2016 IMPACT REPORT

Dear MRCT Center Friends,

What we have accomplished in 2016 at the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) has been made possible by our collaboration with you, our sponsors and friends. In the past year, you have partnered with us to effect needed changes in the practice of clinical trials globally.

As always, our work has been motivated by our belief in the power of research to transform both science and society. The MRCT Center's 2016 Impact Report is a sustained reflection on this belief and a measure of our impact on participants, researchers, and other stakeholders.

Transparency, in particular, has been a special focus of the MRCT Center's 2016 efforts. We are committed to working with sponsors, regulators, investigators and participants to expand discovery of and access to clinical trials data. Responsible data sharing is, we believe, a vital step to advance scientific knowledge and respect participants.

The MRCT Center is proud to introduce Vivli, the not-for-profit organization intended to create, operate, and oversee a global, sustainable data-sharing platform. Vivli, which is slated to launch in 2017, will advance the harmonization of data-sharing practices and, importantly, develop and enable the extraordinary benefits of clinical trials data sharing.

Building upon our work on the return of aggregate results, we launched a workgroup on the return of individual results to participants. This team developed a principled framework and toolkit to enable the communication of individual results to participants, thereby helping to honor their contributions to the public good. We look forward to seeing how our work effects the participant-trial experience.

These projects and more—about which you may read in the following pages and on our website—are evidence of our commitment to transforming the field of clinical trials globally.

We also celebrate the launch of our External Advisory Board, whose expert guidance helps to steer our work going forward to ensure our global impact.

To our sponsors both ongoing and new, we are sincerely grateful for your continuing support. Your decision to champion the ethical conduct of clinical trials worldwide sustains and drives our work. Thank you for helping us to achieve our vision.

As we look toward 2017, we plan to expand our efforts in training of regulators in low and middle-income countries and to advocate for regulatory convergence. We strive for the MRCT Center to continue to act as a positive and powerful force in the practice and ethics of clinical trials.

As always, our work has been motivated by our belief in the power of research to transform both science and society.

Barbara Bierer, MD
Faculty Co-Director

Mark Barnes, JD, LLM
Faculty Co-Director

Rebecca Li, PhD
Executive Director

OUR OBJECTIVES

The MRCT Center develops guidance, training resources and tools that promote safe and ethical clinical trials. We perform our work by convening representatives from industry, not-for-profit organizations, academia, investigators, patients and patient advocacy groups, to create practical resources for the ethical design and conduct of multiregional clinical trials.

OUR VISION

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

OUR MISSION

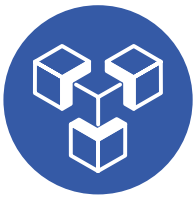
Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

Making an IMPACT

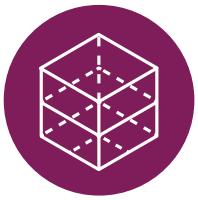
We believe in the extraordinary potential of clinical trials to transform scientific knowledge. Our work is rooted in the belief that all individuals deserve access to effective medicines and therapies and to sustained health. We aim to equip stakeholders in clinical research with practical tools and ethically sound guidance.

Areas of FOCUS

GLOBAL REGULATORY: We identify emerging issues in global clinical trials. We engage and advise global leaders to promote regulatory convergence and internationally accepted best practices. We work with local partners to develop country-specific and culturally-relevant solutions.



ETHICAL FRAMEWORKS: We develop guidance, resources and tools that promote safe and ethical clinical trials.



DATA TRANSPARENCY: We reduce barriers to clinical trial data sharing, and we develop practical, actionable solutions driven through multi-stakeholder participation. We honor clinical trial participants by developing guidance for the return of individual and aggregate results.

TRAINING: We build capacity by training clinical trial professionals with a particular focus in low and middle-income countries.

SAFETY: We build the capacity of data monitoring committees to ensure the integrity of clinical trials.

