

UNDERSTAND ENGAGE ACT

2018 IMPACT REPORT



**MULTI-REGIONAL
CLINICAL TRIALS**

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

Dear MRCT Center Friends and Colleagues,

On the surface, one might think that 2018 was a year of transition in the MRCT Center - a new Executive Director, the start of two workgroup initiatives, and the launch of Vivli, our first project to grow to independence. While there was transition, I saw 2018 as an opportunity. An opportunity to engage and learn from a diverse group of stakeholders, to focus on the emerging issues in global clinical trials, and to create practical and actionable tools that regulators, sponsors, IRBs, and investigators could use each and every day.

And I found that this opportunity existed not only for me, but for everyone that engaged with the MRCT Center. The depth of conversation that occurs on a workgroup call, the diverse perspectives that are discussed during a

“...what we learn from each other in multi-stakeholder groups helps us, all of us, develop the solutions that ultimately improve the safety and integrity of clinical trials.”

Bioethics Collaborative, what we learn from each other in multi-stakeholder groups helps us, all of us, develop the solutions that ultimately improve the safety and integrity of clinical trials.

Along with Barbara and Mark, and without breaking momentum, the MRCT Center team initiated two workgroups in 2018 - Diverse Representation in Clinical Trials and Health Literacy in Clinical Research. With Ropes & Gray

we created a neutral forum that we call R3, the Research, Development, and Regulatory Roundtable. We were endorsed by the Asia-Pacific Economic Cooperation as a Training Center of Excellence in MRCT and GCP. Remaining committed to tackling barriers in data sharing, the MRCT Center advocated for a means to give primary data generators recognition for their scientific contributions. And more. In the pages that follow, you will appreciate a glimpse of the projects to which we have committed our efforts over the past year. We cannot do justice to any, and we welcome you to call, email, or otherwise contact us if you are interested in learning more.

None of this would have been or would be possible without the support of our partners, friends, and sponsors. We are energized by the experience and views of our collaborators and humbled by the perspectives of our patient advocates and participants. To our Executive and Steering Committee members, thank you for your confidence and continued engagement. To our External Advisory Board, thank you for your strategic guidance and direction. To our Senior Advisors, thank you for the depth of knowledge you bring to our work. And to friends and partners, thank you for the unique perspective each of you bring to help us respond to the changing landscape of global clinical trials.



Sarah White

Sarah White, MPH
Executive Director



Barbara Bierer

Barbara Bierer, MD
Faculty Director



Mark Barnes

Mark Barnes, JD, LLM
Faculty Co-Director

UNDERSTAND
ENGAGE
ACT



OUR VISION

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

OUR MISSION

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

OUR COMMUNITY

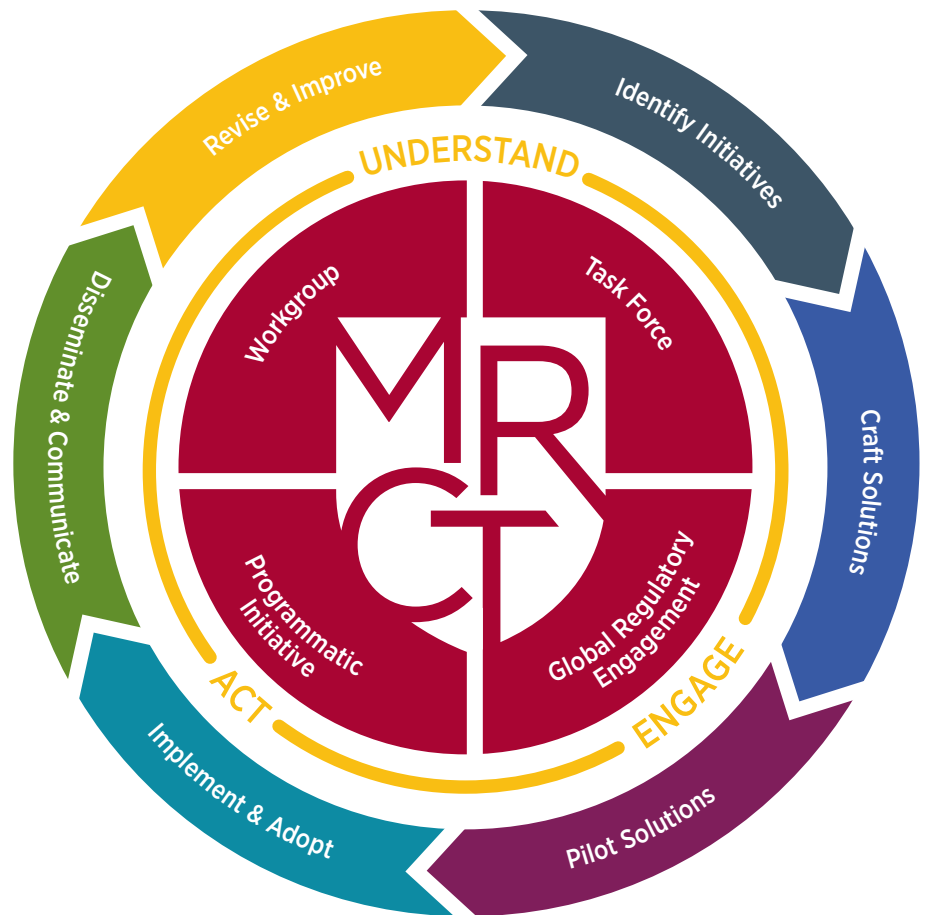
The MRCT Center is an independent convener for global stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and regulatory agencies to address critical issues in the ethics, design, conduct, safety, and oversight of international clinical trials. We explore, learn, and engage with dynamic stakeholders to engineer a different approach forward.

