Proceedings
Harvard Multi-Regional Clinical Trials Center (MRCT)
3rd Annual Meeting

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Loeb House • Cambridge, MA

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Executive Summary

The Harvard MRCT Annual Meeting 2014 focused on the Guidance Document and Toolkit that the Harvard MRCT workgroup developed for returning aggregate results to study participants and included a panel with various stakeholder perspectives on returning of results. In addition, Harvard MRCT co-directors introduced their work of addressing regulatory, trial causality and compensation issues in India.

The Harvard MRCT Return of Results (ROR) workgroup developed two deliverables in 2014:

- ROR Process Reference Guide which includes essential components, logistics and detailed processes, timing and special considerations
- ROR Users Toolkit which includes templates, neutral language guide, endpoints language, and useful checklists.

Invited speakers shared their perspectives on returning results to study participants:

- Ms. Anabel Marçal contributed the European perspective and introduced the EudraCT, EU Clinical Trials Register, EU Portal and EU Database, and the EMA Policy on Clinical Data publication.
- Dr. Richard Moscicki informed that the FDA does not currently have a regulation on return of results and is working on it.
- Dr. Jerry Menikoff from the Office for Human Research Protections (OHRP) shared that return of results is not part of the IRB's responsibility, unless it is stated in the informed consent form.
- Dr. Jeffrey Drazen from the New England Journal of Medicine (NEJM) emphasized the importance to communicate with study participants at the same time or just prior to the public release of the data.
- Dr. Michael Rosenblatt from Merck & Co called for transparent, timely disclosure of return of results to patients, and a need for global harmonization and FDA guidance.
- Ms. Jocelyn Ulrich from PhRMA presented that research volunteers want to be informed about the results of the trials they participated in and that information should be factual and not misleading.
- Ms. Elizabeth Frank, a patient advocate from the Dana Farber Cancer Institute, confirmed that participants in clinical trials want to see results, and that all participants should be offered an opportunity to receive results from the trials they participated in.
- Dr. David Gordon from the National Heart, Lung, and Blood Institute (NHLBI) shared that not all trials funded by NIH get published, with preferential publication of positive results. NIH will start to require that all NIH-funded trials post summary results within 1 year of completing data collection.

A panel discussion addressed issues around promotional language, negative trials, neutral website for posting results, patient privacy and health literacy, helpful information for patients, and other

communication needs such as for primary care physicians that are not part of the trial but may need to answer related questions of their patients.

Then, Harvard MRCT faculty co-directors introduced regulatory issues in India which essentially curtailed or inhibited clinical trials in India. This includes government issued rulings that address:

- Compensation in the case of injury or death during a clinical trial
- Free, indefinite sponsor-provided medical management for injury during the trial
- Financial compensation for a wide range of issues
- Limited number of clinical trials an investigator can be involved in
- Requirement of video-taped consent
- Prohibition of marketing drugs in India that have not involved trials in India

Harvard MRCT has partnered with various stakeholders in India to assist with implementing reforms with clinical trials and co-sponsored a roundtable in Delhi in January 2014. During the last year, Harvard MRCT has focused on India regulatory issues, including:

- proposed India regulatory reforms relating to required certification for investigators and accreditation for research sites and/or IRBs/RECs
- developed a causality module which is a “how to” primer detailing points to consider in determining causality of an adverse event and the likelihood it is caused by the treatment
- co-facilitated a Causality Assessment Workshop for Clinical Trial Investigators in Delhi, India, on November 22, 2014
- wrote op-eds to keep this issue at the forefront in the international literature

Welcome and Introduction

Introduction to Harvard MRCT and the Return of Results Guidance Document

Barbara Bierer, M.D., Harvard MRCT

Dr. Barbara Bierer introduced the agenda, the purpose of the Harvard Multi-Regional Clinical Trials Center (Harvard MRCT) and the members of the Harvard MRCT Return of Results (ROR) workgroup who collaborated on addressing how to return clinical trial results to study participants. The impetus for addressing this at the current time was the European Union (EU) Regulation No 536/2014 (2014) which requires sponsors of clinical trials to submit "a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines." This is consistent with PhRMA and EFPIA principles for transparency. The goal for the Harvard MRCT annual meeting was to convey our work and obtain feedback and discussion from the perspectives of regulators, journal editors, pharmaceutical representatives, investigators and participants on the drafts that the workgroup developed.

Dr. Bierer gave an overview how Harvard MRCT has partnered with other working groups addressing returning results and gained input from multiple stakeholder groups. As a result, Harvard MRCT developed two deliverables:

- ROR Process Reference Guide which includes essential components, logistics and detailed processes, timing and special considerations
- ROR Users Toolkit which includes templates, neutral language guide, endpoints language, and useful checklists.

As addressed in these documents, perceived barriers for returning results include practical considerations such as timing of release and designating a responsible party, logistics such as cost implications and how best to communicate, content and comprehension such as using language that is not too scientific, and ensuring that returning of results is not viewed as a promotion activity. Aggregate study results should be offered to all participants that have been enrolled and, if appropriate, randomized. The method of return can be interactive such as face-to-face or telephone conversation, one-way such as video summary or printed materials, or Internet-based. Trial results summaries should be unbiased and not promotional and translated into languages consistent with translations for informed consent. The EU Layperson Summary requires ten specific content items which are similar to the items in the Harvard MRCT documents. An additional consideration addressed in the Harvard MRCT documents is health literacy as well as numeracy and cultural literacy.

