Proceedings
Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard
5th Annual Meeting

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Loeb House at Harvard University • Cambridge, MA

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Executive Summary

The major themes of the MRCT Center 2016 Annual Meeting included the **draft ICH E17 guidelines**, **data sharing and data transparency**, and **the individual return of results**.

Dr. William Wang (Merck & Co., Inc.) and Dr. Laurie Letvak (Novartis Pharmaceuticals Corporation) discussed the draft ICH E17 guidelines. Dr. Wang explained the history and present state of ICH E17, which delineates guidelines for the development of multi-regional clinical trials (MRCTs) for drug development and approval in regulatory authorities around the world. Dr. Letvak reviewed several comments that emerged at a summit held in Osaka, Japan and were integrated into the document, including topics such as harmonization among regulatory authorities, consistency across regions, definition of region and subpopulation, and sample size requirement for regions. A group discussion followed, addressing issues ranging from how to define a region and the jurisdiction barrier to sample size and drug lag.

Second, data sharing and data transparency were addressed, including the MRCT Center's work to create Vivli, an independent non-profit center for global research data. Invited speakers shared their insights on this pivotal topic, including:

- Dr. Murray Stewart (GlaxoSmithKline), the keynote speaker, addressed the current state of data transparency, and the value of global clinical trial data sharing. He stated that Vivli could address critical needs in the current landscape for a comprehensive data sharing platform. During the panel discussion, Dr. Stewart offered suggestions for optimizing secondary findings of studies, including crowdsourcing questions and further involving patients to discern what is important for patients to gain from clinical trials.

- Dr. Jeffrey Drazen (New England Journal of Medicine) reviewed the SPRINT Data Analysis Challenge sponsored by the New England Journal of Medicine, which promotes the secondary use of clinical trial data. Dr. Drazen urged stakeholders to align their incentives in order for data sharing and data transparency to succeed.

- Dr. Amita Gupta (Johns Hopkins University) detailed her experience leading the first NIH-funded Phase III HIV prevention trial in India. Dr. Gupta stressed that trust of and commitment to the community were critical for the trial's success, and stated that more work remains to be done to improve oversight and guidance of data sharing.

Discussion between panelists and conference participants focused on how to increase the use of secondary data. In addition, common data standards and trial questions, as well as investigator-participant expectations, patient involvement, and the imbalance of power in data ownership, were discussed.

Finally, in 2016 the Individual Return of Results (IRR) Working Group presented two major deliverables: the IRR Recommendation Document and IRR Toolkit. Members of the Working Group—Dr. Debra JH Mathews (Johns Hopkins University), Dr. David Pulford

(GlaxoSmithKline), and Dr. Sandra Prucka (Eli Lilly and Co.)— provided an overview of the workgroup's objectives, methodology, and next steps.

Invited speakers offered their perspectives on the individual return of clinical trial results, and suggested revisions on the MRCT Center's IRR documents, including:

- Dr. Atul Gawande (Ariadne Labs, Harvard T.H. Chan School of Public Health, and Harvard Medical School) relayed the challenges and points to consider in returning individual results to participants in light of current rules and regulations of drug development and health system trials.

- Ms. Barbara LeStage (Clinical Trials Transformation Initiative) emphasized the critical need to consider informed consent, asserting that patients have the right to refuse information, even in the case of urgent or life-threatening findings.

- Dr. Alvaro Pascual-Leone (Beth Israel Deaconess Medical Center and Harvard Medical School) argued for the use of a medical navigator—independent from the research team—to facilitate the informed consent process, avoiding conflicts of interest and preserving patient autonomy and the fiduciary patient-physician relationship.

- Dr. Holly Taylor (Johns Hopkins University) recommended that the IRR Working Group strengthen the ethics section of the guidance document, which includes making the document more accessible to particIpants and expanding the scope of the document beyond clinical trials.

Discussion between panelists and conference participants focused on when to give patients informed consent and the value of evolving this document as the science and medicine advance, as well as addressed concerns regarding returning incidental findings and over-diagnosis.

Welcome and Introduction

Mark Barnes, J.D., LL.M., and Barbara Bierer, M.D., MRCT Center

MRCT Center Faculty Co-Directors, Mr. Barnes and Dr. Bierer opened the meeting and reviewed the mission of the MRCT Center: to engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions. They thanked the MRCT Center sponsors, who provide financial support and invest significant time and energy into the MRCT Center's projects. Two new members of the MRCT Steering Committee were announced: Duke Clinical Research Institute (DCRI) and UCB.

Impact of Draft ICH E17 Guidelines

Introduction to ICH E17 Guidelines

Mark Barnes, J.D., LL.M., MRCT Center

Mr. Mark Barnes, the Faculty Co-Director & Co-Chair of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center), summarized the newly issued draft ICH E17 guidelines and their impact on multi-site/multi-regional clinical trials. The ICH E17 draft addresses issues related to the role of multi-regional clinical trials in drug development, a topic which continues to be debated.

The goal for the first panel of the MRCT Center Annual Meeting was to convey the intent and scope of the draft and discuss the initial feedback received from various stakeholders in order to improve upon the current model. As members of the ICH E17 working group, Drs. Wang and Letvak presented the objectives, scope, impact and feedback they have received to-date.

The Scope and Impact of Draft ICH E17 Guidelines

William Wang, Merck & Co., Inc.

Dr. William Wang, Executive Director of Biostatistics at Merck & Co., Inc., provided a summary of the history and current status of the E17 draft, which is out for public comment in Europe. A final version is targeted for release at the end of 2017. Dr. Wang highlighted the objectives, intended impact and key points of the document.

The purpose of E17 is to describe general principles for the planning and design of multi-regional clinical trials (MRCTs) with the aim of increasing the acceptability of MRCTs in global regulatory submissions. The guidelines focus on those MRCTs designed explicitly to provide data that will be submitted to multiple regulatory authorities for drug approval (including approval

of additional indications, new formulations and new dosing regimens). MRCTs conducted to satisfy post-marketing requirements are also covered under the guidelines.

The ICH E17 guidelines are intended to facilitate drug development in a number of ways, including: (1) avoiding duplication of trials through minimizing the number of standalone regional studies (including bridging studies), (2) promoting international harmonization, (3) accruing more rigorous data for drug approval in each region by encouraging better planning and design of MRCTs based on the latest scientific knowledge and experiences, and (4) delivering innovative therapies to patients more quickly.

The 20-year journey from ICH E5 to ICH E17 was reviewed. ICH E5 was initially developed in 1995 to identify the extrinsic factors of drug use and extrapolate these principles to other regions. E17 is the next step in the era of global drug development. Instead of "bridging" studies, E17 encourages "simultaneous" drug trials. This parallel trial system is consistent with the commitment to move from a local mindset to a global understanding of drug application and effect. A primary assumption made under ICH E17 is that an MRCT is generally the preferred mechanism for investigating a new drug for which the treatment effect is clinically meaningful and relevant to all regions being studied.

Dr. Wang described additional operative concepts in the ICH E17 draft, including "pooled populations." This term refers to participants in those regions that are considered similar with respect to intrinsic or extrinsic factors relevant to the disease area and/or drug under study. In this way, researchers "borrow strength" from prior knowledge of study populations when considering pooled populations. For example, to study how an investigational drug effects in Japanese participants, a researcher may "pool" individuals of Japanese ethnicity across regional boundaries.