HOW WE WORK

OUR MULTI-PRONGED APPROACH

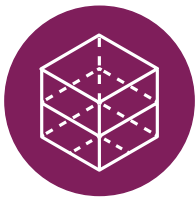
Working with our diverse stakeholder group, we employ a defined and deliberative process to achieve ethical, actionable, and practical solutions. Depending on the initiative, we use one of several multi-pronged approaches to craft solutions:

- **Workgroup:** Large, multi-part issues over an extended period of time
- **Task Force:** Short term for one issue
- **Programmatic Initiative:** Round-table on an issue; meets regularly
- **Global Regulatory Engagement:** Consultation by senior team with governments



AREAS OF FOCUS

Our focus areas address the critical areas of multi-regional clinical trials:



TRANSPARENCY: Engaging the participant in understanding clinical trial and data solutions, we seek to improve the quality of clinical trials and trial reporting, leading to increased transparency in and value of clinical research.



ETHICS, CONDUCT & OVERSIGHT: Tackling critical issues in the ethics, design, conduct and oversight of trials to maximize safety and rigor, we develop practical and pragmatic guidance, resources and tools.



GLOBAL REGULATORY ENGAGEMENT: Engaging global regulatory leaders to promote convergence between local regulations and internationally accepted best practices, we work to develop country-specific and culturally-relevant solutions.



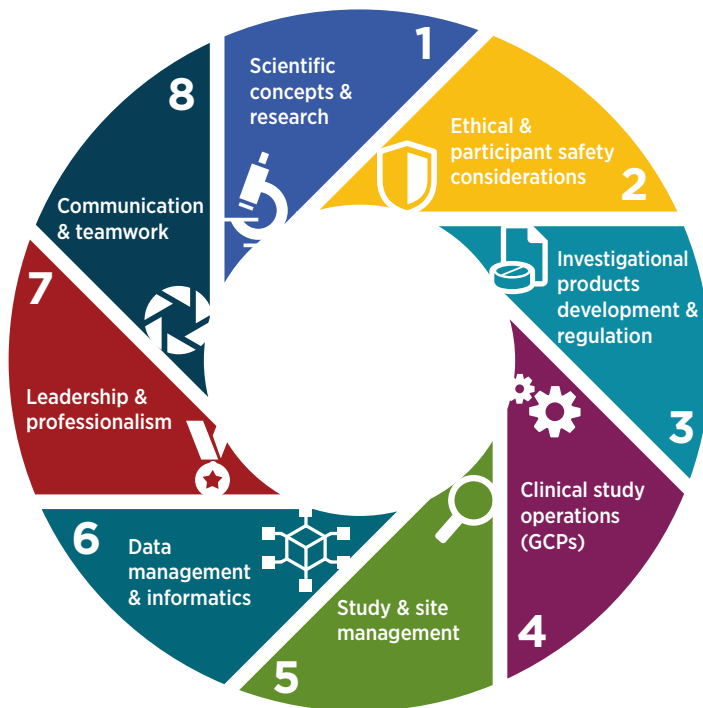
CAPACITY BUILDING: Developing and delivering training and support to regulators, research ethics boards and clinical research personnel to ensure the ethical conduct of research and research integrity.

CAPACITY BUILDING



CORE COMPETENCIES FOR CLINICAL RESEARCH PROFESSIONALS

The Harmonized Core Competency Framework is a universally applicable framework that identifies the skills necessary to be a clinical trial professional. The MRCT Center is host to the Joint Task Force for Clinical Trial Competency (JTF), a multi-disciplinary team dedicated to identifying the competencies necessary for individuals to progress in their careers. In 2018, the JTF defined competencies at Fundamental, Skilled and Advanced levels for all 47 competencies in the Framework. This “leveling” concept applies to recruitment, retention, and professional development of all clinical trial professionals and study team members.



