Global Engagement
Dear MRCT Friends,

As we look back on 2014, we are proud of our achievements and very grateful for your ongoing support. It has been a pivotal year for the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT) as we have completed several projects, launched new focus areas and expanded our global reach. Our multi-stakeholder collaborative efforts included contributions from over 120 individuals from patients and patient advocate groups to pharmaceutical representatives, from regulatory experts to academic investigators. These individuals have worked tirelessly this year to help us meet our milestones, frame and initiate new projects and ensure targets were met.

In response to the shifting regulatory landscape we launched a new initiative in January on returning aggregate research results to trial participants. We have vigorously advanced this project and developed a robust framework to enable responsible sharing of results to participants. In September, we laid the groundwork for a future project in post-trial responsibilities to participants following study closeout, including access to medicines. As progress and consensus building is often derived from sharing ideas across diverse viewpoints, we were delighted to welcome over 130 registrants to our Post-trial Responsibilities Conference in September to help us understand the issues and move towards potential solutions.

2014 program highlights include:

- Achieving important new milestones in (1) returning aggregate results to study participants and (2) informed consent guidance for data sharing
- Working towards comprehensive India clinical trial regulatory reform
- Launching new projects in causality determination and post-trial access responsibilities

We have continued to grow our global mission of improving the quality of clinical trials through expanded international collaborations including key players in China, India, Korea and Japan.

This progress report provides a glimpse into the progress and milestones achieved by our working groups. Their tenacity and hard work has yielded great returns. As our center evolves, and awareness of our mission grows, so too does the number of opportunities for collaboration and positive impact.

We hope you agree that your resources of time and financial support have been put to good use over the past year and look forward to working with you in 2015. We welcome our partnership with six new sponsors that have joined us this year and our executive and steering committee that continues to support our efforts.

Thanks to you all, we are well positioned to advance our mission in making a difference in the ethical conduct of global clinical trials.

Barbara Bierer
Co-Chair, MRCT

Mark Barnes
Co-Chair, MRCT

Rebecca Li
Executive Director, MRCT

To improve the design, conduct, and oversight of multi-regional clinical trials, focusing on trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subject research.
We have six primary areas of focus this year that address pressing issues in multi-regional clinical trials.

1. **Clinical Trial Data Sharing and Transparency**
   - We participated in global conversations regarding clinical trial data sharing. We are now striving towards:
     - A framework for best practices for data sharing
     - Concise informed consent language to allow for broader data sharing
     - Adopting an implementable guidance for how to implement a robust return of study results initiative engaging participants as our partners in research

2. **Data Monitoring Committee (DMC) Training**
   - We have created a training curriculum for DMCs to increase engagement of experts from emerging countries.
     - Bringing clarity to the scientific basis for assigning causality
     - Preparation of training materials for experts that will be making these determinations

3. **Investigator Competence and Training**
   - Both the industry’s interest and the public’s interest would be well-served by the development of mechanisms to improve the capacities of investigator teams and sustainable, professionally run research sites. We aim to develop a framework of core competencies for clinical research team members.

4. **Global Regulatory Engagement**
   - We continue to develop substantive partnerships with leaders in the emerging and developing world. We identify major issues in global clinical trial practice and, in our role as advisors, adopt a country-specific and culturally-relevant approach.

5. **Causality Assessment**
   - Compensation for injury is predicated on the determination of “relatedness” of the injury or death to participation in the clinical trial. This initiative includes:
     - Bringing clarity to the scientific basis for assigning causality
     - Preparation of training materials for experts that will be making these determinations

6. **Ethical Frameworks for Conduct of Clinical Trials**
   - Representatives from industry, not-for-profits, patients, and academia join to create practical resources for the ethical design and conduct of multi-regional clinical trials. Areas of emphasis include:
     - Protocol ethics guidance
     - Post trial access responsibilities
Improving Transparency in Global Clinical Trials through Returning Results to Participants

Returning Results

Returning clinical trial results is an important way for investigators and sponsors to honor the essential contributions and voluntarism of study participants in multi-regional clinical trials, while improving the transparency of those trials.

Returning results refers to giving clinical trial participants plain language summaries of the trial results, providing information both about the outcome of the study as a whole, and potentially a more detailed description of the individual participant’s study arm. While major organizations, including the World Medical Association and the European Medicines Agency, have called for sponsors to institute results return programs, sponsors currently face a number of both logistical and regulatory challenges before instituting a return of results initiative.