With respect to determination of overall sample size, the guiding principle for MRCTs is that the primary hypothesis may be assessed by combining data from all regions in the trial. Sample size allocation to regions (or pooled regions) should be determined such that clinically meaningful differences in treatment effects among regions can be described without substantially increasing the sample size requirements.

Laurie Letvak, M.D., Novartis

Dr. Laurie Letvak, the head of clinical policy development at Novartis Pharmaceuticals Corporation, reviewed the proceedings of the recent ICH summit in Osaka, Japan, where over 800 public comments on the draft ICH E17 were reviewed.

Four key themes in the comments submitted on the draft:

> **(1) Harmonization among regulatory authorities** – This is a key challenge specifically regarding how these discussions should be structured. Should industry facilitate this discussion? How can harmonization be accomplished given the divergent priorities and

resources of the different regulators? An additional barrier to harmonization is differing guidance among regulators.

(2) Consistency across regions - How should consistency be defined? What is the threshold for variability? Who should adjudicate consistency (e.g., regulatory agency, sponsor)? Variability also stems from a number of different sources, including: biological plausibility, consistency of findings internally and externally, strength of evidence, and statistical uncertainty.

(3) Definition of region and subpopulation – How should region or sub-population be defined? Whether the study population is defined by a geographic region or a sub-population, it is a surrogate (for drug metabolism or genotype for example).

(4) Sample size requirement for region – One concern raised was the sample size requirement for each region. For example, China and Japan require a certain number of participants for each clinical trial (representation requirements). These requirements tend to inflate the overall sample size and may at times be unnecessary.

ICH E17 is intended to be a tool for regulators and researchers and to encourage stakeholders in clinical research to strategize and collaborate on key practices. It is not intended to require stakeholders to harmonize practices. Currently several regulators (US, EU, and Japan in particular) collaborate to review data, but this type of collaboration occurs infrequently in the planning stage. In the final version of the document, examples and case studies will be incorporated. Drs. Letvak and Wang were gratified to see that there has been significant participation from regulators to improve the document.

Panel Discussion/Questions

How does ICH E17 address requirements for overall sample size?

Researchers using conventional trial methods often struggle to recruit a sufficient number of participants. The multi-regional approach attempts to alleviate these issues by broadening the base for recruitment; however, incorporating many countries in one trial can inflate the overall sample size (due to regional requirements). For multi-regional clinical trials to be effective, sample sizes must balance statistical principles and logistical limitations.

How does ICH E17 address the current drug lag facing many countries?

It is envisioned that well-designed multi-regional clinical trials, in accordance with ICH E17 guidance, will accelerate drug approval and access. The traditional system of drug development is slow and unsustainable. Because global citizens will receive the drug sooner, the innovative approach to MRCTs outlined in ICH E17 would help meet public health needs.

How does early stage planning factor into the overall strategy outlined in E17?

While guidance for Phase I is included in the document, ICH E17 focuses on confirmatory trials. The goal was to encourage sponsors to consider Phase I MRCTs in certain cases and to encourage planning at earlier stages in order to move towards global approval.

Early stage planning may help to break down some jurisdictional barriers, while also informing later decision about design and regulatory involvement. Conducting an MRCT at an early stage, may turn some of the 'unknown' factors into 'known' factors.

How can non-ICH regions and countries that would benefit from this guidance be encouraged to align with the principles of E17?

The ICH team has been socializing the themes of E17 and working on dissemination. Regulatory jurisdiction should be respected, and this guidance should be tailored to the specific cases if necessary. We encourage regulations to be driven by science rather than political or other non-scientific considerations.

Data Sharing and Data Transparency

Keynote: Data Transparency Today and Tomorrow: Current State, Issues, and Vision

Murray Stewart, M.D., GlaxoSmithKline

Dr. Murray Stewart presented on the state of, rationale for, and challenges to clinical trials data sharing. In addition, Dr. Stewart offered his perspective on and vision for greater transparency.

Rationale for sharing data includes: (1) furthering scientific knowledge and improving patient care and outcomes, (2) decreasing risk to trial participants by avoiding enrollment in duplicative trials, and (3) enabling the review of results from individual clinical trials to validate the results. Moreover, the association between transparency and trust leads Dr. Stewart to believe that sharing clinical trial information may help rebuild the reputation of the pharmaceutical industry. He also emphasized the importance of sharing negative trials and associated data.

The current system used to share clinical trial information is fragmented. Although participants have access to individual databases on clinical trials, they often do not utilize these systems; this discrepancy gives the impression that industry is not committed to transparency. To solve this matter, Dr. Stewart envisioned a broad, independent global solution to allow access to data from clinical trials conducted by multiple companies and organizations. His ideal situation would include only one system, which would bring together the multitude of industry and company members, while also be responsive to the current landscape.

Dr. Stewart mentioned practical points to consider with respect to data sharing, which include: ensuring valid science; risk minimization with attention to participant safety and privacy; funding and equitable distribution of cost; monitoring and oversight; data interoperability; and data ownership. In order to achieve Dr. Stewart's ideal vision for data sharing, each of these issues

will require a thoughtful response and support from industry, academic, and government members.

Dr. Stewart voiced his confidence in the future and in Vivli – the MRCT Center's global platform for data sharing. Vivli is the ideal solution to connect existing platforms (CSDR, Yoda-J&J, DCRI-BMS) and non-industry platforms (NIH and others), while serving as neutral entity to spur academic data sharing and harmonize and standardize governance.

Progress in 2016 and Outlook to 2017

Rebecca Li, PhD, MRCT Center

The MRCT Center is interested in sharing data from clinical trials (including de-identified individual participant data (raw data), metadata, and summary-level data) with other researchers and the general public. Dr. Rebecca Li, Executive Director of the MRCT Center, summarized the Center's efforts in the return of results to researchers.

As a neutral convener, the MRCT Center has brought together various stakeholders (e.g., industry, non-profit, patients, academic, government, journal editors) to create an implementable solution for data sharing and address issues in policy, advocacy, and implementation. The MRCT Center's data sharing workgroup is divided into three subgroups; (1) governance, (2) information technology (IT), and (3) business models.

Policy efforts have focused on harmonizing language and agreements on data sharing among different sectors, including academia, industry, and non-profits. The governance workgroup has developed the 'Data Contributor' and 'Data Use' agreement. Additionally, the workgroup has drafted informed consent documents for data sharing and an Independent Review Panel (IRP) Principles document, which outlines the requirements for any participating IRP for Vivli.

Advocacy efforts have focused on lowering the barriers to data sharing. Specifically, the MRCT Center has (1) convened stakeholders who are currently sharing and those who do not currently share, (2) equipping individuals and institutions with the resources or knowledge to share data, and (3) advanced policy changes that enable academic credit for data that are made widely available for the advancement of science and medicine.

A secondary objective for advocacy is to providing academic credit for data sharing. The current system does not incentivize investigators who share their data. The MRCT Center aims to develop practical, comprehensive recommendations on how data generators should be recognized for the design, curation, completion and dissemination of quality data sets. One such example is the designation 'Data Authors,' a term for those who are responsible for the integrity and curation of the dataset. Currently, the MRCT Center is collaborating with academics, technical experts, researchers, regulators, journal editors to develop a system that would establish and recognize this designation. In its turn, data authorship could factor into decisions on promotions, tenure, funding, and beyond.