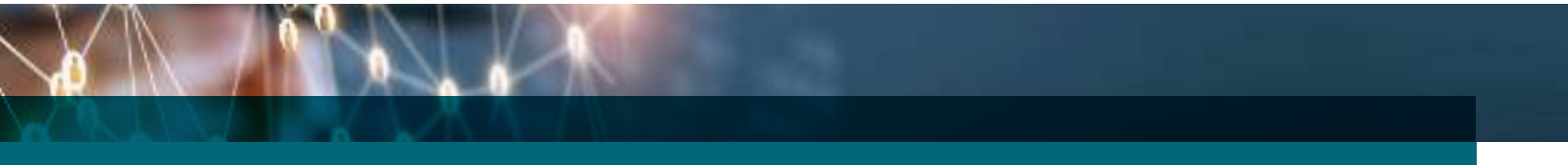
SKILL LEVELS

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

Three levels of competencies have been defined for each of the domains of the Harmonized Core Competency Framework.

“The MRCT Center Trainings in GCPs and MRCTs provide participants with a dynamic opportunity to be exposed to the relevance of current ICH guidance to the design, monitoring, inspection, analysis, interpretation and regulatory review and evaluation of global clinical drug development. The format of the training benefits from the diverse international regulatory and industry participant interactions among the small working groups and the experienced faculty.”

Robert O’Neill, PhD, former Senior Statistical Advisor at USFDA



TRAINING FOR GCP AND MRCT

The MRCT Center has a long-standing commitment to training and capacity building of regulators, institutional ethics committees, and investigators around the world.

In 2018, the MRCT Center was endorsed by the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee to become an APEC Training Center of Excellence for Regulatory Science in the area of Multiregional Clinical Trials and Good Clinical Practices Inspection.

ONLINE TRAINING: INTERPRETATION AND APPLICATION OF ICH E6(R2)

The Training Subcommittee of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) commissioned the MRCT Center to develop an introductory online training on ICH Good Clinical Practice (GCP). A task force of MRCT Center sponsors actively participated in creating 10 modules on key concepts of the revised ICH E6(R2) Guidelines.

Milestones

April 2018

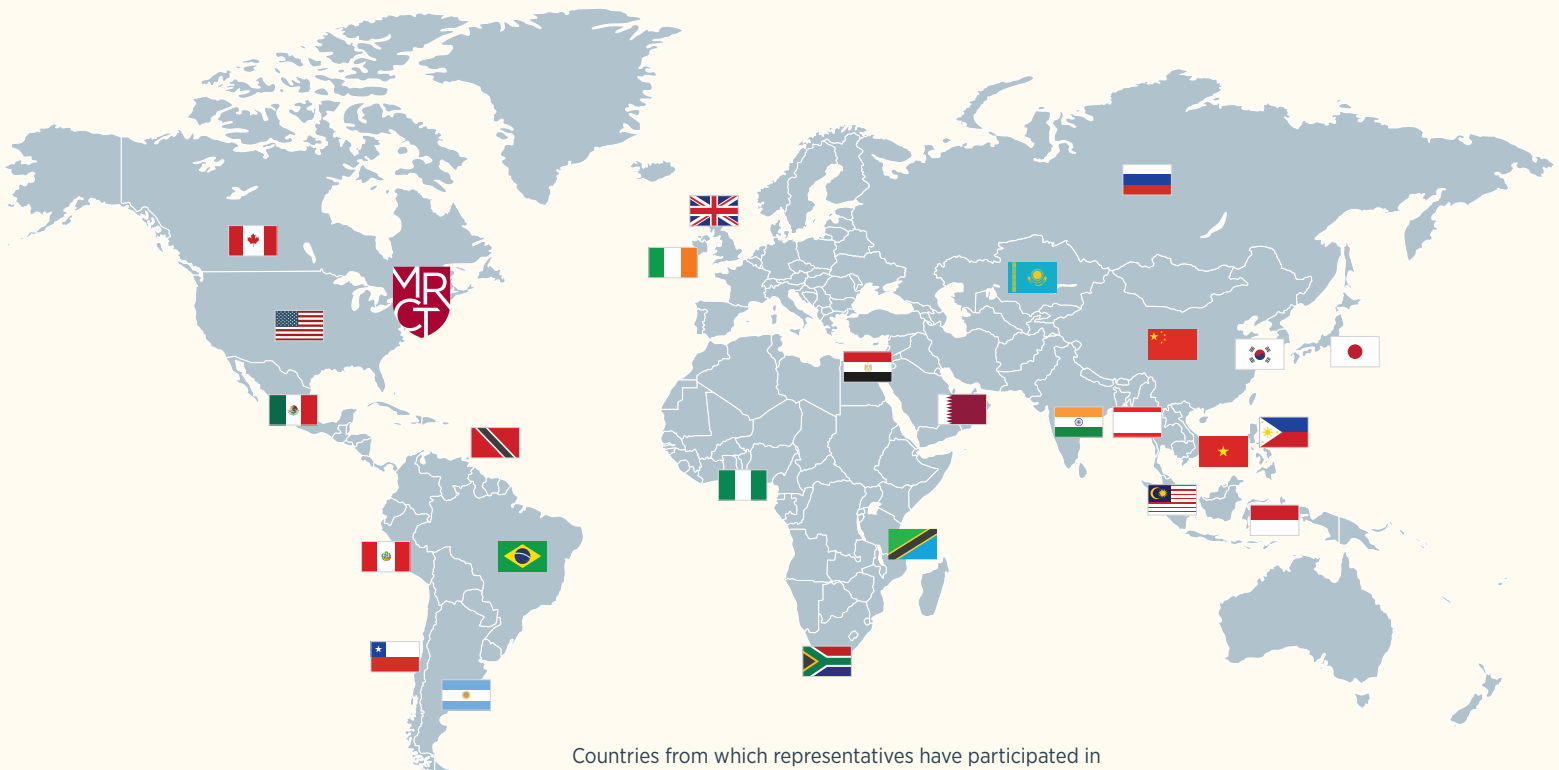
APEC Pilot Center of Excellence Training on MRCT and GCP, Cambridge, MA