The Harvard MRCT ROR Toolkit includes examples for neutral language, sample templates for Phase I and Phase II/III as well as for trials ending early, and descriptions and examples of common endpoints. Suggestions for timing the return of results are also discussed as well as special considerations such as trials that close early, notification to a 3rd party, and vulnerable populations. Special considerations for

the IRB/RECs include whether it has jurisdiction to review ROR materials. There are also considerations for studies that may not warrant return of results such as tissue banking, cluster-randomized studies, and studies of illegal or socially unacceptable behavior. Regulatory requirements prohibit any type of promotional communication prior to marketing approval by FDA or other regulatory agencies.

The current Harvard MRCT ROR Guide and Toolkit are designed for all sponsors to use in all trial types. Since harmonization and consistency is critically important, Harvard MRCT has discussed with TransCelerate and EFPIA potential collaboration and approached NIH to partner in this transparency effort. Next steps include disseminating the draft for further comment and revision, iterative improvement of the guidance, and, eventually, global harmonization in approach and expectations.

Invited Speakers Perspective on Returning Aggregate Results to Study Participants

Clinical Trial Transparency, The European Perspective

Anabela Marçal, European Medicines Agency (EMA)

Ms. Marçal spoke about EU initiatives related to transparency. Clinical trial transparency is important for many reasons, including having a public record, contributing to global registration of all clinical trials, and contributing to innovation and research. She gave an overview of the main tools that the EU has: EudraCT and EUCTR, The EU Portal and EU Database, and other initiatives such as EMA Policy on Clinical Data Publication.

- **EudraCT**: Since October 2013, a sponsor can log on to prepare and post the summary of results of clinical trials (CT). Sponsors are now required to post lay summaries according to various timelines. This was mandatory as of 21 July 2014. The secure database is only accessible by competent authorities, the European Commission, and EMA. Results are provided for the trial and not per CTA. Results can be presented with an attachment only or with structured data. There is a delay of 14 days between the posting data and the publication date.
- **EU Clinical Trials Register**: This was launched in March 2011 and contains protocols and results related to interventional CTs started after May 2004. Summary results contain detailed scientific information for each trial and can be downloaded as PDF.
- **EU Portal and EU Database**: This is based on EU regulation No 546/2014, of which Art 80 requires "a **portal** at Union level as a single entry point for the submission of data and information relation to clinical trials …[which]… shall be technically advanced and user friendly." Art 81 requires a "**EU database** at Union level [for which] the Agency shall be considered to be the controller of the EU database and shall be responsible for avoiding unnecessary duplication between the EU database and the EudraCT and Eudravigilance databases." This will be a single

EU portal and database to support transparency of clinical trial authorization, conduct and results. This EU database will be publically accessible by default, with justified exceptions such as protection of personal data and protection of commercially confidential information. According to Recital 67, data should be presented in an easily searchable format, related documents and data linked together, and include no personal data of subjects participating in the trial. According to Recital 68, CSR should not be considered commercial confidential once MA is granted or application withdrawn. There is a specific obligation on sponsors to submit summary of results and lay person summary one year after the end of the trial, and MAH is required to submit the CSR once the MA procedure is complete (positive or negative) or withdrawn by applicant. There will be penalties for breach of transparency provisions. Annexes spell out the content of the summary of the results of clinical trials and laypersons' summary. The functional specifications of the EU Portal and Database are expected to be completed by March 2015.

- **Other initiatives: The EMA Policy on Clinical Data Publication** (Policy 0070). This includes clinical reports, clinical summaries and CSRs submitted under a centralized procedure. This will be implemented stepwise, starting with the publication of clinical reports only. January 1, 2015 is the effective date for any new MAA submitted, and July 1, 2015 for extensions of indication/line extension applications for CAPs.

Ms. Marçal concluded that Europe is paving the way on further increasing transparency on clinical trials to support public scrutiny and critique--establishing trust and confidence in the system, to inform and enable participation in discussion of clinical trials, and to foster innovation.

Regulatory Perspective, Food and Drug Administration (FDA)

Richard Moscicki, M.D.

Dr. Moscicki, who shared his personal view, said that he believes it is important to return results and is sympathetic to the endeavor; however, statutes prohibit off-label promotion of unapproved drugs, which can create a conflict if returning results is not done in a neutral format. While there are many FDA regulations for non-promotion, none specifically refer to return of aggregate results to study participants. Now might be a good time to create a safe harbor to return results by developing a specific guidance. The FDA is currently engaged in a review of their policies and guidance on promotion in light of recent case law involving the First Amendment. The state of Maine issued an advisory after consulting with CDER Office of Prescription Drug Promotion about posting study results on a public database. The advisory provided advice about how to avoid having the information posted being considered promotional.

Points to consider include:

- The information must be truthful and not misleading.

- The language has to be simple, factual and neutral.
- Information that is provided to patients should not be selective.
- The context cannot be promotional: for example on a company website or with promotional graphics, and should be a scientific communication with the patient.
- The trickiest part of the Harvard MRCT guidance template is addressing the interpretation of results and the issue of, "what does this mean for me." The information to the patient cannot convey if a drug is safe and/or effective until after FDA review.

Dr. Moscicki recognized the work at Harvard MRCT that has laid down important and useful groundwork in returning aggregate results.

Office for Human Research Protections (OHRP) Perspective

Jerry Menikoff, M.D., J.D.