With these challenges in mind, Harvard MRCT convened a multi-stakeholder working group, comprised of leaders in academia, industry, patient advocacy and health literacy, to create a guidance document and toolkit that will detail practical solutions.

For additional information on this focus area: mrc.globalhealth.harvard.edu/pages/clinical-trial-data-sharing-and-transparency
Building Data Monitoring Committee Capacity Globally

Harvard MRCT recognizes that the countries in which global trials are conducted are often underrepresented in the Data Monitoring Committees (DMCs) that oversee safety for these trials. The goal of the DMC training initiative is to identify, train and recruit experts from emerging regions who have expertise in medicine or statistics, experience in clinical trials, and who would like to serve on Data Monitoring Committees (DMCs) also termed Data Safety Monitoring Boards (DSMBs).

Increasing the Engagement of Experts

The mission is to increase engagement of experts from emerging world countries on DMCs. Recognizing the need for more engagement, Harvard MRCT created a training program in 2012, the ultimate goal of which was to transform motivated individuals into DMC champions within their home country.

Focus in Asia

In 2014, our focus has been in Asia with regional trainings held in China, India and Japan and over 120 total participants trained. DMC trainees are drawn from investigators with demonstrated clinical trials experience and prior biostatistics or bioethics training. Additionally, members of industry, clinical research organizations and regulators have been attending trainings to learn more about how DMCs may be implemented in their country.

We thank our fellow presenters and partners in this important endeavor from: Merck, Amgen, Japan Pharmaceutical Manufacturers Association (JPMA), Drug Information Association (DIA) and the Indian Society for Clinical Research (ISCR).

For additional information on this focus area: mRCTglobalHealth.harvard.edu/pages/data-and-safety-monitoring

Data Monitoring Committee Training Objectives

Learning objectives covered during the interactive training include:

- Understand how a DMC functions to oversee trial safety
- Understand how to establish a DMC for a trial
- DMC member roles and responsibilities
- Understand the concepts of monitoring for futility and efficacy
- Learn how multi-regional clinical trials are monitored
- Review in-country regulations for safety monitoring

DMC Training in Shanghai, China
Harvard MRCT, Merck, and Amgen partner to bring DMC training to China, hosted by DIA China.

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DMC Training in Tokyo, Japan
Harvard MRCT, Lilly and JPMA collaborate to bring DMC training to Japan.

DMC Training in Bangalore, India
Harvard MRCT, Amgen and ISCR partner on DMC training in Bangalore in conjunction with the ISCR annual meeting.

DMC Training in Daegu, South Korea
Harvard MRCT and Daegu Catholic University Medical Center partnered to bring DMC training to South Korea.
PHASE 1: Framing the issues
Against the backdrop of the 2013 revision of the Declaration of Helsinki, Harvard MRCT worked towards exploring the expectations behind paragraph 34. Discussion centered around how various stakeholders viewed post-trial responsibilities.

PHASE 2: Development of a Common Ethical Framework for Post-Trial Responsibilities
The term “post-trial access” is used broadly to connote a wide range of possibilities for providing continued access to study interventions (and potentially other care) once a trial is over, or a subject’s participation has ended.

Areas we will address that currently lack clarity include:
1. How are recommendations regarding post-trial responsibilities influenced by the trial phase and/or prior experience with the intervention?
2. What types of interventions or resources should be included within post-trial responsibilities? Do recommendations include ancillary care, treatment of side effects and adverse events, etc.?
3. What is a reasonable duration for post-trial responsibilities to extend?
4. What is the mission and purpose of various stakeholders (sponsors, governments, investigators, etc.) in the conduct of clinical research and how do these roles intersect with post-trial access responsibilities?

Understanding the Multi-Stakeholder View of Post-Trial Responsibilities

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.
Engaging Regulators in India, Europe, and the U.S.

There is a spectrum of benefits associated with providing broader access to clinical trial data, ranging from fostered trust and accountability to improved exploration and discovery. At our 2013 Annual Meeting, Harvard MRCT engaged the European Medicines Agency (Hans Eichler, M.D.), U.S. Food and Drug Administration (Richard Moscicki, M.D.) and key industry leaders including Perry Nisen M.D., Ph.D. (GlaxoSmithKline) towards solutions for a balanced approach for data sharing standards and rules of engagement.