The MRCT Center is a unique multi-stakeholder effort that can elucidate the significant variability in different stakeholder positions and promote an interoperability between working groups. Vivli is an example of this concept being operationalized. The scope of Vivli includes:

Collaboration with the diverse stakeholders of the MRCT Center has allowed the plans for Vivli to take into account the different needs of researchers globally. In this capacity, the MRCT Center can also promote cooperation and interoperability between these groups. The scope of Vivli includes:

1) Hosting data for stakeholders that do not have the ability to do so;
2) Enabling interoperability of data from multiple sources;
3) Coordinating and integrating existing data-sharing initiatives, policies, and processes as appropriate;
4) Promoting reasoned solutions to challenges of data sharing.

What sets Vivli apart from other data sharing platforms its advanced **metadata search** and **discovery** of data residing on other platforms. As the enhanced metadata catalog matures, more data, including externally hosted data, will be discoverable through Vivli.

In the near term, Vivli has the potential to share not just clinical trials data but also real-world patient data, outcomes data, and public health data. This expansion could promote the safety and efficacy evaluation of medical and public health interventions, as well as aid real-time public health decision-making through the use of aggregated public health data.

Responses from Key Stakeholders

Jeffrey Drazen, M.D., New England Journal of Medicine

Dr. Jeffrey Drazen reported on the efficacy and enthusiastic response to the SPRINT Data Analysis Challenge sponsored by the *New England Journal of Medicine*, which aims to promote data sharing and the secondary analysis of data.

As a community, industry, academia, and other stakeholders strive to share clinical trial data in order to honor the human participants who put themselves at risk in research trials. Dr. Drazen identified this as reciprocity, wherein the sponsors recognize the altruism, sacrifices, and efforts of research participants.

For data sharing and data transparency to succeed, Dr. Drazen believes that the stakeholders will need to align their incentives. Only when everyone benefits will a long-lasting, commitment to transparency follow. Vivli represents one mechanism for doing this and there will be other systems as well that will be in use and can serve as potential solutions.

Amita Gupta, M.D., MPH, Johns Hopkins University

Dr. Amita Gupta shared her experience leading the first NIH-funded Phase III HIV prevention trial conducted in India, which aimed to block breast milk associated HIV transmission with the antiviral drug Nevirapine. For the trial to succeed, it was essential to earn community trust and to commit to working in limited resource and infrastructure environment.

Dr. Gupta and her team were asked several probing questions during the trial: What did the investigators seek to benefit from in the trial? Why should government employees (e.g., obstetricians, pediatricians), who already had a large volume of patients, be involved? What would ultimately happen to the data collected? Who owned the data? How would the data be analyzed? Dr. Gupta reminded the audience that these issues needed a thoughtful approach. Local colleagues resisted sharing or pooling the data, citing their belief that the data were unique or owned by them. Ultimately, trust was built between the group members and the data were shared and published.

See revised paragraph below: Dr. Gupta concluded insisted that their long-term outlook, commitment to the public good, and increased longitudinal development of scientific knowledge, scientific writing skills, data analysis, led to trusting relationships and continued success in clinical trial research in India. Further work needs to be done to improve oversight and guidance of data sharing and increase trust.

Dr. Gupta emphasized that the research team's commitment to the public good and the development of scientific analytical skills and knowledge helped to establish trusting relationships and ensure the continued success of clinical research in India. Dr. Gupta encouraged the pursuit of further work to increase trust in and oversight of data sharing.

Murray Stewart, M.D., GlaxoSmithKline

Skeptics of data sharing have understood the lack of secondary research and analysis as evidence of the progress and value of data sharing. Dr. Murray Stewart, however, noted that this indicates shared data is an untapped resource.

Dr. Stewart suggested several ideas for encouraging secondary analyses and for generating greater utilization of these studies. He asserted that there were three reasons why scientists hesitate to request clinical trial data from sponsors for secondary findings research. First, scientists are too intimidated. Second, scientists are often unaware of the questions that have already been asked, nor can they produce new ones. Third, scientists have a difficult time

translating their clinical question into a statistical format to be solved using quantitative methods. Secondary findings research may increase if these problems were addressed.

Dr. Stewart also suggested clinical trialists should consider crowdsourcing questions and increasing patient involvement. Asking what is most important for participants to discover would, in turn, help researchers design clinical trials that are valued by participants.

Panel Discussion

The panel of key stakeholders, moderated by Rebecca Li, addressed the following issues, in response to questions from audience participants:

How might we increase the use of secondary data?

Panelists suggested, as a short-term solution, incentivizing secondary analyses of clinical trial data, which may increase awareness and underscore the value and potential of shared data. The New England Journal of Medicine's SPRINT Data Analysis Challenge is one such example. Researchers would be encouraged to take a novel approach to analyzing existing data, which would be rewarded with a monetary prize, academic credit, or international acclaim. A similar model could be used by sponsors and journal editors in the future.

Are there technical barriers to more widespread data sharing?

In order to facilitate work across data sharing platforms and to encourage extrapolation of data in secondary analysis, data should be collected according to a common set of standards. Interoperability depends upon coherency and a certain level of technical competency.

In addition, investigators have a difficult time framing their clinical question in scientific terms. Support in this area would assist in the technical aspect of data analysis and statistics.

Are managing investigator-participant expectations a challenge to sharing data?

Investigator-participant expectations should be outlined at the beginning of the trial to ensure transparency. This set of rules established a priori in any study or trial—and revisited throughout the trial—will assist in managing the expectations of both the investigator and the participant.

How should the inequity between low resource and higher resourced regions be managed?

Data ownership can result in a power imbalance (e.g., between the Global North and Global South). There is not always fair and equitable distribution of power amongst stakeholders, who include (but are not limited to) clinical trial participants, clinical trialists, data analysts, and other. Each may share key concerns about the ownership of, access to, and interpretation of data. Thoughtful discussions need to take place in order to align incentives and encourage collaboration and trust. Data sharing and transparency initiatives ought not to exacerbate power

imbalances (scientific, social, political, etc.). They must instead work towards establishing equity.

Individual Return of Results Working Group (IRR)

Remit of the Working Group and Overview of IRR Principles

Barbara Bierer, M.D., MRCT Center

The MRCT Center is interested in the sharing of data from clinical trials with other researchers and the general public, including de-identified individual participant data (raw data), metadata, and summary-level data.

Many patients desire to receive individual research data from clinical studies in which they have participated. Standards to facilitate the return of individual research results are lacking, making it difficult to determine whether, what, when, how, by whom, and to whom results are to be returned. To address these issues in returning individual research results to study participants, an international multi-disciplinary working group was launched, coordinated and organized by the MRCT Center. The Individual Return of Results (IRR) Working Group developed a framework for and recommendations on the types of individual research results, benefits and risks of returning them, and related operational issues of returning individual level results. The IRR Working Group debuted this draft framework at the MRCT Center Annual Meeting.

Debra Mathews, PhD, Johns Hopkins Berman Institute

Dr. Debra Mathews reviewed the process, products, and next steps of the IRR Working Group. The objectives of this work group include: (1) determining types of individual research results (IRR) to be offered to participants, (2) developing principles for return of individual results that may be implemented and adopted by all sponsors, researchers and investigators involved in the clinical trial enterprise, and (3) defining methods to plan for return of individual results to participants.

The two deliverables from the group are an IRR Recommendation Document and an IRR Toolkit. The methodology used in developing Version 1.0 of these documents began with sourcing real-life case studies from working group members that were then evaluated to identify and categorize both ethical and practical issues. Based on the categories, the group created a master list of relevant specific issues to be addressed. A set of guiding principles was then created. The Recommendations Document and Toolkit were drafted thereafter. The group integrated commentary from the IRR workgroup meeting—which met on the day prior to the MRCT Center Annual Meeting—and included two additional principles: IRB review and Informed

Consent. The group intends to return to the case studies in order to validate the principles and recommendations.