Dr. Menikoff stated that the Common Rule does not address return of aggregate results and does not require this communication to be reviewed by IRB especially since this activity usually occurs after the study is closed with the IRB. If the process of returning aggregate results is included in the protocol but not in the informed consent, then there is no requirement for IRB review. If return of results is included in the consent form, then the IRB may choose to enforce this. If the consent form only states a commitment to subjects that they will receive a summary prepared by the sponsor, then the IRB's role would be to ensure that the summary was sent out.

Thus, the regulations give some flexibility. It is unlikely that OHRP would enforce IRB compliance with this.

New England Journal of Medicine (NEJM) Perspective

Jeffrey Drazen, M.D.

Dr. Drazen referred to the difficulty to get patients to enroll in clinical trials. Fair treatment and respect for patients are important for patients to maintain interest in participating in trials. Returning results summaries to patients can be important and also prevent them from being surprised by hearing about the results in the news about a trial they participated in. For an effective summary, it is important to communicate in a language that is easy to understand. The NEJM and ClinicalTrials.gov are intended for medical professionals and are not be appropriate for the layperson.

Most studies are negative and will not be clinically relevant for participants. This issue poses the challenge of how to communicate with patients in words that they understand of why the sacrifice they made was important.

It is important to coordinate the release of results to the public with the release to the participants. The NEJM position is that the communication to the patient should be done at the time the results go public, or the night before, so that they are not surprised. The priority for publication selection in NEJM is higher if the company has not already disseminated information so pre-release should be minimized.

Dr. Drazen reminded the audience that the patients are the most precious resource, and that the communication with them needs to be informative and not directive.

Industry Perspective: Return of Results to Participants

Michael Rosenblatt, M.D., Merck & Co.

Dr. Rosenblatt started by recalling the perspective of their founder, George Merck, who said that "we try never to forget that medicine is for people. It is not for profits," and thus he recalled a responsibility beyond their products. His key issues for discussion included:

- Focus on the perspective of the patient/research participant
- Global harmonization of return of results policies
- Need for FDA guidance to industry on promotional questions (a perceived vacuum can lead to inaction and unintended consequences)
- Transparency – clear link between data and conclusions
- Interest in bi-directional exchange with patients: not one-way communication, learning patients' perspective on benefit : risk
- Critical importance of health literacy and clear communication

He presented an example of collaboration in regard to "patient labeling" where Merck partnered with academia (Northwestern/Emory) and engaged FDA. This example demonstrated increased patient understanding and use by optimizing development and testing of a Patient Package Insert. Applying health literacy principles resulted in a high comprehension of more than 90% by respondents with both low and adequate health literacy.

Dr. Rosenblatt's recommendations included:

- Transparent, timely disclosure of return of results to patients
- Continued partnership to model health literate return of results, focusing on the patient
- Alignment of global requirements for return of results
- Engagement with regulators to address promotion issues

PhRMA Perspective: Principles for Communicating Clinical Trial Result Summaries with Study Volunteers

Jocelyn Ulrich

Ms. Ulrich started by confirming that research showed that volunteers want to be informed about the results of the clinical trial they participated in. Many sponsors have indicated interest in making summaries of results available, and Section 801 of FDAA requires study sponsors to make results of "applicable trials" publicly available on the clinicaltrials.gov database. While Section 801 of FDAA provides for the possible dissemination of summaries in non-technical, understandable language for patients, lay summaries can only be *required* through formal rulemaking and if those summaries can be drafted "without being misleading or promotional." Regulations prohibit sponsors from representing an investigational drug as safe or effective and recognize the importance of disseminating clinical trial test results whether they are positive, negative, or inconclusive.

Consequently, principles for communicating clinical trial result summaries with study volunteers include:

- Accurately describe the results of a clinical trial in a format that provides the most important information
- Avoid as much as possible technical or scientific jargon
- Provide a basic description of the results for the efficacy and safety endpoints in the trial that the volunteer participated
- Make clear that the product may not be approved by the FDA for which it was studied
- Make clear that the results studied for the product are current as of the issue date and for the specific study, may not be consistent with how product was approved by FDA, and should not be viewed as certain or final
- Encourage patients to discuss the relevance of the results on their health with their doctor

Information that is communicated should not be false or misleading but provide a factual description of the study results. Study summaries intended for dissemination to clinical study volunteers should be prepared with input by individuals with appropriate scientific and/or medical training. Since study participants have different preferences to access clinical trial information, it is important to maintain flexibility in how the information is disseminated, which can include a written document, password-protected website, posting on ClinicalTrials.gov, electronic transmission, and public posting on company or other website. In summary, public health can be served when study participants receive truthful and non-misleading scientific and medical information regarding the results of the clinical investigations in which they participated.

Patient Perspective

Elizabeth Frank, Patient Advocate, Dana Farber Cancer Institute / Harvard Cancer Center

Ms. Frank recalled that in conversation with advocates she has heard many times and from many people that participants in clinical trials would like to see results. Since patients are partners in research, and therefore a critical part of the clinical trials system, they deserve the opportunity to learn about the results of the studies in which they participate, should be thanked for their participating and have a sense of how their participation contributed to future knowledge.

Clinical trial participants want to know what the results were of the trial in which the participated, how these results help patients, how their own experience compared to that of other participants, if their participation made a difference, and what the results mean for them. Ms. Frank discussed several patient advocate collaborations, which are groups of advocates, academics and sponsors that make summaries available on their websites, but do not notify participants of their availability.