DATA TRANSPARENCY

In March 2016, the MRCT Center, in collaboration with the Wellcome Trust, convened a conference entitled "**Future of Clinical Trials Data Sharing**" in London, UK. At the conference, the MRCT Center presented plans to launch Vivli, the not-for-profit organization intended to create, direct, and oversee a global, sustainable data-sharing platform. The Vivli blueprint is the product of three clinical trials data sharing workgroups: governance, information technology, and business models.

Vivli
CENTER FOR GLOBAL CLINICAL RESEARCH DATA

In recent years, data sharing has become a fiercely debated issue, especially in light of a proposal from the International Committee of Medical Journal Editors to require data sharing of contributors and authors. The MRCT Center has been committed to participating in these dialogues as we develop the Vivli platform. In this spirit, the MRCT Center has invited public comments on Vivli and published a perspective in the *New England Journal of Medicine*, vol. 374, June 23, 2016, "A Global, Neutral Platform for Sharing Trial Data."

We intend for Vivli to function as a neutral global platform for hosting clinical trials data, and we have designed it to link to existing data-sharing platforms. Vivli aims to harmonize data sharing practices and demonstrate the extraordinary potential of data sharing to advance scientific knowledge and honor clinical trial participants.

MILESTONES / TIMELINE

March 2016

Future of Clinical Trials Data Sharing Conference

May 2016

Perspective in ***NEJM***

Fall 2016

Incorporation of Vivli

Selection of vendors for assembly and development

Early 2017

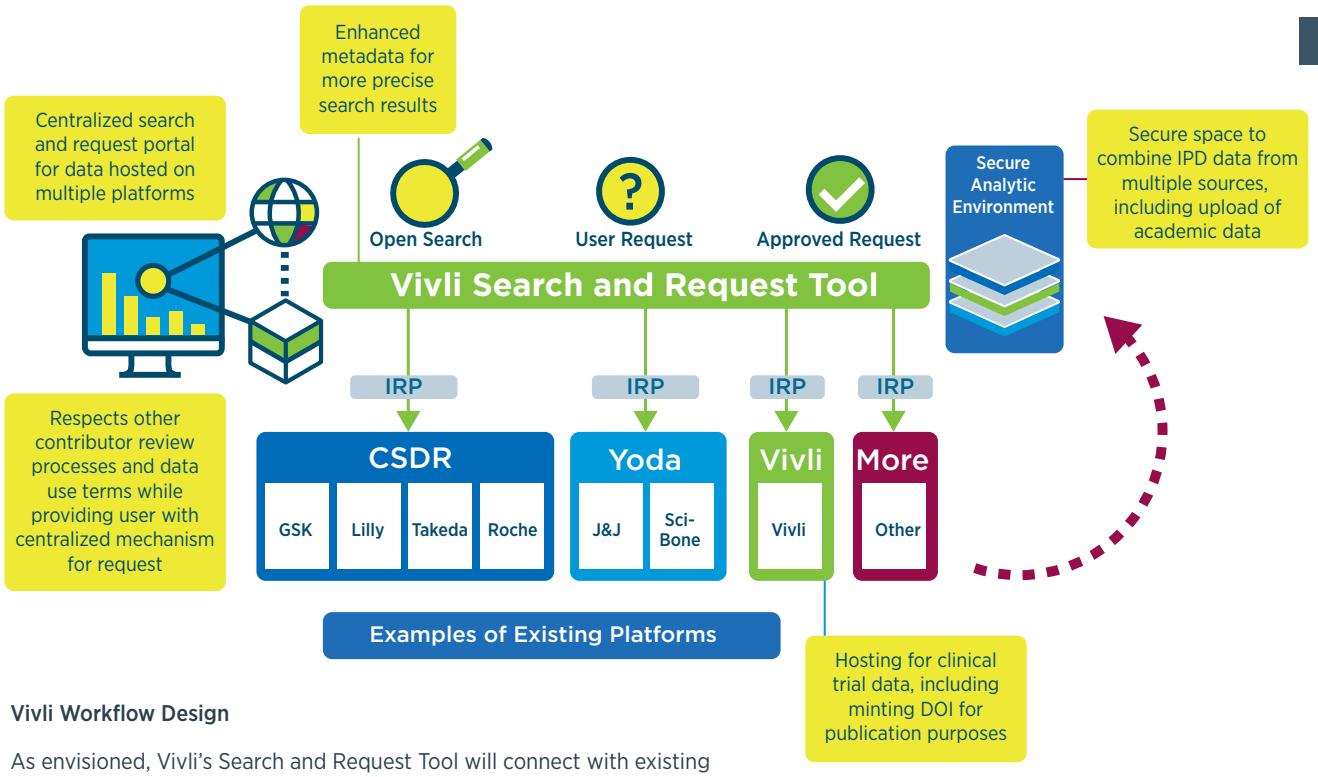
Vivli incorporated as a scientific, not-for-profit entity

