institutions	Reviewing IRB and Relying Institution	Local storage; available on request
Study-specific review and approval notifications	Reviewing IRB and Relying Institutions	Reviewing IRB and Lead Study Team
Other general correspondence between the Relying Institution and the Reviewing IRB	Reviewing IRB and Relying Institution	Reviewing IRB and Lead Study Team; available upon request
Study-specific determinations related to ceding review to a Reviewing IRB (e.g., forms documenting decision to cede review; any outstanding concerns or requirements that must be addressed by the Reviewing IRB, and any institutional requirements related to the ceded study that the Reviewing IRB must take into consideration.)	Relying Institution and Reviewing Institution	Local storage

SMART IRB Standard Operating Procedures
VERSION DATE: 9/8/2016 | Page 22 of 36

SOP Manual available at
https://smartirb.org/sites/default/files/SMART_IRB_SOP-090816.pdf

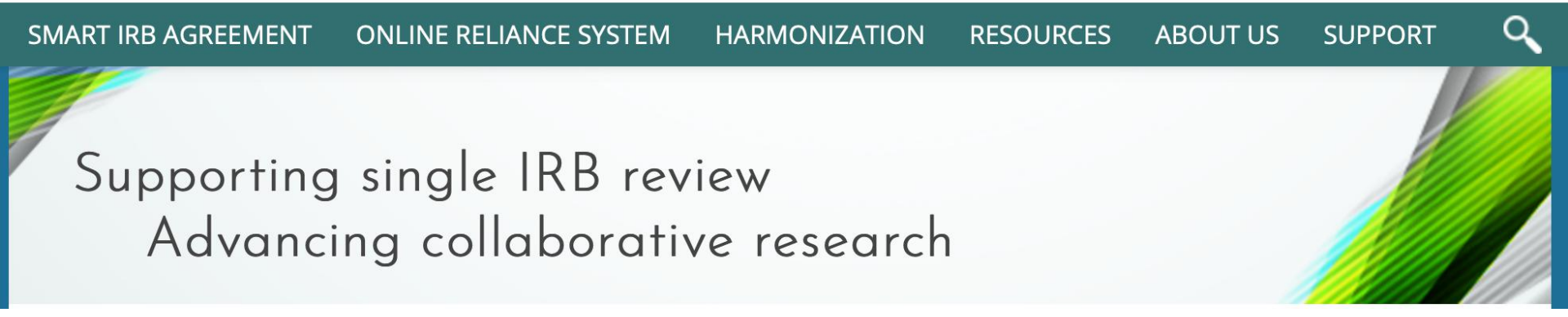
How to find out who's joined SMART IRB

- Visit smartirb.org to find the full list of SMART IRB Participating Institutions.
- Once an institution's joinder is activated, they are listed on the Participating Institutions page.

Click on "Participating Institutions"