Clinical Trial Regulatory Reform In India

Crippling Regulations Mean Clinical Trials on Hold

Over the last two years, India has implemented a series of regulations that had a detrimental effect on the Indian clinical research industry. The most damaging provision of the new regulations was the requirement that sponsors provide compensation for any clinical trial participant who is injured or who dies while in a trial, regardless of whether participation in the trial directly caused the injury or death. The provisions also required sponsors to provide compensation for an agent failing to provide its intended therapeutic effect. In response to this increased liability, many global sponsors, such as the National Institutes of Health, placed ongoing clinical trials in India on hold.

Developing Alternative Reforms

After being apprised of the details of this political and regulatory environment by its contacts within India, Harvard MRCT began working with relevant industry stakeholders and government officials to develop alternative reforms that would not only reinvigorate the industry but also ensure the welfare of trial participants. As part of its engagement, Harvard MRCT convened a two-day roundtable discussion in Delhi between leading academicians, investigators, industry representatives, and government officials. The roundtable culminated with Harvard MRCT meeting privately with the Indian Secretary of Health and Family Welfare to detail consensus opinions reached by the roundtable.

For additional information on this focus area:
http://mrct.globalhealth.harvard.edu/pages/global-regulatory-initiative
CAUSALITY ASSESSMENT

A Scientific Approach to Causality Assessment in Clinical Trials

In April 2014, Harvard MRCT partnered with the Indian Society for Clinical Research to establish a Causality Workgroup. The co-chairs of the workgroup are Usharani Pingali of the Nizam’s Institute of Medical Sciences and Shobal Mukherjee of Quintiles. Other integral members of the workgroup include Anirban Ray Chowdhury of Merck, Ritika Bajaj of Biogen Idec, and Veena Jaguste of Amgen. The goal of the workgroup is to create guidance documents and training materials to enable clinicians and ethics committee members to determine causality for participant injuries, illnesses or death occurring in the course of a clinical trial.

As countries such as India begin incorporating causality analysis into their injury compensation mandate, the modules created by the workgroup will assist ethics committees and investigators in making causality determinations.

For additional information on this focus area: mrci.globalhealth.harvard.edu/pages/causality-assessment

DOMAINS AND CORE COMPETENCIES

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

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APRIL 2014
Causality Workgroup Launched in Delhi, India
Harvard MRCT traveled to Delhi to launch the group in conjunction with the Indian Society for Clinical Research and Indian Council for Medical Research. The group’s deliverables and plan for implementation were outlined.

DECEMBER 2014
Causality Training Module and Materials are Drafted for Harvard MRCT Executive Committee Review
This module will be piloted in India November 2014 by Harvard MRCT.

INVESTIGATOR COMPETENCE AND TRAINING

Improve Compliance through Competency

A universally applicable, globally relevant framework that identifies relevant competency domains and associated skills necessary to conduct clinical trials has been developed in collaboration with a number of institutions including ACRP, DIA, MAGI, Transcelerate and others. A competency-based approach has been embraced by several institutions and training organizations to standardize training requirements and define performance evaluations.

Possible uses of and outcomes that can result from the adoption and use of the Core Competency Framework:

- Education
  - Standardizing educational requirements
- Job Descriptions
  - Defining job descriptions
- Site Qualification
  - Defining criteria for site selection and qualification
- Investigator Selection
  - Defining criteria for investigator selection
- Development of Accreditation Standards
  - Defining standards for accreditation
- Training Requirements
  - Standardizing and streamlining training requirements

For additional information on this focus area: mrci.globalhealth.harvard.edu/pages/investigator-competence

MILESTONE

SUMMER 2014
Simultaneous publication of the framework in Clinical Researcher, Journal of Clinical Research Best Practices and Applied Clinical Trials
The core competency framework attempts to bridge the gap between “what to do” and “how to do it.” The framework identifies competency domains and associated cognitive skills required to conduct a quality and ethical clinical trial.

**2014 ACCOMPLISHMENTS**

**CLINICAL TRIAL DATA SHARING & RETURN OF RESULTS**

**RETURN OF RESULTS**

**Return of Results Summary Guidance**
A practical guidance document for all sponsors (industry, non-profit, academic) that addresses key challenges in returning results and potential solutions.