Acquire funding

Build leadership team

Late 2017

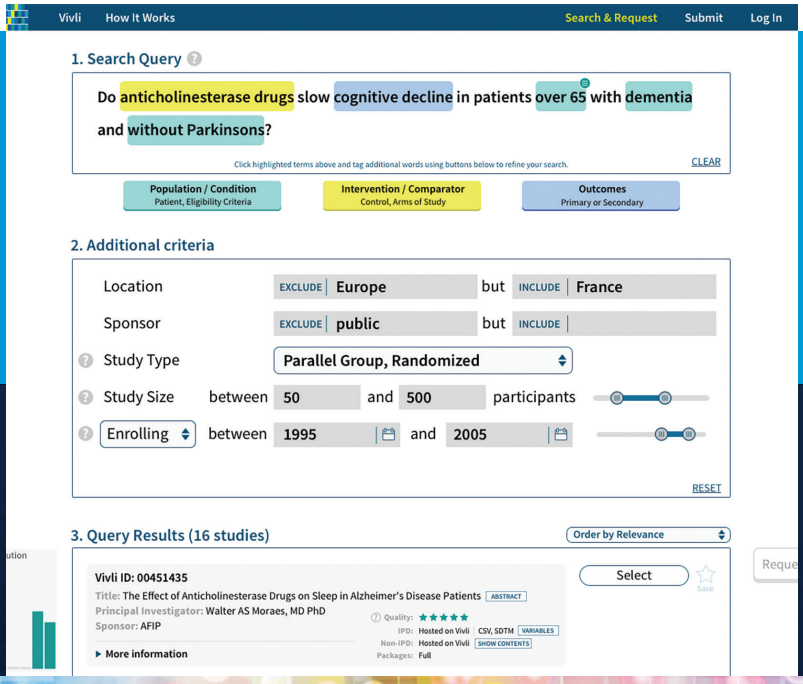
Launch of Vivli



Vivli Workflow Design

As envisioned, Vivli's Search and Request Tool will connect with existing platforms and enable users to discover data hosted on Vivli and elsewhere.

Visit **Vivli.org** for a full demo of search and submit capabilities



Example of Vivli Search Capabilities

Return of Individual Results

Participants have a right to receive both individual and aggregate research results from the clinical studies in which they have participated. This right, however, is difficult to vindicate, given the lack of standard guidelines and resources in this area. To that end, the MRCT Center has a lasting commitment to providing guidance and tools for the return of results. Previously, we developed guidance on the return of aggregate results; in 2016, our particular focus has been the return of individual results.