623 Participating Institutions
including all CTSA hubs

Join SMART IRB



Streamline efficiencies

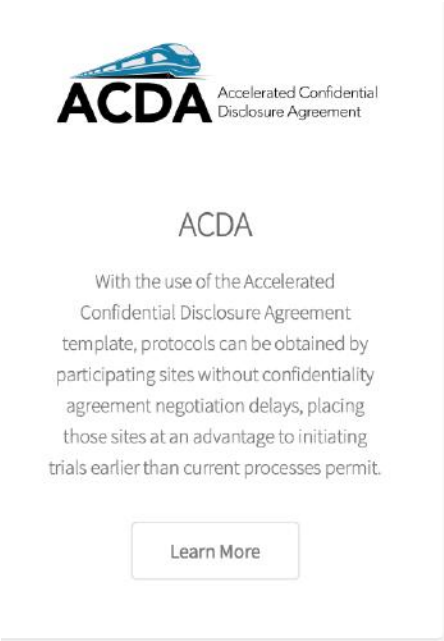
- Training
- IRB/EC
- Contracting

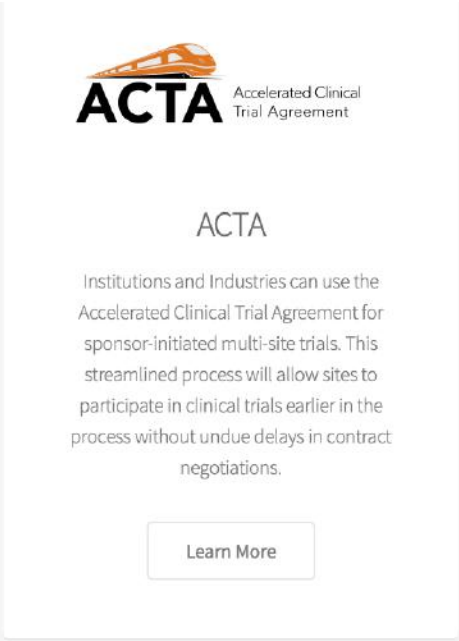
Example: Accelerated Master Agreements

- Confidential Disclosure Agreement
- Clinical Trial Agreement
- Data Transfer Use Agreement
- Fixed Price Clinical Trial Subaward Agreement

- The exchange of research materials under material transfer agreements (MTAs).
- Collaborative research conducted under cooperative research and development agreements (CRADAs).
- Clinical studies to determine the safety and efficacy of new agents under clinical trial agreements (CTAs).
- Exchange of confidential information under confidential disclosure agreements (CDAs).
- Informal collaborations that involve the transfer of materials and data under a Research Collaboration Agreement (RCA).

https://www.ara4us.org





Model agreements

Forms & Model Agreements

Licensing Application and Agreements

Used to when industry is interested in licensing a technology.

- Inter-Institutional Agreements
- Public Health Service License Agreements
- License Application

Confidential Disclosure Agreements (CDAs)

Used to exchange confidential information.

- NCATS Model 2-Way CDA (Word - 23KB)
  For two parties sharing confidential information.
- NCATS 1-Way Out CDA (Word - 28KB)
  For an outside party receiving confidential information from NIH.
- NCATS 1-Way In CDA (Word - 27KB)
  For an outside party providing confidential information to NIH.

Research Collaboration Agreement (RCA)

Used in a collaborative project where confidential information and materials may be exchanging hands.

- RCA Template (Word - 31KB)

Employee Invention Report

Used when NCATS employees create new technologies.

- PHS Employee Discovery and Invention Report (Word - 113KB)

Cooperative Research and Development Agreements (CRADAs)

Used when NIH and industry collaborate to further develop a technology for commercialization.

- Model NIH Materials CRADA (Word - 27KB)
  For collaborative studies of basic research.
- Model PHS CRADA (Word - 49KB)
  For collaborative studies of basic research.
- Intramural Clinical Trial CRADA (Word - 47KB)
  For collaborative studies that include a clinical trial conducted at NIH.
- Extramural Clinical Trial CRADA (Word - 49KB)
  For collaborative studies that include a clinical trial conducted at NIH-funded sites.

Research Collaboration Agreement (RCA)

Used in a collaborative project where confidential information and materials may be exchanging hands.

- RCA Template (Word - 31KB)

Material Transfer Agreements (MTAs)

Used to exchange research materials.

- NCATS Provider MTA (Word - 27KB)
- NCATS Recipient MTA (Word - 29KB)

https://ncats.nih.gov/alliances/forms

Streamline efficiencies

- Training
- IRB/EC
- Contracting
- Recruitment
  - Makes clinical trials slow and more costly;
  - Limits the validity of trial results and, in turn, researchers' ability to apply the findings broadly to the general population; and
  - Stops a trial prematurely or prevents it from taking place at all.