For instance, the DF/HCC Breast Center Advocates is a group of 14 breast cancer patients/survivors interested in research related issues. This group was created eight years ago with the mission to support and enhance the work of the DC/HCC investigators by providing an informed patient perspective. They led a project, together with a physician at Dana Farber, Dr. Ann Partridge, to develop tools and procedures for sharing the results of an investigator-initiated trial to patient participants. This study showed that 94% of the respondents believed that clinical trial results should be offered to participants, and 88% were happy to receive the summary in the mail. However, only 55% felt that the clinical trial results summary included all the material they wanted. Most who felt differently wanted more details. Almost all of the respondents reported reading the entire results summary. Being offered the results summary (RSS) resulted in 56% of the participants feeling more appreciated for their participation, and 88% reported that reading the RSS did not have an effect on how often they felt anxious. Furthermore, 97% were glad to have been offered the results summary.

Ms. Frank drew the following conclusions:

- All stakeholders benefit from offering to return research results
- Patients choosing to receive results are not likely to experience unreasonable increased anxiety or concern
- The level of detail and the type of information expected in a RRS varies among participants
- Protocols for clinical trials should routinely include a plan to offer RSS to interested participants

NIH Perspective: Publication of National Heart, Lung, and Blood Institute (NHLBI) Cardiovascular Trials

David Gordon, MD, PhD

Dr. Gordon started his presentation with a quote from BMJ[1] that stated that "fewer than half of trials funded by NIH are published in a peer reviewed biomedical journal … within 30 months. Moreover, after a median of 51 months after trial completion, a third of trials remained unpublished." According to Dr. Gordon, failure to publish complete trial results reneges on the investigator's implicit promise to trial participants to use the results to help others, wastes taxpayer funds and opportunity cost, and may foster promulgation of ineffective treatments. Thus, sharing data—at least at the study level—is not merely desirable, it is an ethical mandate.

Dr. Gordon presented an analysis of 244 NHLBI cardiovascular trials between 2000 and 2011, showing the percentage published and the annual citation rates. This showed that large trials with clinical event endpoints and budgets of more than $5 million publish quickly and are widely cited. Relatively inexpensive surrogate endpoint trials (which comprise more than 70% of NHLBI trials and consume 20% of the clinical trial budget) are slow to publish and make little impact. The two publications from the WHI hormone replacement therapy trials garnered >10,000 citations by the end of 2012 -- nearly 4 times as many as the 176 small surrogate endpoint trials combined. There is also a modest bias toward more rapid publication of positive trials.

Reasons why investigators do not publish primary results include: flaws in design or execution, lack of principal investigator follow-up, and journal disinterest and/or delay. The NIH response to this is that all NIH-funded trials (and not just those subject to FDAAA) will be required to register in ClinicalTrials.gov within 21 days of initiating enrollment and post summary results within 1 year of completing primary data collection. Failure to comply could negatively affect future NIH funding of grantee and principal investigator.

Panel Discussion

Anabela Marçal, EMA; Richard Moscicki, FDA; Jerry Menikoff, OHRP; Jeffrey Drazen, NEJM; Michael Rosenblatt, Merck; Jocelyn Ulrich, PhRMA; Elizabeth Frank, Patient Advocate; David Gordon, NIH — Moderated by Mark Barnes, Harvard MRCT

The following issues were discussed:

- Promotional language:

[1] Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. (2012). Publication of NIH funded trials registered in Clinical Trials.gov: cross sectional analysis, *BMJ,* 344:d7292. doi: 10.1136/bmj.d7292

  - Factual representation of aggregate results should not be promotional but informative in plain language, and not misleading or selective
  - Upcoming FDA guidance may provide language to provide a safe harbor to disseminate results appropriately to patients
  - In Europe, the laws of each member state define what is considered promotional language and determine penalties
  - Posting results on a company website could have the appearance of a promotional activity and must be considered in context
- Negative trials (results do not support the primary endpoint):
  - Making trial results sound less negative could be misleading to patients
  - Factual representation of negative trials is not considered promotional
  - Negative trials should not be treated fundamentally differently from successful ones
- EMA's view on offering aggregate results crossing regulatory rights:
  - Responsibility of defining rules and penalties lies with member states, not EMA
- Creating a EMA & FDA "neutral website" with neutral language:
  - A third party website could be set up to give guidance; clinical trials.gov was suggested but it was unclear whether this was within their mandate
  - FDA guidance might provide a safe harbor, but FDA cannot offer a roadmap or collaborative effort today since they are still intensely working on this
- Patient privacy/ Health literacy:
  - Would not recommend to patients to go to ClinicalTrials.gov, though ClinicalTrials.gov would have the potential to maintain plain language results, if equipped to do so
  - Who should offer results to the patient? Sponsor, funder, IRB, investigator?
  - Our discussion concerns pre-approval information, since after a drug is approved, patient information is contained in the package insert
- Being helpful for the patient:
  - Since all patients are different, there will likely not be any one document that satisfies every patient
  - Return of results communication should end with referring patient to his/her personal physician; however, it was unclear how much the primary care physician would know about the trial
  - All were in agreement that we should express appreciation for the patient's participation in the trial
  - We are in the early days of defining communication with patients and need guidance to do so; while we all would like to see this situation improved, it is a process that takes time
- Other communication needs:
  - Primary care physicians who are not investigators in clinical trials need support to answer questions of patients who participate in trials; there was a suggestion to add a summary for physicians to the functionality of ClinicalTrials.gov
  - Third party website for summaries (not from industry or investigator)

  - Disease-specific advocacy groups
- Other comments:
  - It takes truly a collaborative effort to make this happen
  - The most direct, safest route for guidance will be from FDA; however, it is imperative to generate results summaries for patients, even without FDA guidance using strictly neutral language
  - Results need to be presented as neutral, not using "safe" or "effective" in summaries
  - Most informed consent forms say that results will be posted on ClinicalTrials.gov, but the site is not in plain language, and the information is not timely when it is posted as it is typically already in the public domain.