August 2018

MRCT Center endorsed as APEC Center of Excellence

December 2018

Launch of online training on ICH E6(R2) Guideline on GCP



ETHICS, CONDUCT & OVERSIGHT



REPRESENTATION OF DIVERSE POPULATIONS IN CLINICAL TRIALS

Worldwide, regulatory approvals for investigational products are based on carefully designed, blinded, randomized clinical trials. To provide generalizable knowledge, the participant population enrolled in clinical trials should reflect the composition of the general population or those affected by the disease. However, very often this does not happen. This failure to achieve meaningful diversity limits information about drug response and measures of safety and efficacy in historically under-represented and under-studied populations, in particular women, ethnic and racial minorities, children, and the elderly.

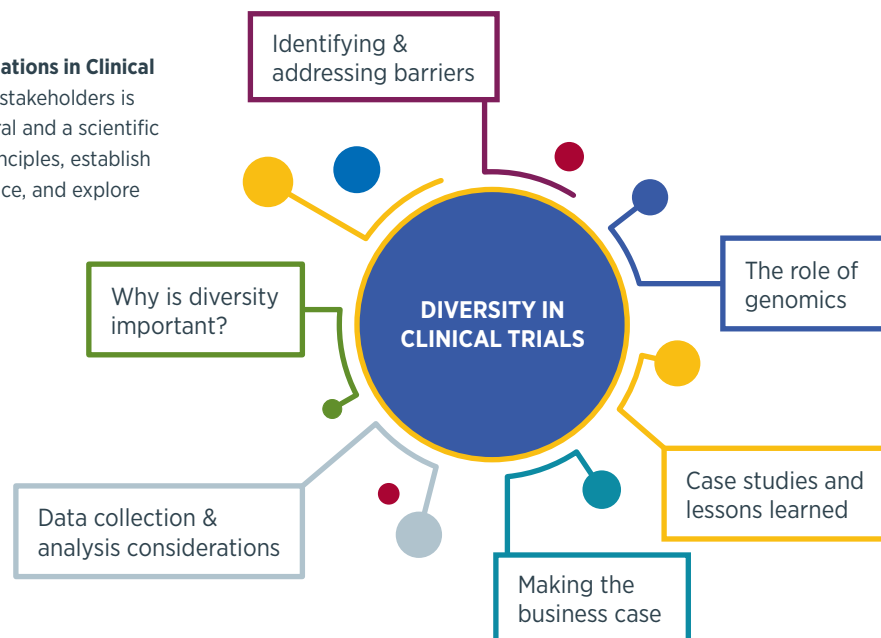
“Addressing diversity in clinical research—as it affects both patients and the entire research enterprise—will result in better, more comprehensive knowledge of health, disease, and effective treatments. It also has the potential to move society as a whole toward greater trust in the research and clinical care system for everyone.”

Elizabeth Cahn, Patient Advocate

To address this challenge, the MRCT Center convened a workgroup of diverse stakeholders to define guiding ethical principles, establish standards of approach and practice, and explore solutions to common scientific and sociocultural barriers to meaningful diversity in clinical trials.