A subsequent version will include a section dedicated to genomic considerations for IRR. A survey is being designed to understand communication channels between sponsors, Principal Investigators (PIs), primary care providers, and participants. The next phase will include a dissemination and implementation plan for PIs and sponsors, and the development of educational and training materials.

Version 1.0 of the IRR Recommendation Document includes eight key principles for IRR. These principles address who should receive the individual results, the responsibilities of sponsors and investigators, the ways in which results should be shared, and the purpose of returning individual results to participants.

Next steps after the MRCT Annual Meeting include integrating feedback from key stakeholders and audience and finalizing Recommendations Document and Toolkit.

Responses from Key Stakeholders:

Atul Gawande, M.D., MPH, Ariadne Labs, Harvard T.H. Chan School of Public Health; Harvard Medical School

Dr. Atul Gawande remarked that the return of individual clinical trial results has not been aligned with current rules and regulations of drug development and health systems trials. It will take time, he believes, for the regulations to harmonize with the practices of returning results. In his experience, return of results in health systems is a challenge. Reporting critical results is streamlined in academic institutions, whereas smaller, regional centers may not have the same infrastructure and capabilities.

Over-diagnosis, Dr. Gawande noted, is a second point to consider. Incidental results that lead to clinical action are often invasive (e.g., discovering cancer via MRI that leads to the operating room). He recommended that this issue should be addressed, taking into account the risks and benefits of such interventions.

Dr. Gawande posited that that the return of results in implementation and systems trials draw upon the limited financial, technical, and personnel resources of clinical trials. He raised additional questions including: How do we balance ethics and our limited resources? Is it sufficient to return results through media in certain cases? Can results be returned through government officials? How will we handle large-scale studies? Dr. Gawande recommended that some of these challenging cases be included in the case-study collection.

Barbara LeStage, M.H.P., Clinical Trials Transformation Initiative

Ms. Barbara LeStage, a patient advocate, discussed the necessity of adequate informed consent, during which the participant can determine whether findings may be received or withheld. She believes that the patient has a right to refuse information, even if urgent or life-saving. Therefore, decisions about receiving or refusing information should be clarified in the informed consent process; this issue should receive special attention in the MRCT Center's IRR documents. Ms. LeStage reminded the audience that the views espoused by the researchers should not be translated as the view of the participant.

Alvaro Pascual-Leone, M.D., PhD, Beth Israel Deaconess Medical Center, Harvard Medical School

Dr. Alvaro Pascual-Leone offered some questions based on his experiences in neurology and incidental findings: What if patients do not have designated primary care physicians? To whom, then, do sponsors return the information? Who should be returning the information and managing the possible conflicts of interest that may result depending on the research setting (e.g., patient care or research)?

Dr. Pascual-Leone made a strong case for use of a medical navigator, who would serve to facilitate the informed consent process and would be a role separate from the research team. The goal is to bridge between the primary care physician and the patient/participant, and to ensure the patient is entirely aware of the consequences of receiving or refusing incidental findings information. The concept is consistent with the desire to preserve patient autonomy and the fiduciary patient-physician relationship. The current discussion raises the question: If the patients opt out, is there still a responsibility to ensure the patient's wellbeing? Dr. Pascual-Leone suggested that the information could still be useful as a manifestation of the pathology leading to the medical problem.

Holly Taylor, PhD, MPH, Johns Hopkins University

Dr. Holly Taylor suggested strengthening the ethics section in the guidance document to improve the justification for the approach described and to educate end-users. In particular, she recommended elevating several ethical principles including favorable risk/benefit ratio, accountability, integrity, social justice alongside the traditional four principles (autonomy, beneficence, nonmaleficence, justice). The idea of personal utility was particularly relevant to this discussion, and it deserves full treatment in the document.

Other points to consider mentioned by Dr. Taylor included, (1) broadening the scope of the recommendations document to more than clinical trials (e.g., observational trials), (2) increasing the level of readability for participants (i.e., currently very sponsor-centric), (3) acknowledging that both IRR documents assume a functioning health care system and a U.S.-based system of ethics, and (4) recognizing that a coordinated team of professionals may be needed to disclose results when individual circumstance may exceed current professional expertise.

Panel Discussion

The panel of key stakeholders moderated by Barbara Bierer addressed the following issues, in response to questions from audience participants:

Discussion/Questions

When should the decision to receive or withhold results be made?

This issue of timing is not specified in the principles. Some participants may choose not to receive their information; therefore, it may be optimal to complete an early informed consent agreement. Overall, it is important to respect the decision to opt out, regardless of how dire the disease/implications. Additionally, it is important to remember that re-contacting patients is difficult and HIPAA rules may present challenges. Revisiting informed consent later in the trial, prior to returning the results, is an important part of the process, as some participants may change their mind over the course of the trial.

How might the ethical justification of returning results be improved?

The panel emphasized enhancing the ethical justification of the recommendations. There was further discussion and debate about whether the need to communicate results outweighs the potential negatives of increasing transparency, and whether to return results using a tiered methodology may be a way to manage this challenge.

What may be done to address the issues surrounding incidental findings?

The panel discussed the challenge that health systems encountered in the return of incidental findings. 'Fishing' may occur during imaging studies or whole panel results, yet there is not always a step-wise action to returning these findings, which may lead to malpractice lawsuits. The consent form should include this return process, and it is critical to ensure a clinician will take responsibility for the process. When incidental findings are identified, test results may expose patients to more invasive opportunities. There is a needed to develop guidance on dealing with over-diagnosis and incidental findings, when disclosure may lead to more interventions and more harm.

The panel applauded the overall effort of the IRR Working Group, who will take into account the panel's suggested revisions in order broaden the impact of their work.

Closing Remarks

Barbara Bierer, M.D., and Mark Barnes, JD, LLM, MRCT Center

In their closing remarks, the leaders of the MRCT Center thanked all of the speakers and attendees for their active participation during the meeting. The MRCT Center has received and will continue to receive important feedback from stakeholders and community members to help focus its work and mission in its core areas of focus. They remarked that this is only possible with the continued enthusiasm and commitment of the sponsors and wider community which is greatly appreciated. They thanked all participants, sponsors, and encouraged continued engagement throughout the next year.