India Regulatory, Trial Causality and Compensation Program

Barbara Bierer, MD, and Mark Barnes, JD, LLM, Harvard MRCT

Dr. Bierer introduced Harvard MRCT's work in India. In 2011, the Indian Parliament formed a committee to report on the functioning of the Central Drugs Standard Control Organization (CDSCO) following the death of seven girls who had died while on a HPV vaccine observational study. In 2012, a public interest litigation (PIL) was filed before the Supreme Court of India against the Ministry of Health and Family Welfare (MoHFW) alleging several flaws in the regulatory framework surrounding clinical trials in India. In early 2013, the Supreme Court suspended the power of CDSCO/DCGI to approve clinical trials. In January and February 2013, the government issued new rulings that essentially curtailed or inhibited the introduction of new trials in India. These rulings mandated:

- Compensation in the case of injury or death during a clinical trial, to be provided by sponsor. "Trial related injury or death" is defined very broadly, and includes the failure of the experimental agent to have the desired effect; any harmful effect of a clinical trial procedure, even if the procedure was part of the standard of care for the condition; and the worsening of a condition that could have been expected due to the natural history of the disease condition.
- Sponsor to provide subject free medical management for injury during trial, for as long as required.
- If injury is related to the clinical trial, subject is also entitled to financial compensation from sponsor. A compensation formula determines exactly how much to pay, which ranges from $6,667 to $122,666. The amendment clarifying expectations for compensation of clinical trial related injury or death states that compensation will be made for: adverse effect of investigational product(s), violation of the approved protocol, failure of investigational product to provide intended therapeutic effect, use of placebo in placebo-controlled trial, adverse effect due to concomitant medication, and any clinical trial procedures involved in the study.

- If subject dies during trial, his/her nominee is entitled to financial compensation "over and above any expenses incurred on the medical management of the subject."

Additional regulations include: ancillary care for any other illness afflicting patients in a clinical trial; clinical trials must be conducted in accredited site after review by accredited IRB/REC and only involve certified investigators; clinical investigators may participate in no more than three clinical trials at any one time; 50% of clinical trials must be performed in public hospitals with over 50 beds; and every informed consent must be video-taped by a videographer and preserved. Structural issues include: drugs to be marketed in India must involve trials in India; drugs marketed for more than 4 years outside of India may apply for a license for sale in India with 'bridging' studies or 4 year monitoring studies. There are no regulations for devices.

Harvard MRCT has partnered with AIIMS, AHERF, ISCR, FERCI and others to assist with implementing reforms with clinical trials and co-sponsored a roundtable in Delhi in January 2014. During the last year, Harvard MRCT has focused on India regulatory issues, including:

- proposed India regulatory reforms relating to required certification for investigators and accreditation for research sites and/or IRBs/RECs
- conducted global comparative research for compensation for injury standards
- provided understanding of causality assessment for determination of relatedness
- addressed confidentiality and ethics related to videotaping of informed consent process and limitation of involvement of most competent investigators to three trials

In the meantime, in May 2014, a new prime minister was elected with a mandate for change and a new Minister of Health and Family Welfare was appointed, though many believe that little will be finalized before resolution of the pending Supreme Court PIL case. The Quality Council of India (QCI) was chosen as central agency in charge of standards and accreditation. QCI published draft standards for which comments are due by December 15, 2014. These draft standards include: audiovisual recording to be mandated only for a subset of clinical trials (for vulnerable populations and those unwilling to provide written consent); alter the limit of three trials per investigator; compensation only for injury related to clinical trial and not for therapeutic failure of experimental agent or for placebo arm only if standard of care has been denied. Even with these modifications, many questions remain.

Harvard MRCT has been working on a causality module, which is a "how to" primer detailing points to consider in determining causality of an adverse event and the likelihood it is caused by the treatment. This guidance can be used to assure causality assessments are conducted consistently across jurisdictions, deliver training in various international settings, delineate when unblinding is justified, and develop case studies. Harvard MRCT co-facilitated a Causality Assessment Workshop for Clinical Trial Investigators in Delhi, India, on November 22, 2014, which was attended by about 35 principal investigators and at which the guidance draft document was circulated. The next Causality Assessment for Clinical Trial Investigators workshop is scheduled for February 2015, which will feature revised training and guidance materials. Furthermore, a pilot of the WHO-UHS revision is planned as well as the

development of an online training module for dissemination. Harvard MRCT is also writing op-eds to keep this issue at the forefront.

Discussion

The bottom line from this presentation is that this is not an optimal time to test a product in India since the regulations are anti-scientific and anti-humanity, and even major Indian companies have moved trials out of India. Local CROs have gone out of business and laid off staff, or use staff for data analysis for data from other countries. Approximately 10,000 jobs have been lost.