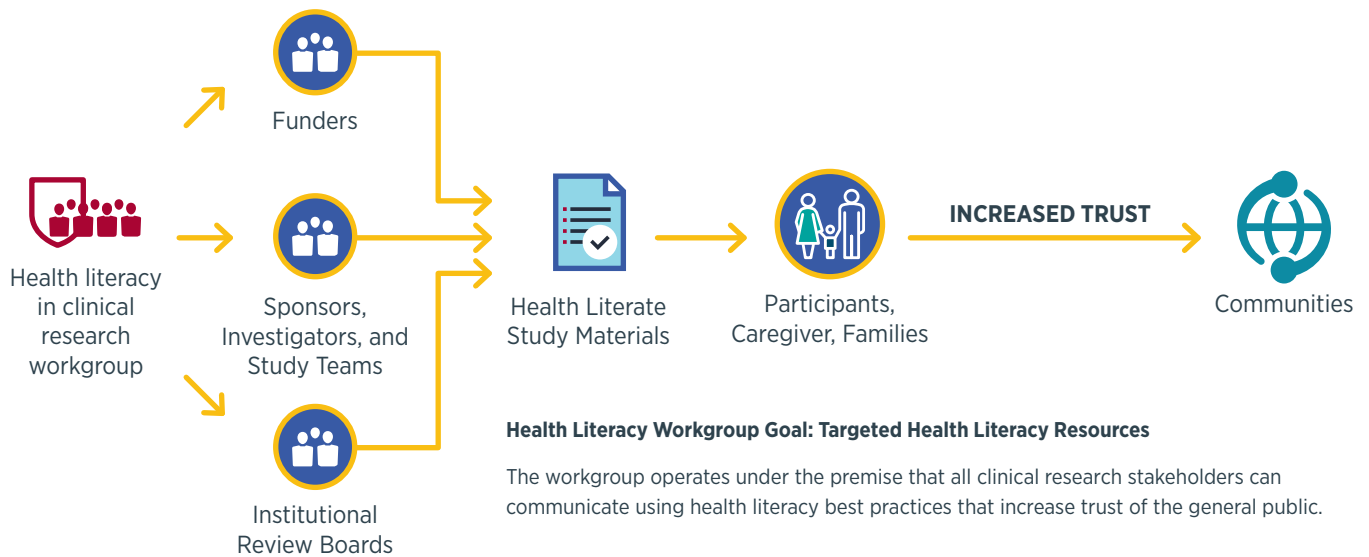
Representation of Diverse Populations in Clinical Trials:

The workgroup of diverse stakeholders is tackling issues from a sociocultural and a scientific perspective to define guiding principles, establish standards of approach and practice, and explore solutions.



HEALTH LITERACY IN CLINICAL RESEARCH

The MRCT Center endorses the adoption and application of health literacy principles in the communication of clinical research information for patients and participants. We support the sharing of understandable research information throughout the entire research life cycle, by all stakeholders in the clinical research environment. Launched in April of 2018, the Health Literacy in Clinical Research workgroup is developing resources that help communicators present health literate information at all points of the participant's clinical trial journey.



“Health literacy and the law are not mutually exclusive. We can increase compliance, reduce liability, and improve participant understanding through health literacy if we only endeavor to try.”

Christopher Trudeau, JD; UAMS

Co-leader of the MRCT Center Health Literacy in Clinical Research Workgroup

ETHICS, CONDUCT & OVERSIGHT



BIOETHICS COLLABORATIVE

The MRCT Center Bioethics Collaborative convenes diverse stakeholders to define, study, and deliberate emerging issues related to the ethical conduct of global clinical research. Over the past year, the MRCT Center Bioethics Collaborative explored the following topics:

Sponsors

The MRCT Center is grateful to the following sponsors of the MRCT Center Bioethics Collaborative:

Genentech
Johnson & Johnson, Inc.
Merck
Pfizer, Inc.
Sanofi
Takeda Pharmaceuticals International, Inc.

Join Us

Contact
MRCT@bwh.harvard.edu

OCTOBER
2017

Recruitment of and Fair Payment to International Research Participants

Offers of payment for research participation must navigate between the extremes of undue inducement and exploitation. The meeting focused on the importance of identifying and understanding cultural norms in payment considerations and the oversight and evaluation of payment processes.

JANUARY
2018

Enabling Informed Selection of Clinical Trials: Institution, Provider, and Participant Responsibilities

The information available to patients regarding their clinical trial options is incomplete. Participants explored mechanisms by which patients may obtain clinical trial information that is understandable and accessible, disambiguating the responsibilities of stakeholders in the process.

APRIL
2018

Return of Individual Results to Research Participants and Axes of Communication

Building on previous work of the MRCT Center, meeting participants explored the pragmatic considerations underlying the return of individual research results to research participants. Attendees explored the practical challenges of communicating the results of clinical trials, focusing on the roles and responsibilities of the sponsor, investigator, healthcare provider and patient in the process.



MULTI-REGIONAL CLINICAL TRIALS
BIOETHICS
COLLABORATIVE

RESEARCH, DEVELOPMENT, AND REGULATORY ROUNDTABLE (R3) OF THE MRCT CENTER AND ROPES & GRAY LLP



Research,
Development,
and Regulatory
Roundtable

Vision of the R3

To provide a neutral forum wherein academia, industry, and regulators may openly discuss pre-competitive issues in drug and device development, regulatory oversight of clinical trials, and human subjects research.