The Return of Individual Results Workgroup launched in December 2015. The Workgroup aimed to:

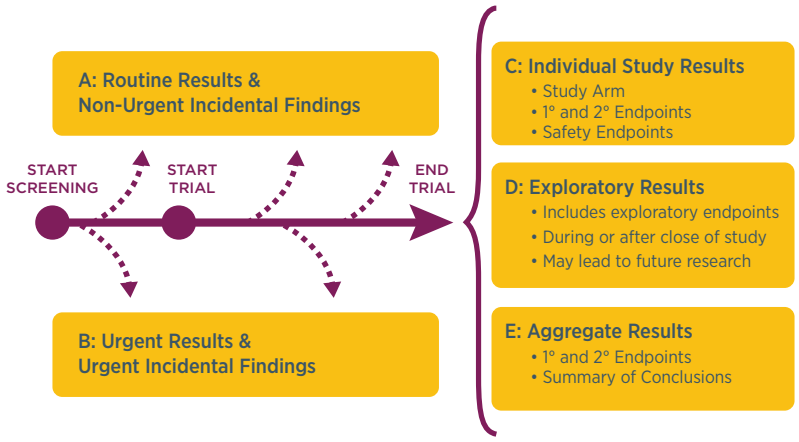
(1) determine the principles and methodologies best suited for return of individual results;

(2) define methods to facilitate disclosure and communication of results to individuals;

(3) create best practices to manage disclosure and follow-up of individuals; and

(4) develop a framework to manage the global context for returning results.

In December 2016, the Workgroup presented the MRCT Center Return of Individual Results Guidance Document and Toolkit Version 1.0. This guidance is based on the experiences of participants, bioethical principles, and feasibility considerations and represents a harmonized approach to how study results are reported.



Members of the Individual Return of Results Work-group met at the MRCT Center in December 2015 to begin their work.

MILESTONES

December 2015

Launch of Return of Individual Results Working Group

August 2016

Released Return of Individual Results: Summary Principles and Approach, for public review and comments

December 2016

Released Return of Individual Results Recommendations Document and Toolkit

RELATED PROJECTS

JULY 2016: Released Version 2.1 of Return of Results Guidance Document and Version 2.2 of Aggregate Return of Results Toolkit.

SEPTEMBER 2016: In collaboration with the Comprehensive and Integrative Medicine Institute (CIMI), Daegu Catholic University Medical Center (DCUMC) and Dana-Farber Cancer Institute (DFCI), completed a qualitative survey of comprehension and preferences of the return of aggregate results.

Principles for the Return of Individual Results to Participants:

1. The participants or their designees should be the recipient of individual research results.
2. Providing individual research results responds to the expressed interests and expectations of many clinical trial participants for results to be communicated.
3. Considerations pertaining to the return of individual research results to clinical trial participants should be integrated into the clinical trial and proactively planned.
4. Participants should be able to choose whether or not to receive their individual research results, if results are offered.
5. Sponsors and investigators have an obligation to return individual research results responsibly, taking into account medical significance, analytical validity, and medical actionability.
6. Individual research results should be returned in ways and at times that maintain the integrity of the study, insofar as the safety and welfare of the research participants are not at risk.
7. The purpose of research is not clinical care, and return of individual research results cannot substitute for appropriate clinical care and advice.
8. Return of individual research results should be planned and executed in compliance with institutional policies and local, regional, and national laws and regulations.

Harmonized Core Competencies Workshop

1. Scientific Concepts and Research Design
2. Ethical Considerations, Patient Care and Safety
3. Medicines Development and Regulation
4. Clinical Trials Operations (Good Clinical Practice)
5. Study and Site Management
6. Data Management and Informatics
7. Leadership and Professionalism
8. Communication and Teamwork

Professional competency is the foundation of the ethical conduct and regulatory compliance of clinical research professionals. This was the operating principle of the Joint Task Force for Clinical Trial Competency (JTF), which convened in 2013 to establish globally relevant, universally applicable competency standards for the field. In 2014, the JTF released a harmonized framework of core competencies for clinical research professionals, which has since been utilized by more than 15 institutions to develop job descriptions, training modules, and other training resources.

On October 19, 2016 the MRCT Center hosted a conference entitled "**Core Competencies in Clinical Research: Real World Applications, Convergence, and Evolution of a Framework.**" Participants and representatives from academia, industry, government, and professional societies shared applications of the framework both in the United States and abroad. Discussion focused on lessons learned, potential revisions to the framework, opportunities for collaboration, and the creation of resources, job descriptions, and metrics.