Nevertheless, some potential steps forward were discussed:

- Industry could comment on standards: what is good, what they miss, how to meet standards
- Harvard MRCT has developed good local allies, including a coalition of researchers
- Hope that causality assessment will be taken up
- Need for another effort to address compensation and other issues
- Real core issue is social justice, which has been addressed with Harvard MRCT op-eds; voicing these issues in India will hopefully establish a firewall in other countries
- Media efforts with op-eds, roundtable in collaboration with Times of India
- Empowering patient advocates, which is almost non-existent in India, except for a few India chapters of international organizations
- Empowering scientific capacity which is understaffed and underpaid and responses from career civil servants are often incomprehensible or defensive

Appendix 1: Meeting Participants

Last Name:	First Name:	Company:	Job Title:	Affiliation:
Aldinger	Carmen	Harvard MRCT Center	Program Manager, MRCT	Staff
Barnes	Mark	Ropes & Gray LLP/ Harvard MRCT Center	Partner	Staff
Bierer	Barbara	Brigham and Women's/ Harvard MRCT Center	Senior Vice President for Research/ Prof. of Med.	Staff
Bohn	Laurie	Merck	Learning Consultant	Sponsor
Carbone	Kathy	Biogen Idec	Director, Quality Operations Capability	Sponsor
Chayab	Lara	Hoffmann La Roche	Patient Recruitment Strategist	
Cohen	Theodora	HCRI	Executive Director, Biostatistics and ARO Programs	Sponsor
Cooper	Jeffrey	WIRB-Copernicus Group	Vice President Global Consulting	Sponsor
Dogas	Dimitrios	Harvard MRCT Center	Staff Assistant	Staff
Drazen	Jeffrey	NEJM	Editor-In-Chief	Speaker
Dunayevich	Eduardo	Amgen	Global Development Executive Medical Director	Sponsor
Fingert	Howard	Takeda Pharmaceuticals	Senior Medical Director	Sponsor
Frank	Liz	Dana Farber Cancer Institute	Patient Advocate	Speaker
Georgianna	Land	Homo & Natura Universita Popolare		
Hallinan	Zachary	CISCRP	Director, Patient Communication & Engagement	
Hayes-Licitra	Sandra	Janssen Research and Development	Associate Director, Medical Writing	Sponsor
Henderson	Cindy	Veristat	Executive Vice President, Operations	Sponsor
Hill	Nina	Pfizer	VP Policy Center of Excellence	Sponsor
Hinkley	Terri	ACRP	Deputy Executive Director	Sponsor
Kress	Barbara	Merck	Department Head: Disclosure and Data Access	Sponsor

Kupelnick	Bruce	Tufts/NEMC	Epidemiologist	
Kush	Rebecca	CDISC	President	Sponsor
Laderman	Ross	Kowa Research Institute	Vice President, Regulatory Affairs	Sponsor
Letvak	Laurie	Novartis Pharmaceuticals	VP, Head of Clinical Development Policy	Sponsor
Li	Rebecca	Harvard MRCT Center	Executive Director	Staff
Lynch	Holly	Petrie-Flom Center, Harvard Law School	Executive Director	
McCarthy	Justin	Pfizer	SVP - Global Policy & International Public Affairs	Sponsor
McNair	Lindsay	WIRB-Copernicus Group	Chief Medical Officer	Sponsor
Menikoff	Jerry	OHRP	Director, Office for Human Research Protections	Speaker
Miller	Jennifer	Harvard University	Fellow	
Mitchel	Jules	Target Health Inc.	President	Sponsor
Morris	Sandra	Johnson & Johnson	VP Strategic Realization	Sponsor
Moscicki	Richard	FDA	Deputy Center Director for Science Operations	Speaker
Myers	Laurie	Merck	Leader, Health Literacy Strategy	Sponsor
Nam	Jun Yeb	Daegu Catholic Univ. Medical Center / CIMI	Medical Researcher	Sponsor
Okada	Ellie	Boston Cancer Policy Institute	Senior Fellow, President	
O'Rourke	Pearl	Partners HealthCare Systems	Director	
Potts	Jeannette	Takeda Pharmaceuticals	Vice President - Legal	Sponsor
Rajan	Rohin	Deloitte Consulting	Management Consultant	Sponsor
Rosenblatt	Michael	Merck	Executive Vice President, Chief Medical Officer	Sponsor, Speaker
Rossignol	Natalie	Bill & Melinda Gates Foundation	Senior Program Manager	Sponsor
Rotz	Ben	Eli Lilly	Advisor - Office of Medical Transparency	Sponsor
Russell	Donald	Eli Lilly	Sr. Director, Global Clinical Operations	Sponsor
Scott	Jessica	GSK	Director, North America Medical Policy & Advocacy	Sponsor