Mission of the R3

To foster a broader understanding of the laws and regulations that influence therapeutic innovation, product approval, and the protection of human research subjects on the global stage.

JULY 2018

INAUGURAL CONFERENCE

Application of the General Data Protection Regulation to Research: Legal, Practical, and Strategic Implications

The EU GDPR presents a number of challenges for clinical research, biobanking and data banking, and big data research, including international data transfer, data anonymization, and authorization for future uses of personal data. Attendees addressed these issues by sharing operational practices and illuminating the need for additional guidance.

NOVEMBER 2018

SECOND MEETING

Right to Try vs. Expanded Access: Practical, Legal, and Regulatory Considerations

Roundtable attendees discussed the advantages and drawbacks of the two pathways by which patients may request access to investigational therapies. Among other things, participants considered the impact of each pathway on long-term drug development, the resources necessary for handling requests in a timely and consistent manner, and the optimal contents of organizational policies.

Sponsors

The MRCT Center is grateful to the following sponsors of the R3:

Advarra IRB

Baim Institute for
Clinical Research

Dana-Farber Cancer Institute

Genentech

Johnson & Johnson, Inc.

Novartis

Pfizer, Inc.

Sanofi

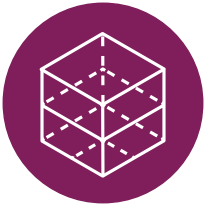
Takeda Pharmaceuticals
International, Inc.