Appendix 1: Meeting Participants

Last Name:	First Name:	Institution:	Job Title:
Aldinger	Carmen	MRCT Center	Program Manager
Alesci	Salvatore	Takeda Development Center Americas, Inc.	Head R&D Global Science and Bio Medical Policy
Allen	Mary Ellen	Genentech, Inc.	Assistant General Counsel
Bahador	Behtash	CISCRP	Program Manager
Barnes	Mark	MRCT Center / Ropes & Gray, LLP	Faculty Co-Director
Bienfait	Karina	Merck & Co., Inc.	Principal Scientist
Bierer	Barbara	MRCT Center / Harvard Medical School / Brigham and Women's Hospital	Faculty Co-Director
Bolt	Kristen	MRCT Center	Program Manager
Brickman	Marla Jo	Pfizer, Inc.	Senior Director / Team Leader
Childers	Karla	Johnson & Johnson	Senior Director, Strategic Projects
Clary	Cathryn	Novartis International AG	Global Head, Patient Affairs and Policy, CMO
Clyburne-Sherin	April	Sense About Science USA	AllTrials USA Campaign Manager
Cohen	Theodora	Baim Institute for Clinical Research	Executive Director, Biostatistics and ARO Services
Coulbourne	Kelly	AstraZeneca	Information Manager
Cullinan	Patrick	Takeda Pharmaceuticals International, Inc	Senior Director, Clinical Data Transparency
Daniels	Louisa	Pfizer, Inc.	Vice President & Assistant General Counsel
Drazen	Jeffrey	New England Journal of Medicine / Harvard Medical School	Editor-in-Chief

Fingert	Howard	Takeda Pharmaceuticals International, Inc	
Flaherty	Jamie	Ropes & Gray, LLP	Associate
Foldesy	Robin	Quintiles IMS Consulting Services	Vice President, Project Management
Frielich	Jonah	CISCRP	Assistant Project Manager
Galperin	Julia	Roche	Global Head Regulatory Disclosures, Data Sharing
Gawande	Atul	Ariadne Labs / Harvard T. H. Chan School of Public Health / Harvard Medical School	Executive Director / Professor / Professor of Surgery
Gelinas	Luke	Harvard Law School	
Goldsmith	Jennifer	Brigham and Women's Hospital	Director of Administration, Global Health Equity
Gupta	Amita	Johns Hopkins School of Medicine	Associate Professor
Houman	Fariba	Massachusetts Eye and Ear and Schepens Eye Research Institute	Director of the Human Research Protections Program
Hurley	Elisa	Public Responsibility in Medicine and Research	Executive Director
Ivanushko	Olga	GlaxoSmithKline	Student
Jackson	Camille	Pharmaceutical Research and Manufacturers of America	Senior Director
Jacobs	Sheryl	Amgen Inc.	Vice President, Global Study Operations (GSO)
Jeong	Jaehong	Daegu Catholic University Medical Center	Medical Researcher / GUMC Affiliated Scholar
Kabacinski	Christopher	MRCT Center	Program Coordinator
Kiesler	Alison	Amgen Inc.	Sr. Project Manager
Krause	Janet	Biogen-Idec	
Kroft	Joanna	Biogen-Idec	
Kush	Rebecca	CDISC	President and CEO
Larson	Sarah	Biogen-Idec	Director, Clinical Trial Transparency
LeStage	Barbara	Clinical Trials Transformation Initiative	Steering Committee Member and Patient Advocate
Letvak	Laurie	Novartis International AG	Vice President, Head, Clinical Policy and Medical Ethics
Levenstein	Marcia	Pfizer, Inc.	Vice President, Statistics
Leventhal	David	Pfizer, Inc.	Director, Clinical Innovation
Li	Rebecca	MRCT Center / Harvard Medical School	Executive Director
Liwski	Richard	Critical Path Institute	Chief Technology Officer; DCC Director

Lockman	Shahin	Brigham and Women's Hospital	
Marashi	Dylan	MRCT Center	Student Intern
Mathews	Debra	Johns Hopkins University School of Medicine / Johns Hopkins Berman Institute of Bioethics	Associate Professor / Assistant Director of Scientific Programs
Medina-Jordan	Andres	Ropes & Gray, LLP	Associate
Niedzielska	Dana	August Research	CEO
Pan	Sharon	Pfizer, Inc.	Senior Director
Parrish	Mitchell	Quorum Review Institutional Review Board; Kinetiq	Vice President, Legal Affairs
Pascual-Leone	Alvaro	Harvard Medical School	Professor of Neurology
Prucka	Sandra	Eli Lilly and Company / Clinical Innovations	Innovation Lead
Pulford	David	GlaxoSmithKline	Genetics TA Head Rare Diseases & ADD
Rich	Sarah	MRCT Center	Administrative Assistant II
Rosenfeld	Stephen	Quorum Review Institutional Review Board	Executive IRB Chair
Scott	Jessica	GlaxoSmithKline	Director NA Med Advocacy and Policy
Seton	Lewis	Brigham and Women's Hospital	Senior Grants Administrator
Shah	Jina	Genentech, Inc.	Medical Ethics Leader
Shin	Im Hee	Daegu Catholic University Medical Center	Professor / Harvard MRCT Fellow
Silver	Lori	Partners In Health	General Counsel
Sleeper	Lynn	Boston Children's Hospital / Harvard Medical	Scientific Director, Clinical Research / Associate Professor
St. John	Cristy	Sense About Science USA	Outreach and Education Manager, AllTrials
Stewart	Murray	GlaxoSmithKline	Chief Medical Officer
Taber	Magdalena	Independent Consultant	Consultant
Tadmor	Brigitta	Novartis Institutes for Biomedical Research	Advisor, Global Health
Taylor	Holly	Johns Hopkins Bloomberg School of Public Health / Johns Hopkins Berman Institute of Bioethics	Associate Professor
Tomai	Tom	Microsoft Corporation	Enterprise Cloud Specialist
Turik	Michael	Eli Lilly and Company	Chair, Bioethics Advisory Committee
Wang	William	Merck & Co., Inc.	Executive Director, Biostatistics and Research Decision Sciences

Weil	Carol	National Cancer Institute, National Institutes of Health	Program Director, Ethical and Regulatory Affairs
Wilken	Brad	Bill and Melinda Gates Foundation	Deputy Director Product Development Operations
Woolston	Crispin	Sanofi	Senior Director, Science Policy
Wright	David	Kowa Research Institute, Inc.	Senior Director, Regulatory Affairs
Zhao	Ming	BioESSE	Director

Appendix 2: Meeting Agenda

MRCT Center 2016 Annual Meeting: Data Sharing for the Public Good

Wednesday, December 7, 2016

Loeb House, 17 Quincy Street, Cambridge, MA

7:30 – 8:00	Breakfast & Registration
8:00 – 8:15	Welcome & Introductions
8:15 – 9:15	**Discussion of the Impact of Draft ICH E17 Guidelines** • **Laurie Letvak**, Novartis Pharmaceuticals Corporation • **William Wang,** Merck & Co., Inc. Moderator: **Mark Barnes**, MRCT Center; Ropes & Gray LLP Followed by group discussion and Q&A
9:15 – 10:45	**Data Sharing and Data Transparency** **Keynote**: Data transparency today and tomorrow: current state, issues, and vision • **Murray Stewart,** GlaxoSmithKline Progress in 2016 and outlook to 2017 • **Rebecca Li**, MRCT Center; Instructor in Medicine; Harvard Medical School Responses from key stakeholders • **Jeffrey Drazen,** *New England Journal of Medicine* • **Amita Gupta**, Johns Hopkins University • **Murray Stewart,** GlaxoSmithKline Moderator: **Rebecca Li**, MRCT Center; Harvard Medical School Followed by group discussion and Q&A
10:45 – 11:00	Break

11:00 – 12:30	**Individual Return of Results Working Group** Remit of the Working Group and Overview of IRR Principles • **Debra JH Mathews**, Johns Hopkins University • **David Pulford**, GlaxoSmithKline • **Sandra Prucka**, Eli Lilly and Co. Responses from key stakeholders • **Atul Gawande**, Ariadne Labs; Harvard T.H. Chan School of Public Health; Harvard Medical School • **Barbara LeStage**, Clinical Trials Transformation Initiative • **Alvaro Pascual-Leone**, Beth Israel Deaconess Medical Center; Harvard Medical School • **Holly Taylor**, Johns Hopkins University Moderator**: Barbara Bierer**, MRCT Center; Harvard Medical School Followed by group discussion and Q&A
12:30 – 12:45	Closing Remarks
12:45 – 1:15	Lunch

Meeting of the Executive and Steering Committee
Please note: This is a closed meeting, however participants from sponsors attending the Annual Meeting are welcome.