Seltzer	Jonathan	ACI Clinical	President	Sponsor
Shah	Amish	Harvard Law/Harvard MRCT Center	Grduate Legal Fellow	Staff
Shapiro	Zach	Harvard Law/Harvard MRCT Center	Grduate Legal Fellow	Staff
Shin	Im Hee	Daegu Catholic Univ. Medical Center / CIMI	Professor	Sponsor
Shull	Anthony	Attorney	Attorney	
Skirboll	Lana	Sanofi	VP Scientific and Academic Affairs	Sponsor
Smith	Jack	Harvard Alumni	Law Office	
Srinivasan	Subasree	Bristol-Myers Squibb	Medical Lead	
Stockwell	Caroline	Pfizer	Assistant General Counsel	Sponsor
Taber	Magdalena	Independent Consultant	Owner	
Teden	Patricia	Teden Consulting	Principal	
Thomasell	James	ACRP	Executive Director	Sponsor
Ulrich	Jocelyn	PhRMA	Director, Scientific and Regulatory Affairs	Sponsor, Speaker
Van Denmark	Lynn	MedTrials, Inc. / ACRP	CEO / ACRP Chair	
Wacholtz	Mary	Janssen Research and Development	Senior Director	Sponsor
Wendel	Jeffrey	Chesapeake IRB	CEO	Sponsor
Wilenzick	Marc	International Aids Vaccine Initiative	Deputy GC	Sponsor
Winkler	Sabune	The Harvard Catalyst	Regulatory Affairs Director	

Appendix 2: Meeting Agenda

Harvard MRCT 3rd Annual Meeting and Dinner

- *Dinner*- 2nd December 2014 from 6:00-8:00 pm, Henrietta's Table, 1 Bennett St, Cambridge, MA
  Annual Meeting- 3rd December 2014 from 7:30 am-5:00 pm, Loeb House, 17 Quincy Street, Cambridge, MA

Participants: MRCT Executive Committee, Steering Committee and Interested Stakeholders

2nd December 2014, Dinner PART ONE (for Executive Committee, Steering Committee, & Conference Speakers

6:00 – 8:00 pm	**Dinner at Henrietta's Table; welcoming Harvard MRCT Executive and Steering Committee members and conference speakers**

3rd December 2014, Annual Meeting
PART TWO (Open to all registered participants)

7:30 – 8:00 am	**Participants' Arrival, Registration, and Breakfast**

Welcome

8:00 – 8:30 am	• **Welcome** • **Introduction to Harvard MRCT and the Return of Results Guidance Document**	• **Barbara Bierer, M.D.** • **Mark Barnes, J.D.**

Invited Speakers Perspectives on Returning Aggregate Results to Study Participants

8:30 – 8:50 am	• **Regulatory perspective, EMA**	• **Anabela Marcal, PharmD**
8:50 – 9:05 am	• **Regulatory perspective, FDA**	• **Richard Moscicki, M.D.**
9:05 – 9:20 am	• **OHRP perspective**	• **Jerry Menikoff, M.D., J.D.**
9:20 – 9:35 am	• **NEJM perspective**	• **Jeffrey Drazen, M.D.**
9:35 – 9:50 am	• **Industry perspective, Merck**	• **Michael Rosenblatt, M.D.**
9:50 – 10:05 am	• **PhRMA perspective**	• **Jocelyn Ulrich**
10:05 – 10:20 am	• **Patient perspective, Dana-Farber**	• **Elizabeth Frank**
10:20 – 10:30 am	• **NIH perspective**	• **David Gordon, M.D., MPH, PhD**
10:30 – 11:00 am	• **Panel Discussion**	• **Mark Barnes, J.D. (Moderator)**

Break 11:00 – 11:20 am

11:20 – 12:00 pm	• **India Regulatory** • **Trial Causality and Compensation Program**	• **Barbara Bierer, M.D.** • **Mark Barnes, J.D.**

PART THREE

12:00 – 4:00 pm	**Closed Meeting for Executive and Steering Committees** • **Lunch for Executive/Steering Committees and Speakers served**

PART FOUR

4:00 – 5:00 pm	**Executive Committee Session**

Appendix 3: Speaker Biographies

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

Mark teaches health care law and research law as a faculty member at Harvard Law School and formerly served as the associate provost and senior research officer for Harvard University.

Mark has served as executive vice president and chief administrative officer at St. Jude Children's Research Hospital, had held senior appointed positions in the New York State and City departments of health, was the founding executive director of Harvard PEPFAR's AIDS treatment programs in Nigeria, Tanzania, and Botswana, and headed the national HIV/AIDS lobbying effort in 1995-96 as the executive director of AIDS Action Council, the DC-based national AIDS advocacy coalition. He is currently the NIH ethics advisor to the HPTN 071 trial of HIV testing and treatment interventions with one million participants.

Barbara E. Bierer, M.D., is the faculty co-chair of the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT), 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 sciences 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 focus for entrepreneurship and innovation. In addition, she was the Founding Director of the Center for Faculty Development and Diversity at the BWH.

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.

Jeffrey Drazen, M.D., Born and raised in Clayton, Missouri, Dr. Drazen majored in applied physics at Tufts University and graduated from Harvard Medical School in 1972. After serving his medical internship at Peter Bent Brigham Hospital in Boston, he joined the pulmonary divisions of the Harvard hospitals. He served as chief of Pulmonary Medicine at the Beth Israel Hospital, chief of the combined Pulmonary Divisions of the Beth Israel and Brigham and Women's Hospitals, and then as chief of Pulmonary Medicine at Brigham and Women's Hospital.

Through his research, Dr. Drazen defined the role of novel endogenous chemical agents in asthma, leading to four new licensed pharmaceuticals for asthma with millions of people on treatment worldwide. In 2000, he assumed the post of editor-in-chief of the New England Journal of Medicine. During his tenure, the Journal has published major papers advancing the science of medicine, including the first descriptions of SARS, coverage of the Ebola epidemic, and modifications in the treatment of cancer, heart disease and lung disease. It has also been at the forefront of the international effort to register all clinical trials. The Journal, which has over a million readers every week, has the highest impact factor of any journal publishing original research.