Washington University
in St. Louis

Join Us

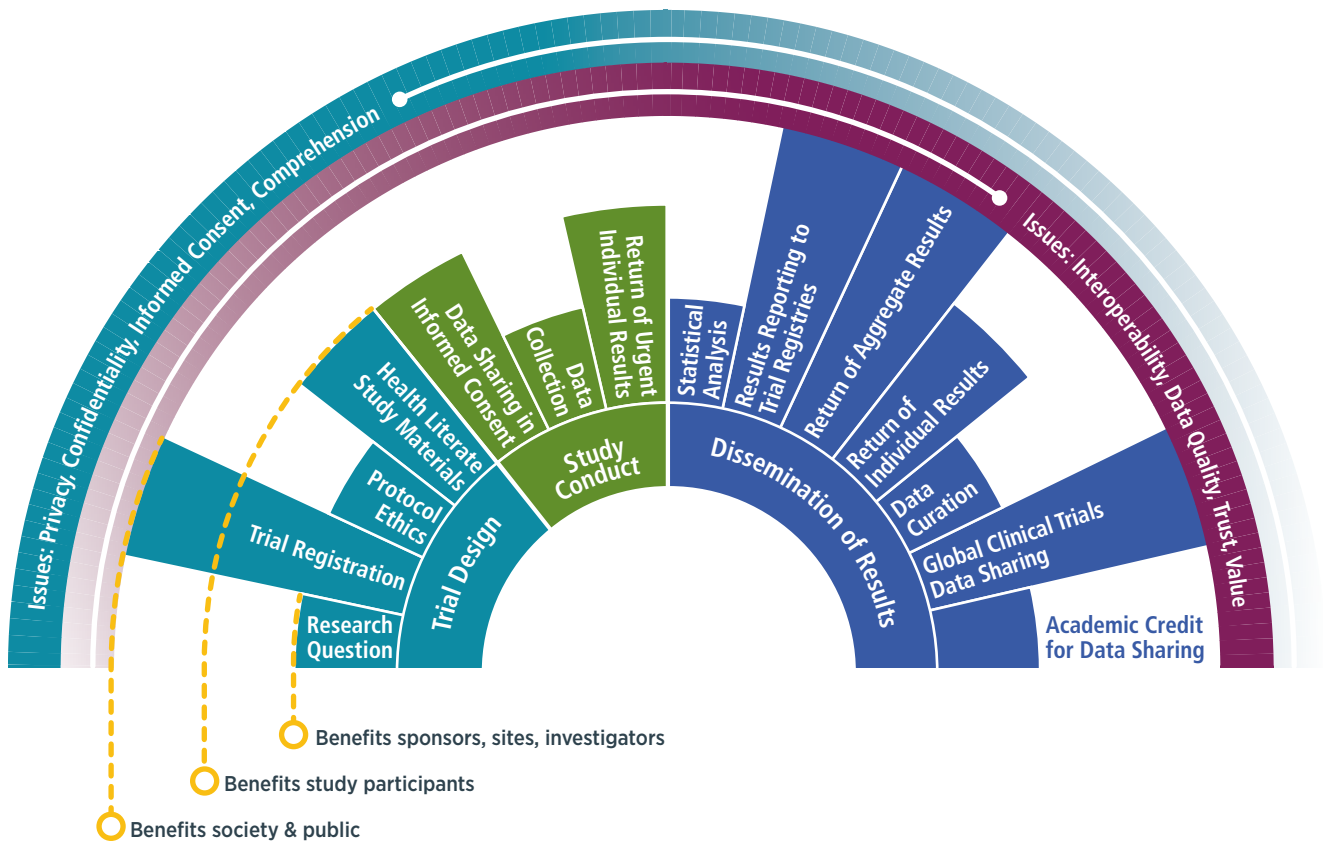
Contact
MRCT@bwh.harvard.edu

TRANSPARENCY



THE TRANSPARENCY CONTINUUM

Since 2009, the MRCT Center has been committed to transparency across the clinical trial life-cycle, from trial design to dissemination of results. We have examined barriers of trust, privacy, confidentiality, value and quality – and collaborated across our multi-stakeholder group to develop thoughtful and practical solutions. The rays of this figure illustrate our specific project efforts and highlight how the deliverables may benefit our multi-stakeholder groups that range from the participant, the sponsor, to the public.



HARMONIZED GOVERNANCE TOOLS

Access to and sharing of clinical research data are essential for the advancement of science. Sharing and combining of datasets will be optimized by developing and utilizing data sharing agreements whose terms and conditions are in alignment. Supported by and working with the Patient-Centered Outcomes Research Institute's (PCORI) Open Science Pilot Project, the MRCT Center developed three harmonized governance tools for adoption among both PCORI grantees and the general public:

- **Data Contributor Agreement (DCA):** Clarifies data contributor responsibilities, institutional safeguards, and requirements for deposition of data in data repository.
- **Data Use Agreement (DUA):** Delineates responsibilities and requirements for requestors of data from data repositories.
- **Data Sharing Section of an Informed Consent Form (ICF):** Enables secondary use of collected data for open science; summarizes complex data sharing concepts; is committed to participant autonomy and privacy.

CREDIT FOR DATA SHARING

Biomedical sciences are a data-driven endeavor, but individuals who share data are rarely recognized for data preparation and curation nor for making data available to others for secondary analysis. The MRCT Center, in partnership with the Association of American Medical Colleges (AAMC) and the New England Journal of Medicine (NEJM), has advocated for a system that tracks the origin and uses of datasets over time so that data generators may receive appropriate recognition for their contributions to scientific knowledge.

This dataset-centric system of recognition allows for the linking of research funding sources, data generators, researchers, institutions, repositories, data sharing platforms, and publications or other scholarly products via the use of Persistent Identifiers (PIDs).

“This initiative is engaging stakeholders from across the research ecosystem to create a process to allow for the tracking and use of shared datasets. Ultimately, this will provide a more accurate and comprehensive understanding of the potential benefits of data sharing, as well as information and metrics that can be utilized by institutions, funders, and journals as they adapt to a 21st century model of research.”

Heather Pierce, JP, MPH
Senior Director, Science Policy, Regulatory Counsel, Scientific Affairs
Association of American Medical Colleges

Milestones

October 2017-February 2018

The MRCT Center and AAMC hosted a series of calls with technical leaders to develop and refine the dataset-centric system of credit

April 2018

AAMC facilitated a workshop in Washington, D.C. entitled, “Implementing a System to Enable Credit for Data Sharing”

GLOBAL REGULATORY ENGAGEMENT



We work with national regulatory agencies, sponsors, and investigators to identify the major issues in international clinical trial practice. We strive to promote a country-specific and culturally-relevant approach.

GLOBAL REGULATORY ENGAGEMENT FOCUS: INDIA

Over the last five years, the MRCT Center has worked with Indian regulators, non-profit organizations, and industry representatives to rewrite and reposition problematic regulations to promote the reintroduction of clinical trials while ensuring the protection of the rights, welfare, and well-being of all participants. In 2018, Indian regulators announced the completion of a new set of rules that reflect international standards of clinical trial performance.

REAL WORLD EVIDENCE IN REGULATORY DECISION MAKING

Including electronic health records, pharmacy and claims data, and mobile health technologies, Real World Evidence (RWE) may be used in regulatory decision-making, potentially bringing innovative products to patients more quickly and reliably. To understand the utility and limits of RWE, the MRCT Center partnered with OptumLabs to design project OPERAND that seeks to better inform the use of RWE from retrospective observational studies in regulatory decision-making and medicine.

Using electronic health records (EHR) and claims data, project OPERAND seeks to replicate randomized clinical trials submitted for regulatory decision making, develop empirical data to understand data quality and its limitations, and uncover whether and how the addition of EHR to claims data improves the sensitivity and utility of data.