1:15 – 5:00	**Update and discussion of ongoing MRCT projects** • Update on 2016 initiatives • Discussion of new projects

Appendix 3: Speaker Biographies

Jeffrey Drazen, M.D., is Editor-in-Chief at New England Journal of Medicine, a position he has held since 2000. Born in Clayton, Missouri, Dr. Drazen graduated from Tufts University and Harvard Medical School. He served his medical internship and residency at Boston's Peter Bent Brigham Hospital and was a clinical fellow and research fellow at Harvard Medical School and Harvard School of Public Health. Thereafter, he joined the Pulmonary Divisions of the Brigham and Women's and Beth Israel Hospitals, serving as chief of their Pulmonary Divisions for many years.

His current appointments include senior physician at Brigham and Women's Hospital, Distinguished Parker B. Francis Professor of Medicine at Harvard Medical School, professor of physiology at the Harvard School of Public Health and adjunct professor of medicine at the Boston University School of Medicine.

Dr. Drazen is an elected member of the American Society for Clinical Investigation, the Association of American Physicians, the Interurban Clinical Club and the National Academy of Medicine.

He has served on the NIH's Respiratory and Applied Physiology Study Section, Pulmonary Disease Advisory Council, Lung Biology and Pathology Study Section, and NHLBI Advisory Council and on the VA's National Research Advisory Council. He currently serves on the National Institute of Medicine's Forum on Drug Discovery, Development and Translation.

Dr. Drazen's research defined the role of novel endogenous chemical agents in asthma, leading to four licensed pharmaceuticals used in the treatment of tens of millions of asthmatics worldwide. He has published over 500 papers and edited ten books. He has served on the editorial boards of many prestigious journals and has been an associate editor of the *Journal of Clinical Investigation* and the *American Review of Respiratory Disease*.

In 2000, he became editor-in-chief of the *New England Journal of Medicine.* Since then, the *Journal* has published major papers advancing the science of medicine, including the first descriptions of SARS, timely coverage of the Ebola and Zika virus epidemics, and major advances in the treatment of cancer, heart disease and lung disease. It has been at the forefront of worldwide efforts to register all clinical trials and to share clinical trial data. The *Journal* has more than a million and a half readers every week and the highest impact factor of any medical journal publishing original research.

Atul Gawande M.D., MPH, is a surgeon, writer, and public health researcher. He practices general and endocrine surgery at Brigham and Women's Hospital and is professor in both the Department of Health Policy and Management at the Harvard T.H. Chan School of Public Health and the Department of Surgery at Harvard Medical School. He is Executive Director of Ariadne Labs, a joint center for health systems innovation, and also chairman of Lifebox, a nonprofit making surgery safer globally. In addition, he has been a staff writer at the *New Yorker* magazine since 1998.

Amita Gupta, M.D., MPH, is Deputy Director of the Johns Hopkins (JH) Center for Clinical Global Health Education (CCGHE), and Associate Professor of Infectious Diseases at the JH School of Medicine, with a joint appointment in international health at the JH Bloomberg School of Public Health.

Board certified by the American Board of Internal Medicine in internal medicine and infectious diseases, Dr. Gupta specializes in international public health, clinical research, and education in infectious diseases, HIV/AIDS, and tuberculosis (TB). Since 2002, her work has been focused primarily on India, where she leads several Indo-JHU research collaborations, including the C-TRIUMPH and RePORT consortium for tuberculosis (TB) research funded by the US National Institutes of Health (NIH) and the government of India. Dr. Gupta is also Co-principal Investigator of the NIH-funded Baltimore-Washington-India (BWI) HIV and Infectious Diseases Clinical Trials Unit (CTU), and she is an active clinical investigator in multi-country HIV/TB trials conducted by the AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Trials Network (IMPAACT). Additionally, she has been awarded research grants from the NIH, CDC, and several philanthropic foundations to investigate TB in children and pregnant women, malnutrition, infection and inflammation, HIV treatment outcomes, and antibiotic resistance.

Dr. Gupta is an author of more than 90 peer-reviewed research publications and 7 book chapters, primarily on prevention and treatment of HIV, TB, and bacterial infections, predominantly in low- and middle-income settings. She has also mentored more than 30 junior scientists in India to run research studies and submit their own scientific findings to peer-reviewed publications.

From 2000–2002, Dr. Gupta worked for the US Centers for Disease Control and Prevention (CDC), where she was engaged in global public health projects in Guatemala, Vietnam, and Micronesia.

Dr. Gupta received an undergraduate degree from MIT, a Doctor of Medicine from Harvard Medical School, and a Masters in Health Sciences in clinical investigation from JH Bloomberg School of Public Health. She completed her internal medicine training at San Francisco General Hospital-University of California, San Francisco, followed by a post-doctoral fellowships with the Epidemic Intelligence Service at the US Centers for Disease Control and Prevention and at the JHU School of Medicine.

Barbara LeStage, M.H.P. (Health Administration), B.S., is a Steering Committee Member and Patient Advocate at Clinical Trials Transformation Initiative. When Ms. LeStage was fifteen, her 41 year old mother died of pancreatic cancer. In the 1970s her father was diagnosed with spindle cell carcinoma of the face requiring extensive surgery, radiation and plastic surgery. Ms. LeStage herself is a 20 year survivor of Stage 1 carcinoma of the breast. Her career as a cancer advocate began in 1975 and as a cancer research advocate in 1993. Since then, much of her life has been committed to reviewing research applications and protocols and participating in the design of clinical trials.

Ms. LeStage is a past chair of NCI's Director's Consumer Liaison Group (now the Council of Research Advocates) and past member of NCI's Central IRB and Advisory Committee to the Director. She was the first person selected to chair the Patient Advocacy Committee of the American College of Radiology Imaging Network (ACRIN) and was a member of ACRIN's Executive Committee. Her primary responsibility in all these positions was to represent the patient perspective in clinical research through in-person meetings, teleconferences and written reviews.

Ms. LeStage is a past faculty member of the Clinical Trials Methodology Workshop conducted by the Radiological Society of North America and was a faculty member at the ASCO/AACR Methods in Clinical Cancer Research Workshop for six years. In these positions she was responsible for working with young researchers as they developed their first clinical trial protocol. She provided by working with them individually or in small groups,

writing a daily review of each section of their protocol as it was completed, and giving presentations on informed consent and trial accrual both to small groups and during general sessions.

Ms. LeStage currently serves on the Dana Farber/Harvard Cancer Center Breast Cancer Advocacy Group, NCI's Clinical Imaging and Patient Advocate Steering Committees and the Clinical Trials Transformation Initiative Steering Committee.

Ms. LeStage obtained her B.S. from Denison University and her MHP from Northeastern University's Bouve College of Health Sciences. Ms. LeStage attended the National Breast Cancer Coalition's Project LEAD, twice participated in the American Association for Cancer Research's Scientist-Survivor Program, attended the American Cancer Society's Stakeholder Training and participated in the Summit Series on Clinical Trials for five years.