In 2017, the JTF will work to revise the framework based on feedback from institutions that have utilized the competencies. From there, the JTF aims to create additional resources for organizations, including a leveling system, competency portfolios, and metrics.

CORE COMPETENCIES FRAMEWORK

Phase 1 (2013 – 2016)

Developing, and Implementing the Core Competency Framework

October 2016

Core Competencies in Clinical Research Workshop at Harvard University

Phase 2 (2017)

Revising and Disseminating the Framework, Creating Levelling System

Phase 3 (2018)

Developing Metrics, Evaluations, and Competency Portfolios

CASE STUDIES

Evolving the Core Competency Framework to meet the needs of clinical researchers is possible only through the collaboration of academia, industry and professional organizations in the United States and abroad. In this spirit, the Core Competencies Workshop was structured around case studies, which highlighted innovation, challenges, and lessons learned.

International Applications

The Acceptance and Application of the Competencies in the EU
Esther Daemen, TRIUM Clinical Consulting

Competence-Based Certification in Clinical Research in Mexico
Matilde Damian and Jose Viramontes, Association of Clinical Research Professionals (APEIC), Mexico

Developing Excellence in Research Design and Practice
Ian Kerridge, PRAXIS Australia Ltd and University of Sydney, Australia

Developing an Integrated Workforce Framework in the UK
Fiona O'Neill, NIHR Clinical Research Network, UK

The JTF Core Competencies in Latin America: Inter- and Intra-Regional Differences
Honorio Silva, Rutgers University

Domestic Applications

Developing Job Classifications and Workforce Development Initiatives
Rebecca Brouwer and Denise Snyder, Duke University

Re-shaping an Academic Clinical Research Administration (CRA) Graduate Program
Joan Butler and Beth Harper, George Washington University

Mission Achievement through Competence Development
Terri Hinkley, Association of Clinical Research Professionals (ACRP)

Developing a Clinical Trials Implementation Program
Penelope Jester, University of Alabama, Birmingham

Utilization of JTF Framework for CTSI Grant Renewal
Robert Kolb, University of Florida

Building a Professional Clinical Research Workforce for the Future
Greg Koski, Alliance for Clinical Research Excellence and Safety (ACRES)

Competency-Based Training for Entry-Level CRAs
Tammi Masters, INC Research

Education and Training of Clinical & Translational Study Personnel
Thomas Perorazio, University of Michigan
Michelle Wartak, Tufts Clinical and Translational Science Institute

Applying the Framework to Improve the Overall Training and Career Development of Physicians in Industry Involved with Clinical Trials
Subasree Srinivasan, Alexion; formerly Bristol-Myers-Squibb

Dr. Stephen Sonstein (Director, Clinical Research Administration at Eastern Michigan University and Co-Chair Joint Task Force for Clinical Trial Competency) gave opening remarks at the October 19 Workshop, "Core Competencies in Clinical Research"

Post Trial Responsibilities

MILESTONES

September 2014

Conference, convened at Harvard Law School, on Post-Trial Responsibilities: Ethics and Implementation