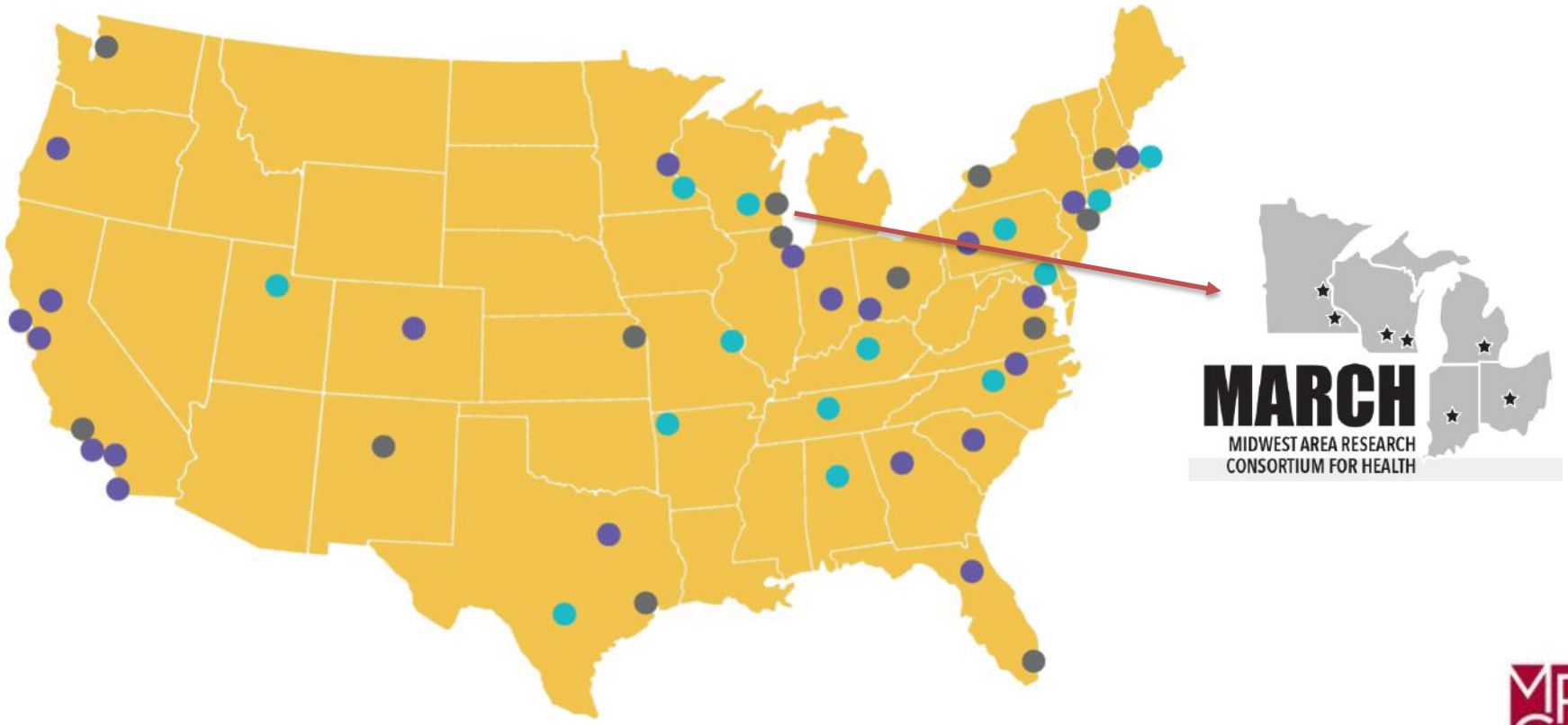
Technology Platforms

The CTSA ACT technology platform has two major components:

1. Informatics for Integrating Biology and the Bedside (**i2b2**), a software package that converts raw records into de-identified and searchable participant information stored in a central database.
2. Shared Health Research Informatics Network (**SHRINE**), a search engine for i2b2. With appropriate agreements in place, an ACT investigator can use SHRINE to search de-identified records using a customized set of participant criteria. SHRINE queries all network institutions and provides an approximate number of participants at each site who meet the criteria.

Accrual to Clinical Trials (ACT) Network

- Discovery, exploration, and validation of patient cohorts for investigator-initiated multi-site or single-site clinical trials



CTSA Trial Innovation Network (TIN)

TRIAL INNOVATION NETWORK

metrics	NETWORK PROPOSAL SUBMISSIONS		SIRB (more metrics)		STANDARD AGREEMENT (in FDP-CTSA)	
	# of institutions	# of therapeutic areas	# of relying sites	# of studies	# of sites	# of studies
	66	49	171	45	73	9