Laurie Letvak, M.D., is Vice President and Head of Clinical Development Policy at Novartis, a position she has held since June 2014. Laurie has been with Novartis for over 20 years in a variety of positions. She played a key role in the development of Glivec® since joining the International Project Team in 2001, responsible for Global Medical Affairs. From 2008-2012, she was the Global Program Head for Glivec and Tasigna®. In this role, she was responsible for leading the global development efforts for both drugs, including registration programs for new indications.

Laurie assumed the position of Global Development Head for the Critical Care Franchise in 2012. In that role, she was responsible for the strategic development and execution of plans for the evolving portfolio, which focused on specialty cardiovascular (with emphasis on heart failure) and metabolic products, particularly for lipids and atherosclerosis.

Laurie received her undergraduate and medical degrees from Cornell University. She did her internal medicine training at Boston University and her Hematology-Oncology fellowship at New York University Medical Center and worked for Lederle Laboratories with experience in Medical Development and Business Development prior to joining Novartis in 1994.

Debra JH Mathews, Ph.D., M.A., is the Assistant Director for Science Programs for the Johns Hopkins Berman Institute of Bioethics, and an Associate Professor in the Department of Pediatrics, Johns Hopkins School of Medicine, and affiliate faculty in the Institute of Genetic Medicine. Dr. Mathews earned her PhD in genetics from Case Western Reserve University. Concurrent with her PhD, she earned a Master's degree in bioethics, also from Case. She completed a Post-Doctoral Fellowship in genetics at Johns Hopkins, and the Greenwall Fellowship in Bioethics and Health Policy at Johns Hopkins and Georgetown Universities. Dr. Mathews has also spent time at the Genetics and Public Policy Center, the US Department of Health and Human Services, and the Presidential Commission for the Study of Bioethical Issues, working in various capacities on science policy. As the Assistant Director for Science Programs, she is responsible for overseeing the Stem Cell Policy and Ethics program (SCoPE) and the Program in Ethics and Brain Sciences, as well as other Institute initiatives in policy and ethics related to biomedical research. Dr. Mathews is a member of the steering committee of the Hinxton Group, an international collective of scientists, ethicists, policymakers and others, interested in ethical and well-regulated science, and whose work focuses primarily on stem cell research. Dr. Mathews' academic work focuses on ethics and policy issues raised by emerging biotechnologies, with particular focus on genetics, stem cell science, neuroscience and synthetic biology.

Alvaro Pascual-Leone, M.D., Ph.D., is Professor of Neurology and an Associate Dean for Clinical and Translational Research at Harvard Medical School. He serves as the Chief for the Division of Cognitive Neurology and the Director of the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center.

Dr. Pascual-Leone received his M.D. in 1984 and his Ph.D. in Neurophysiology in 1985, both from Albert-Ludwigs University in Freiburg, Germany. Following an internship in Medicine at *Staedtisches Klinikum Karlsruhe* in Germany and residency in Internal Medicine at *Hospital Universitario de Valencia* in Spain, Dr. Pascual-Leone completed a Neurology residency at the University of Minnesota, and then trained in Clinical Neurophysiology and Human Motor Control at the University of Minnesota and the National Institutes of Health. He joined Harvard Medical School and Beth Israel Deaconess Medical Center in 1997, after several years at the Cajal Institute of the Spanish Research Council.

Dr. Pascual-Leone works as a practicing cognitive neurologist at Beth Israel Deaconess Medical Center. His research aims at understanding the mechanisms that control brain plasticity across the life span to be able to modify them for the patient's optimal behavioral outcome, prevent age-related cognitive decline, reduce the risk for dementia, and minimize the impact of neurodevelopmental disorders (www.brainfitclub.org).

Dr. Pascual-Leone is a world leader in the field of noninvasive brain stimulation where his contributions span from technology development, through basic neurobiologic insights from animal studies and modeling approaches, to human proof-of-principle and multicenter clinical trials. His research has been fundamental in establishing the field of therapeutic brain stimulation. His work has provided evidence for the efficacy of noninvasive brain stimulation in treating various neurologic and psychiatric conditions, including epilepsy, stroke, Parkinson's disease, chronic pain, autism, and drug-resistant depression.

Dr. Pascual-Leone has authored more than 600 scientific papers as well as several books, and is listed inventor in several patents. His work is highly regarded for its innovation and quality and is highly cited. Dr. Pascual-Leone ranks number 1 among authors worldwide in the specific field of "Transcranial Magnetic Stimulation" and "Noninvasive Brain Stimulation" (http://www.authoratory.com/) and has an H-index of 130. Dr. Pascual-Leone is also one of the directors of the Football Players Health Study at Harvard University (https://footballplayershealth.harvard.edu).

Sandra Prucka, M.S., Licensed and Certified Genetic Counselor (LCGC), is an Innovation Lead in the Clinical Innovations Group at Eli Lilly and Company (Lilly). In this role she works to make it easier for research professionals to participate in clinical research and care for their patients. Prior to joining the Clinical Innovations group in June 2016, Ms. Prucka had worked for 7 years in Lilly's Tailored Therapeutics group where she supported pharmacogenomic (PGx) and biomarker sample collection efforts from global clinical trials, with specific expertise in areas of bioethics, global laws/regulations affecting biomarker research, informed consent, return of individual research results and genetic education. She is a co-chair of the Industry Pharmacogenomic Working Group (I-PWG) and also leads their Education and Communication Task Force. She also previously led an I-PWG task force to examine the Return of Individual Research Results and has published on this topic.

Prior to joining Lilly Ms. Prucka was a clinical genetic counselor at the University of Alabama at Birmingham (UAB) where she served as the Director of Genetic Counseling Services and provided prenatal, pediatric, cardiovascular, and cancer genetic counseling.

Ms. Prucka received her B.S. from the University of Michigan and her M.S. in Genetic Counseling from the University of Pittsburgh.

David Pulford, Ph.D. Biochemistry, BSc (Hons) Genetics and Cell Biology, is Genetics Therapy Area Head Rare Diseases at GlaxoSmithKline in the United Kingdom. Dr. Pulford has over 20 years of experience working in molecular biology in both academia and the pharmaceutical industry. His work has focused on the application of genome science to improve understanding of the mechanisms underpinning disease and drug response. Most recently at GSK he has been working in the fields of rare diseases and pharmacogenetic (PGx) research to identify and validate novel molecular targets, understand variable drug response and to clearly communicate the goals of this research across discovery and clinical development. He has a wealth of experience of the challenges encountered in conducting genetic research in a global pharmaceutical R&D environment and has published on a variety of topics, from target discovery to medical ethics in PGx research.

Murray Stewart, M.D., is Chief Medical Officer at GlaxoSmithKline, a position he has held since April 2014. Dr. Stewart joined GSK in 2000 as Associate Director for Clinical Research & Development in the UK and since then has held a variety of positions in GSK he worked in Biopharm, was Therapy Area Head for the Cardiovascular and Metabolic therapy area. Currently he is Chief Medical Officer for GSK and as such has global responsibility for patient well-being across the vaccines, pharmaceutical and consumer business units. He has had extensive clinical development experience and worldwide regulatory interactions. Before joining the pharmaceutical industry, Murray worked as a diabetes consultant and senior lecturer and was Consultant Physician/Honorary Senior Lecturer and Head of Clinical Services at the Diabetes Centre, Newcastle upon Tyne in the UK. His research was in lipid metabolism in type-2 diabetes, and he completed his medical training at Southampton Medical School in the UK and is a Fellow of the Royal College of Physicians.