December 2015

Post-Trial Responsibilities Workgroup Meeting

Presentation of Draft Framework at MRCT Center 2015 Annual Meeting

March 2016

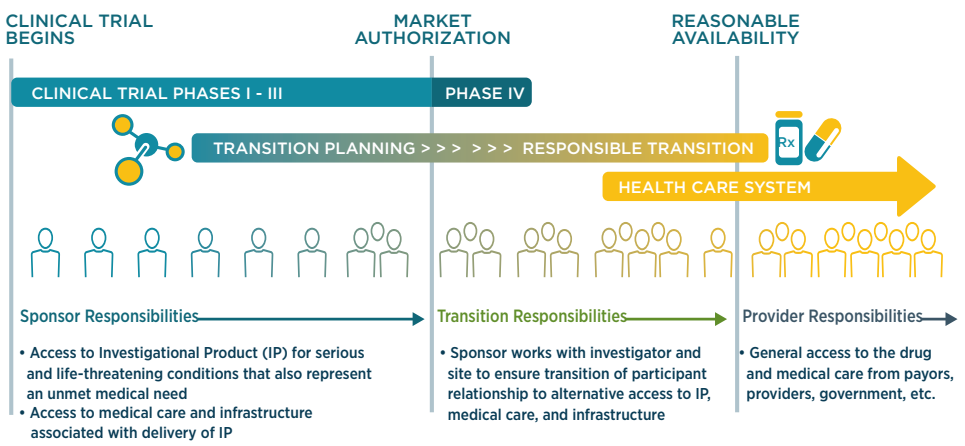
Meeting in Sao Paolo, Brazil, co-sponsored by the Soceidade Brasileira de Medicina Formaceutica (SBMF) to discuss PTR and access to investigational medicines.

December 2016

Release of MRCT Center Post-Trial Responsibilities Framework Version 1.0.

When a clinical trial is completed, stakeholders in clinical research have certain ethical responsibilities to study participants. Although the Declaration of Helsinki and other ethical documents establish the principles of these responsibilities, ambiguity remains. Which responsibilities are owed? To whom are they owed? How are these responsibilities apportioned among stakeholders?

In order to address this ambiguity and define these responsibilities, the MRCT Center assembled a workgroup comprising representatives from academia, industry, government, patient groups, and beyond. Released in December 2016, the MRCT Center Post-Trial Responsibilities (PTR) Framework Version 1.0 is the culmination of this effort. The Framework aims to provide stakeholders with ethically sound and practically applicable guidance



MULTI-REGIONAL CLINICAL TRIALS BIOETHICS COLLABORATIVE

With the launch of the Bioethics Collaborative, the MRCT Center is addressing emerging bioethical issues in the development of drugs and devices and the conduct of international multi-regional clinical trials. We hope to advance the collective understanding of pressing matters by convening diverse stakeholders and sharing our perspectives in a neutral forum.

These meetings occur two or three times annually, bringing together a small group of individuals from industry, academia, not-for-profit organizations, regulatory agencies, government, and patient advocacy groups. Following each meeting, the group will decide together whether and how to embark upon future work.

The inaugural meeting of the MRCT Center Bioethics Collaborative occurred on October 24, 2016, focusing on expanded access, the provision of investigational new products to patients outside of a clinical trial. The discussion addressed the factors that physicians and sponsors may consider when deciding whether or not to recommend or to make available, respectively, the investigational product to an affected individual.

Dr. Barbara Bierer guided the discussion at the first meeting of the MRCT Center Bioethics Collaborative on October 24, 2016.

SPONSORS

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PLANNING COMMITTEE MEMBERS

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Kathleen Stern
Takeda Pharmaceuticals International Inc.

Walter Straus
Merck & Co.

Robert Truog
Center for Bioethics, Harvard Medical School

GLOBAL REGULATORY

(Top): Dr. Bierer met with leaders of CanKids KidsCan, a nonprofit organization that works to provide better treatment, care and support services for children with cancer and their families in India (March 2016)

(Bottom): Joint Symposium on Simultaneous Drug Development in Beijing, China (May 2016)

India and China

In 2016, the MRCT Center continued working with global regulatory leaders and local stakeholders in China and India to promote the rigorous and ethical conduct of clinical trials. As advisors and capacity builders, we provide international perspectives on country-specific issues and provide recommendations to local regulators and clinical researchers. We strive to harmonize regulations and best practices globally and create worldwide standards for and access to clinical trials.

We continue to engage with and provide resources for regulators and clinical researchers to advance and ensure the integrity of clinical trials.

MILESTONES

INDIA

March 2016

The MRCT Center leadership traveled to Delhi and Mumbai to participate in meetings organized by the Indian Council for Research on International Economic Relations and by the Organisation of Pharmaceutical Producers of India. Additionally, we met with regulators, investigators, and representatives of industry, academia, non-profit organizations, and patient advocacy groups.