212 Proposals Submitted

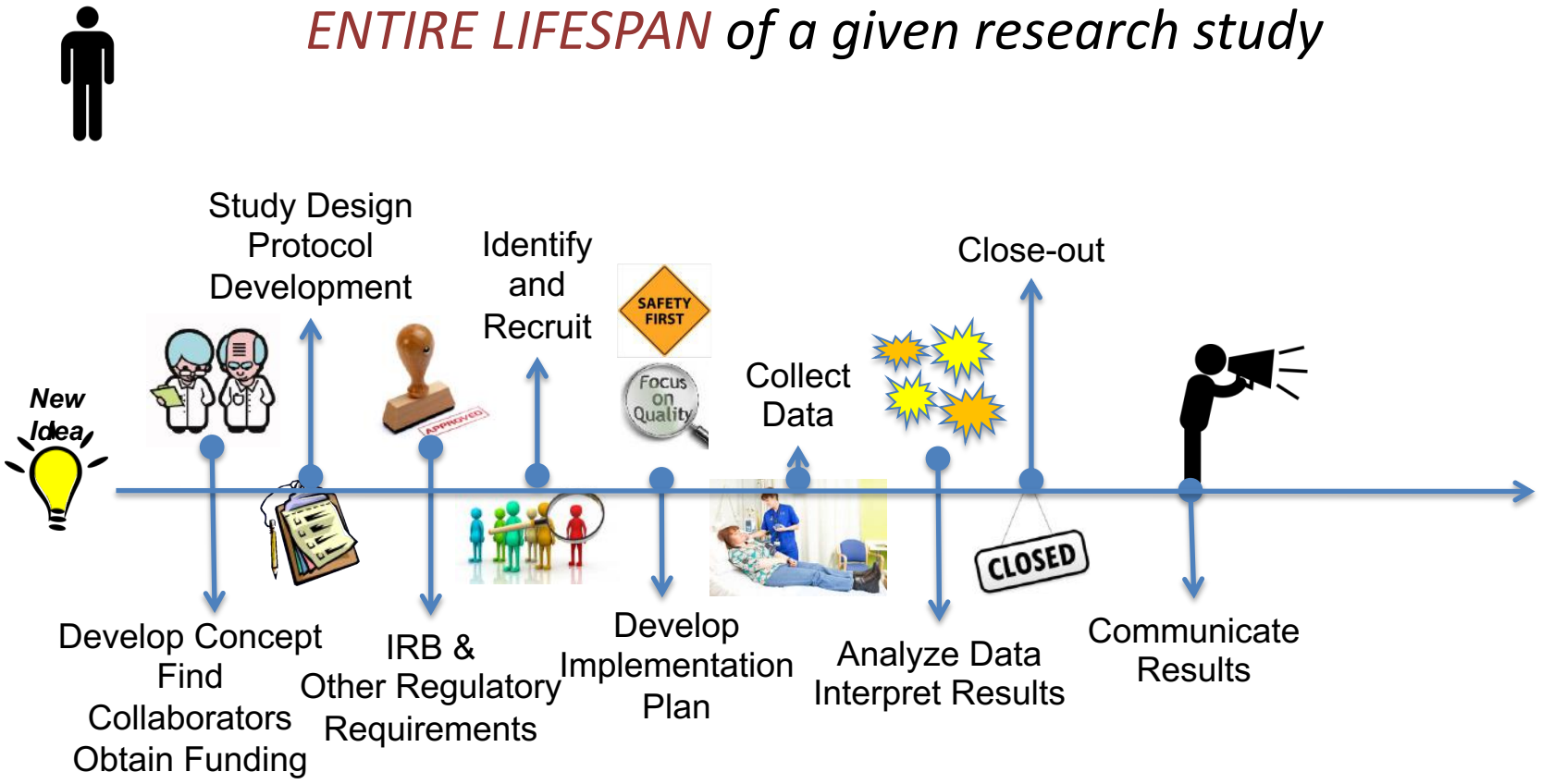
https://trialinnovationnetwork.org

International resources

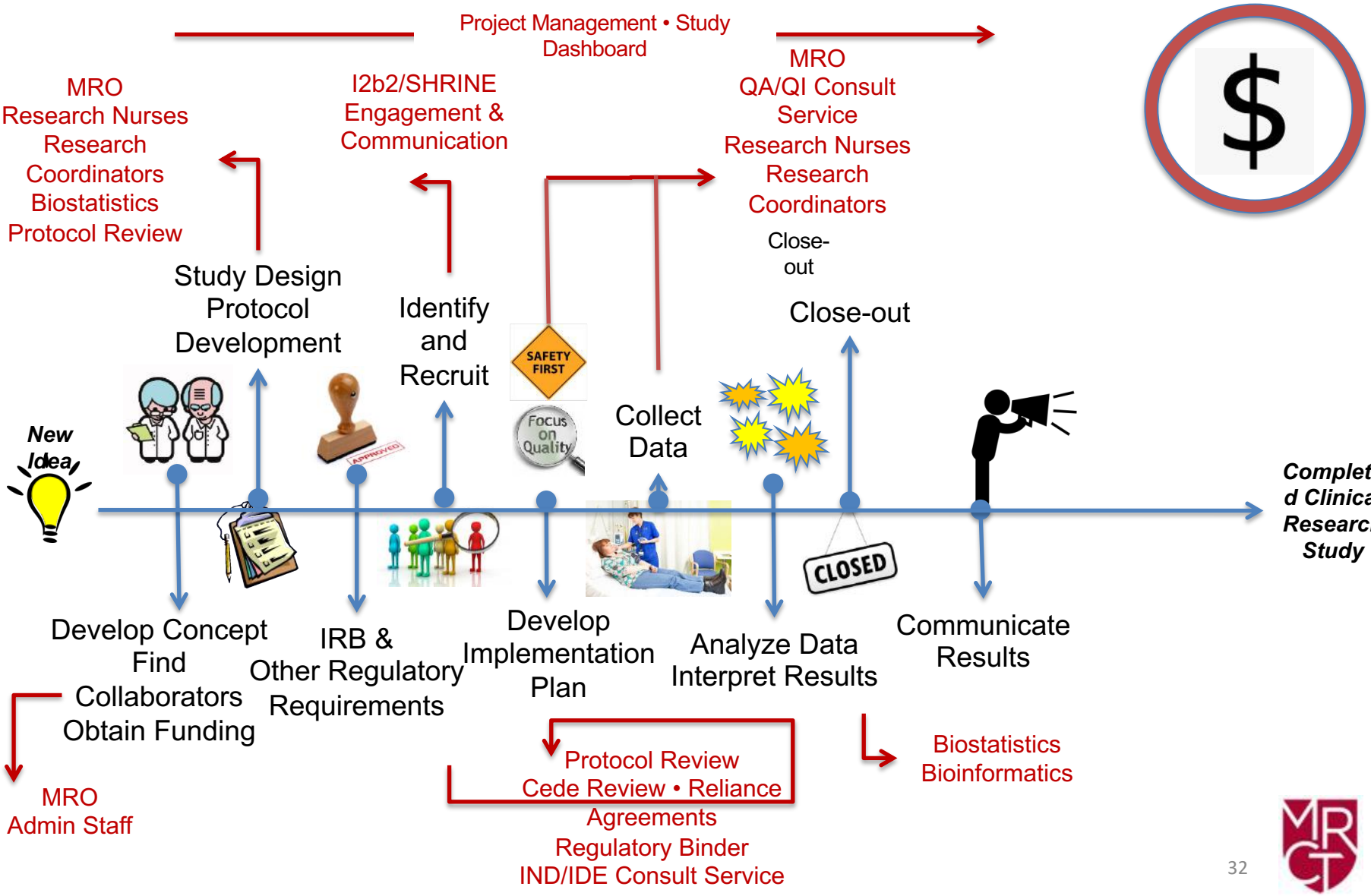
https://clinregs.niaid.nih.gov

Support the individual investigator

One focus is on the INVESTIGATOR over the ENTIRE LIFESPAN of a given research study



Support across the clinical trial enterprise



Making the case

- Research is not the primary concern of most hospitals and academic institutions
- Frame the case:
  - Financial
  - Care improvement (and therefore financial)
  - Market share, referrals, visibility
  - Public good
- If object of clinical research is attracting industry trials → speed, IRB/EC, contract execution, recruitment (first patient on trial, number of patients on trial), data integrity, oversight
- If object is academic trials, must have clinical significance and impact → develop care pathway, business model
- Ideally, (re)engineer IT system and EHR to incorporate outcomes research as an outgrowth of clinical care

Where there's a will…

- Political will to proceed … and to compromise
  - Common goals, vision
  - Trust
  - Time in planning
- Common resources and interdependencies
- Financial alignment (and resources)
- Metrics and measurement
- Accountability
- Governance

Thank you

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Sarah White, MPH
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www.mrctcenter.org

Everything should be made as simple as possible – but not one bit simpler”

Albert Einstein