[Link](http://mrcglobalhealth.harvard.edu/harvard-mrct-return-results-guidance-2014)

**Health Research Authority Draft Document “Guidance on Participant Information at the End of a Study (Active)” Comments**
Harvard MRCT commented on a number of important areas in this document that would benefit from further consideration and/or clarification.

[Link](http://mrcglobalhealth.harvard.edu/harvard-mrct-comments-uk-hra)

**INFORMED CONSENT AND DATA SHARING**

Harvard MRCT commented on this new proposed guidance including considerations for inclusion of individuals of low literacy and numeracy, non-English speakers, and vulnerable populations.

[Link](http://mrcglobalhealth.harvard.edu/files/mrct/files/harvard_mrct_fda_ic_final_comments_9_12_14.pdf)

**Harvard MRCT Provides Informed Consent Template Language to Enable Data Sharing**
Harvard MRCT’s Data Sharing Implementation workgroup has drafted language that may be used in consent forms to enable confidential data sharing.

[Link](http://mrcglobalhealth.harvard.edu/pages/clinical-trial-data-sharing-and-transparency)

**GLOBAL REGULATORY ENGAGEMENT**

**Executive Summary of AIIMS/Harvard MRCT/AHERF Roundtable**
Summary of recommendations embodying the consensus of various stakeholders including leading academics, industry and government officials who attended the invitation-only meeting on regulatory reform in India.

[Link](http://mrcglobalhealth.harvard.edu/executive-summary-aiimsharvard-mrctaherf-roundtable)

**Financial Express “Clinical Trials, a Lost Opportunity for India”**

[Link](http://mrcglobalhealth.harvard.edu/india-clinical-trials-op-ed-financial-express)

**PROTOCOL ETHICS**

**Post Trial Access Responsibilities**
Proceedings from September 18th conference highlighting the range of perspectives on this issue.

[Link](http://mrcglobalhealth.harvard.edu/mrct-post-trial-responsibilities-conference-proceedings-september-18-2014)

**Ethics Training Module Launched with Partner Global Health Training Centre**
An e-learning resource was created by the University of Oxford’s Global Health Network adapted from the Harvard MRCT Ethics Tool kit to promote clear documentation of ethical issues in the design of studies.

[Link](http://globalhealthtrainingcentre.tghn.org/essential-elements-ethics/)

**CAUSALITY ASSESSMENT**

**Training Module for Causality Assessment Released**
A best practice primer for determination of causality of an adverse event and likelihood it is caused by the investigational product. This guidance can be used to deliver training in various international settings.

[Link](http://mrcglobalhealth.harvard.edu/pages/causality-assessment)
Thank you Harvard MRCT friends for making 2014 a year of tremendous progress.

We are so grateful for all of you that have been on this journey with us towards a better world for clinical trials. Your work as co-chairs, workgroup members, reviewers and ambassadors for Harvard MRCT is greatly appreciated.

Moving Forward into 2015

We will not falter from our mission to impact pressing issues in multi-regional clinical trials and we will continue to build our work globally.

We look to 2015 to be one in which we continue at an invigorating pace, forge new partnerships and make even greater strides. We will delve deeper into areas such as offering guidance in regulatory harmonization in the area of returning results to study participants and the provision of access to medicines to participants after a trial has ended. We also hope that we might engage those of you that have not yet actively participated to bring new perspectives and solutions to the challenges you face in your own work.

This year we have expanded our stakeholders to include more patient advocates and investigators in our work—those at the front lines of clinical research and those most directly impacted by our projects. We look to include patients, patient advocates and investigators in all aspects of our work in 2015.

We also hope to expand our sponsor base of support and collaborators to ensure our objectives and projects can expand to meet the needs of the global clinical trials community.

Thank you,
The Harvard MRCT Team

THANK YOU FOR CONTRIBUTING YOUR EXPERTISE to improve the quality standards for global clinical trials and for engaging with other like-minded organizations and stakeholders to address the common challenges associated with globalization of clinical research. Your commitment ensures that your institution continues to be a leader to the ethical conduct of clinical trials and benefits from best practice discussions and Harvard MRCT projects.

EXECUTIVE COMMITTEE

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Veristat
ViS Research Institute
Western Institutional Review Board
Copernicus Group
Multi-Regional Clinical Trials (MRCT) Center
14 Story Street, 4th Floor
Cambridge, Massachusetts 02138
617-496-8063
mrct@harvard.edu

The MRCT Center at Harvard