CHINA

May 2016

The MRCT Center co-sponsored a joint symposium organized by the Beijing Biometrics Association (BBA), the Beijing Biometrics Forum (BBF) and Johnson & Johnson on the topic of simultaneous drug development. This conference convened more than 120 diverse stakeholders from government, industry, and academia in order to discuss the regulatory, logistical and statistical challenges of global drug development.

September 2016

The MRCT Center conducted, in partnership with industry and academic collaborators, a workshop on MRCTs for senior China FDA leaders at Yale. Topics for the day included the benefits and challenges of MRCTs, international regulatory considerations, rationale for accepting foreign data, and requirements for bridging study data.

To See Our Resources Please go to mrctcenter.org/resources and View by Project

PUBLICATIONS

Responsibilities of Data Monitoring Committees: Consensus Recommendations
Therapeutic Innovation & Regulatory Science, May 2016
http://dij.sagepub.com/content/50/5/648.full

A Global, Neutral Platform for Sharing Trial Data
New England Journal of Medicine, May 2016
http://www.nejm.org/doi/full/10.1056/NEJMp1605348

Incorporating Ethical Principles into Clinical Research Protocols: A Tool for Protocol Writers and Ethics Committees
Journal of Medicine Ethics, January 2016
http://jme.bmj.com/content/early/2016/01/25/medethics-2014-102540

MRCT CENTER-DEVELOPED RESOURCES

MRCT Return of Aggregate Results Guidance Document (Version 2.1) – July 2016

MRCT Return of Aggregate Results Toolkit (Version 2.2) – July 2016

MRCT Post-Trial Responsibilities Guidance Document (Version 1.0) – December 2016

MRCT Individual Return of Results Recommendations Document (Version 1.0) – December 2016

Vivli Website: **Vivli.org**

AWARDS

Annual Award for Best Practice for MRCT Return of Results Guidance,

Awards for Excellence in Human Research Protection, December 2015

EVENTS

March 21 & 22, 2016: The Future of Clinical Trials Data Sharing Conference

June 29, 2016: First Meeting of the MRCT Center External Advisory Board

October 19, 2016: Core Competencies in Clinical Research Workshop

October 24, 2016: Bioethics Collaborative, First Meeting

December 6, 2016: Individual Return of Results Working Group Meeting

December 7, 2016: MRCT Center Annual Meeting

December 9, 2016: Paying Research Participants: Ethical and Regulatory Parameters Symposium

MRCT COMMITTEES

Thank you to our sponsors for contributing your expertise and resources towards improving the quality standards of clinical trials. Your contributions ensure that your institution continues to be a leader in its commitment to the ethical conduct of clinical trials and benefits from best practice discussions and MRCT projects.

EXTERNAL ADVISORY BOARD (EAB)

Launched in June 2016, the EAB reviews and advises the MRCT Center's vision, projects, and long-term strategy. The EAB Provides an outside critical perspectives on our work. We wish to express our sincerest gratitude to the members of the EAB for their time, expertise, and guidance.

Dr. Bernard Lo (Chair)
Greenwall Foundation

Dr. Joshua Boger
Formerly Vertex

Dr. Cristina Csimma
Biopharmaceutical Board Director and Independent Consultant

Dr. Jeffrey Drazen
New England Journal of Medicine

Dr. Atul Gawande
Ariadne Labs

Dr. Margaret Hamburg
Global Advisory Council, Harvard University

Dr. Michael Rosenblatt
Flagship Ventures

Dr. Ara Tahmassian
Harvard University

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Association of Clinical Research Professionals (ACRP)

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Clinical Data Interchange Standards Consortium, Inc. (CDISC)

Chesapeake IRB

Comprehensive and Integrative Medicine Institute (CIMI)

Critical Path Institute

Daegu Catholic University Medical Center

Deloitte Consulting

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MULTI-REGIONAL CLINICAL TRIALS
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