Partner
with OptumLabs



Collaborate
with stakeholders from
across the healthcare
industry

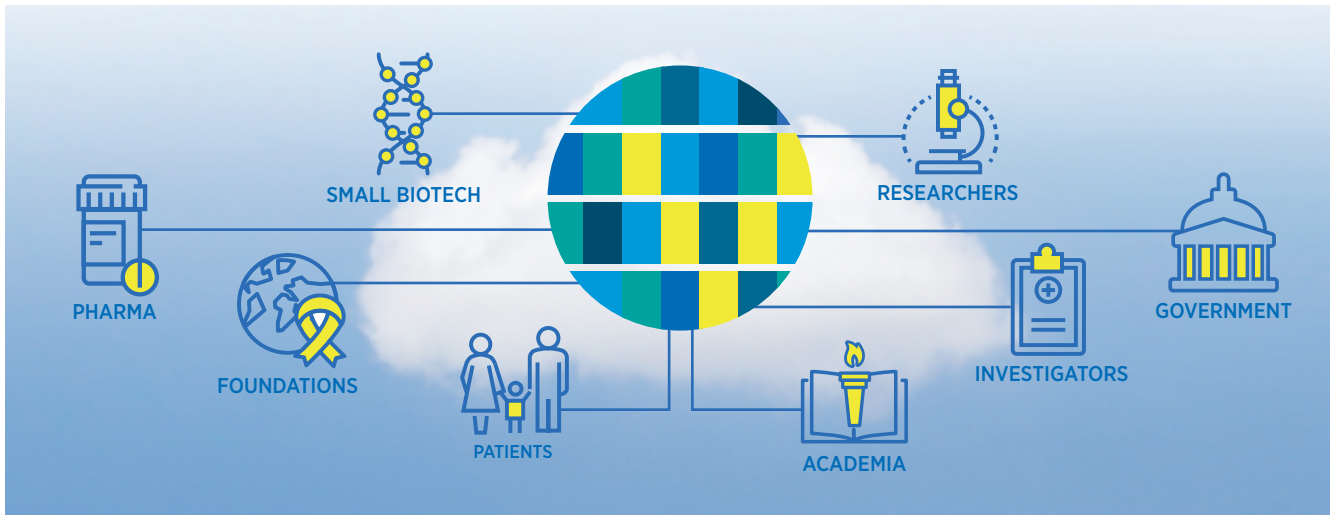


Establish
a framework for how
RWE can support
approval of new drug
indications and post
approval requirements



Understand
circumstances for which
evidence from obser-
vational studies is most
credible

VIVLI 2018 LAUNCH



3100+
TRIALS AT
LAUNCH

100
COUNTRIES

15
MEMBERS

1.4
PARTICIPANTS

“The MRCT Center is where projects are transformed from vision into implementable reality. Vivli is an example whereby working together with key stakeholders, countless hours of hard work and the backing of key funders, the MRCT Center has launched this first of many successful future independent initiatives. The MRCT Center, Vivli’s Founding Organization, will always remain a close partner.”

Rebecca Li, PhD, Executive Director, Vivli

PROJECTS ON THE HORIZON

Pediatrics: To expedite pediatric-specific safety and efficacy data and to overcome present barriers to pediatric research, we intend to convene experts and diverse stakeholders to generate and advance ethical and regulatory resources for global pediatric trials.

Advancement of clinical research enterprise: The MRCT Center will scope how the current ethical and scientific aspects of initiation, conduct, analysis and reporting of studies that involve human participants can be improved to advance the clinical research enterprise.

Proactive Safety Surveillance: While many current methods to detect safety signals are complementary, none systematically harness the power of real-world data, machine learning, or stakeholder cooperativity to identify safety signals. We plan to nucleate a “think tank” to scope an approach to proactive safety surveillance to complement, and later perhaps replace, adverse event reporting.

Thank you to our sponsors for contributing both expertise and support towards improving the quality standards of clinical trials. Your contributions ensure that we, collectively and collaboratively, commit to the ethical conduct of clinical trials across the globe.

EXTERNAL ADVISORY BOARD (EAB)

Dr. Bernard Lo (Chair)
Greenwall Foundation

Dr. Joshua Boger
Vertex Founder and former CEO

Dr. Cristina Csimma
*Biopharmaceutical Board Director
and Independent Consultant*

Dr. Jeffrey Drazen
New England Journal of Medicine

Dr. Margaret Hamburg
Former FDA Commissioner

Dr. Michael Rosenblatt
Flagship Ventures

Dr. Ara Tahmassian
Harvard University

MRCT CENTER COMMITTEES

EXECUTIVE COMMITTEE

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GlaxoSmithKline	PhRMA
Harvard University	Ropes & Gray LLP
Johnson & Johnson	Takeda Pharmaceuticals U.S.A., Inc.
Kowa Research Institute	

STEERING COMMITTEE

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Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP)	Indian Society for Clinical Research
Association of Clinical Research Professionals (ACRP)	IQVIA
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