Holly A. Taylor, Ph.D., **MPH,** is a Core Faculty member of the Johns Hopkins Berman Institute of Bioethics and Associate Professor in the Department of Health Policy and Management (HPM), Bloomberg School of Public Health. Dr. Taylor is trained as a social scientist and uses both qualitative and quantitative methods to explore topics in the ethics of human subject research and ethical considerations in public health approaches to infectious disease.

Dr. Taylor is currently working on projects on informed consent and central IRBs as well as projects related to the willingness of local health department staff to respond during an emergency and MDR-TB in Southern Africa. In the past she has worked on the recruitment of women, minorities and children in clinical research, the delivery of ancillary care to those participating in public health research and the role of the study partner in the conduct of research with patients with dementia.

Dr. Taylor has served on the Institutional Review Boards (IRB) of the Bloomberg School of Public Health and the Johns Hopkins School of Medicine as well as IRBs in the public and private sector. She is the Director of the Johns Hopkins Institute for Clinical and Translational Research – Research Ethics Consultation Service. Dr. Taylor is the Director of the PhD Program in Bioethics and Health Policy in HPM, leads the Bioethics and Public Health Policy Certificate Program and teaches a course – Ethical Issues in Health Policy: Public Health and Health Care.

Dr. Taylor received her BA from Stanford University, her MPH from the School of Public Health at the University of Michigan and her PhD in health policy with a concentration in bioethics from the Bloomberg School of Public Health, Johns Hopkins University.

Before pursuing her doctoral degree, Dr. Taylor was selected as a Presidential Management Intern in the Department of Health and Human Services and spent two years rotating through AIDS related policy positions at the National AIDS Program Office, National Commission on AIDS, the San Mateo County Health Department and the Senate Committee on Labor and Human Resources. After completing her internship, Dr. Taylor spent two years as Special Assistant to the Director of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

William (Bill) Wang, Ph.D., is Executive Director, Biostatistics and Research Decision Sciences, Merck & Co Inc. He has over 22 years of experience in the pharmaceutical industry, with expertise and research publications in statistical design, analysis, clinical data management and their technology enablement. During his 17-year tenure at Merck, he has supported regulatory filings in multiple therapeutic areas and led the establishment of the BARDS Asia Pacific operation. Since 2010, he has served on the DIA China Regional Advisory Board and the DIA's Global Community Leadership Council (CLC). He was also the founding chair of the Shanghai Biostatistics Forum (2008-present) and the DIA China Quantitative Science Forum (2012-present); both have become important regional platforms for scientific exchange in pharmaceutical and regulatory statistics. He was a recipient of the DIA global outstanding service award in 2012. He is currently chairing an American Statistical Association (ASA) safety monitoring working group, a deputy topics-leader in the ICH E17 working group on multi-regional clinical trials, and a member of the Merck benefit-risk strategy team.

MRCT Center Faculty and Staff

Mark Barnes, J.D., LL.M, is the faculty co-chair of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard and practices law as a partner at Ropes & Gray LLP, where he represents academic institutions and industry in matters related to research with humans and animals, clinical trials, research grants and contracts, and research fraud.

Mark's law practice and his teaching at Yale focus on health care law and finance, human and animal research, stem cell and genetic research, research grants and contracts, research misconduct, and international research.

Mark formerly served at Harvard as the Senior Associate Provost and University Senior Research Officer and started and directed Harvard's HIV/AIDS treatment programs in Nigeria, Tanzania and Botswana. He serves on the Ethics Working Group of the NIH's HIV Prevention Trials Network (HPTN) and is the ethics advisor to HPTN Trial 071 in South Africa and Zambia. Mark has held senior appointed positions in the New York City and State departments of health.

Barbara E. Bierer, M.D., is the faculty co-chair of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center), a Professor of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston and a hematologist/oncologist. She is the Director of the Regulatory Foundations, Ethics and the Law Program of the Harvard Clinical and Translational Science Center. Previously, she served as Senior Vice President, Research at the Brigham and Women's Hospital for 11 years, and was the institutional official for human subjects and animal research, for biosafety and for research integrity. She initiated the Brigham Research Institute and the Innovation Hub (iHub), a resource center for entrepreneurs and innovators. In addition, she was the Founding Director of the Center for Faculty Development and Diversity at Brigham and Women's Hospital.

In addition to her academic responsibilities, she serves on the Board of Directors of Public Responsibility in Medicine and Research (PRIM&R), dedicated to promoting the ethical conduct of biomedical and behavioral research; Management Sciences for Health (MSH), an international organization working in partnership globally to strengthen health care, local capability, and access; and the Edward P Evans Foundation, a foundation supporting biomedical research. Previously she has served as the chair of the Board of Directors of the Association for Accreditation of Human Research Protection Programs (AAHRPP) and as chair of the Secretary's Advisory Committee on Human Research Protections, HHS. She has authored or co-authored over 180 publications and is on the editorial boards of a number of journals including *Current Protocols of Immunology.*

Dr. Bierer received a B.S. from Yale University and an M.D. from Harvard Medical School.

Rebecca Li, Ph.D., has over 17 years of experience spanning the entire drug development process with experience in Biotech, Pharma and CRO environments. Dr. Li currently serves as the Executive Director of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard The Center was chartered to improve the design, conduct and oversight of multi-regional clinical trials in the developing world and simplifying research through best practices. She is also a Fellow in the Division of Medical Ethics at Harvard Medical School. Prior to joining Harvard, Dr. Li served as the VP of Clinical Research at the New England Research Institutes for 6 years. She also was employed at Wyeth Research as

the Associate Director in Translational Clinical Research. She earned her PhD in Chemical and Biomolecular Engineering from Johns Hopkins University.

Carmen Aldinger, Ph.D., MPH, is Program Manager at the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). Carmen joined the MRCT Center in October 2014. She provides managerial, logistical and administrative oversight for several workgroups, including return of individual results and return of aggregate results, post-trial responsibilities, and core competencies for clinical researchers. She also manages the MRCT Center website and newsletter and other operational and procedural aspects of the MRCT Center.

Dr. Aldinger has 20 years of experience in global health, including project management and leadership, materials development and capacity building, monitoring and evaluation, collaboration and coordination. Prior to coming to the MRCT Center, she has worked as a Project Director and Associate Center Director at Education Development Center's Health and Human Development Division, Global Programs, co-directed the World Health Organization Collaborating Center to Promote Health through Schools and Communities, and subsequently worked as an independent consultant for United Nations agencies and non-profit organizations. Dr. Aldinger has a Ph.D. in Educational Studies from Lesley University, a Master of Public Health in international health from Yale University, and a Bachelor's degree in health education from Towson University.

Kris Bolt, ALB, is Program Manager for Data Sharing. Kris joined the MRCT Center in February 2016 as Program Manager for Global Clinical Trial Data Sharing with primary focus on the information technology component of the Data Sharing and Transparency Initiative. Kris brings 14 years of experience from Harvard University where she created and grew many successful data sharing programs working with investigators, data generators and institutional administrators to reduce burdens and speed research. Kris is also the Co-Chair of the Research Data Management and Security committee for the Harvard Clinical and Translational Science Center.

Christopher Kabacinski, B.A., is Program Coordinator for MRCT Center. Christopher joined the MRCT Center of Brigham and Women's Hospital and Harvard as Program Coordinator in July 2016. Prior to joining the MRCT Center team, Christopher worked in publishing, higher education, and the nonprofit sector. He received his Bachelor of Arts in English with a minor in medical humanities from Boston College.