Elizabeth Frank, Liz Frank is the lead patient advocate for the Dana Farber/Harvard Cancer Center (DF/HCC) Breast Cancer Patient Advocacy Group, where she coordinates and organizes a group of about 14 patient advocates, and develops opportunities for members to collaborate with translational and clinical researchers. Liz is a ten year breast cancer survivor. She attended the National Breast Cancer Coalition's Project LEAD Science Course in 2006, the Clinical Trials LEAD in November 2008 and Quality LEAD in 2009. Liz currently serves on the NCI Breast Cancer Steering Committee and is Co-Chair of the NCI Patient Advocate Steering Committee.

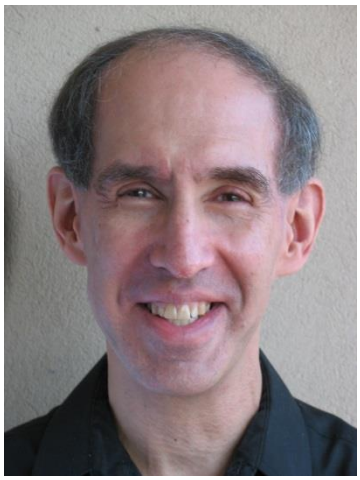
Additionally, she serves as a patient advocate for the DF/HCC Breast Cancer Clinical Trials Group, the Translational Breast Cancer Research Consortium (TBCRC), and is a member of the DSMB for the ISPY-2 Trial. Liz has been a member of the Multi-Regional Trial Working Group on Returning Results and has also collaborated on return of results efforts for a single academic cancer center and a national clinical trials group. Liz is particularly interested in increasing the effectiveness of patient advocates, issues related to educating and consenting of patients on clinical trials and the return of clinical trial results. Liz received her B.A. from Boston University in economics and a Master's degree from the Harvard School of Education in education research and program evaluation.

Rebecca Li, PhD, 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 Trial Center at 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.

Anabela Luis De Lima Marcal, PharmD, is Head of Compliance and Inspections at the European Medicines Agency.

She received a professional certification degree in hospital pharmacy in 1994 and also a degree in pharmacy in 1991.



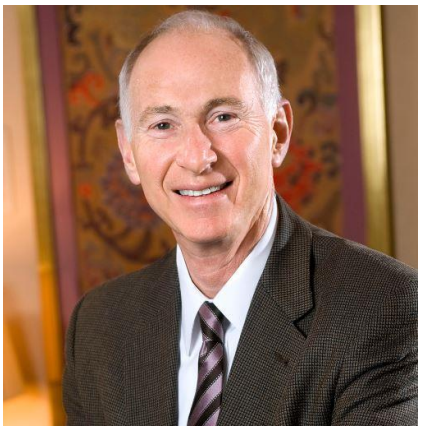
Jerry Menikoff, M.D., J.D., is the Director of the Office for Human Research Protections (OHRP), an office within the U.S. Department of Health and Human Services. That office is one of the lead units of the U.S. government responsible for protecting research subjects. Prior to joining OHRP, Dr. Menikoff served as the director of the NIH Office of Human Subjects Research, responsible for protecting subjects enrolled in NIH intramural research.

Prior to that, he was Associate Professor of Law, Ethics and Medicine at the University of Kansas. Among the books he has authored or co-authored are Law and Bioethics: An Introduction (Georgetown University Press) and What the Doctor Didn't Say: The Hidden Truth about Medical Research (Oxford University Press).

Richard Moscicki, M.D., serves as CDER's Deputy Center Director for Science Operations. He shares in the executive direction of Center operations and provides leadership in overseeing the development, implementation, and direction of our programs.

Before joining CDER, Dr. Moscicki served as senior vice president (SVP), Head of Clinical Development at Genzyme Corporation. He joined Genzyme in 1992 as medical director and became the chief medical officer and SVP of biomedical and regulatory affairs in 1996 -- holding that post until 2011. Over the past two decades, Dr. Moscicki has been responsible for worldwide global regulatory and pharmacovigilance matters, as well as all aspects of clinical research and medical affairs for the company.

Dr. Moscicki received his medical degree from Northwestern University Medical School. He is board certified in internal medicine, diagnostic and laboratory immunology, and allergy and immunology. He completed his residency with a focus on immunology, followed by a four-year fellowship at Massachusetts General Hospital (MGH) in immunology and immunopathology. He remains on staff at MGH and on the faculty of Harvard Medical School.



Michael Rosenblatt, M.D., is executive vice president and chief medical officer at Merck. He is the company's primary external advocate on medical issues and represents the voice of the patient inside Merck.

Dr. Rosenblatt previously was Dean of Tufts University School of Medicine; the George R. Minot Professor of Medicine at Harvard Medical School; and president of Beth Israel Deaconess Medical Center (BIDMC). He was the Harvard faculty dean and senior vice president for academic programs at BIDMC. He was also director of the Harvard-MIT Division of Health Sciences and Technology.

Prior to these leadership positions, he was senior vice president for research at Merck where he co-led the worldwide development team for alendronate (FOSAMAX®). Earlier, he was chief of the Endocrine Unit at the Massachusetts General Hospital.

Committed to innovation, he has served on the board of directors and scientific advisory boards of several biotechnology companies and is a scientific founder of ProScript, Radius Pharmaceuticals and Theracrine.

Dr. Rosenblatt was elected to the American Society of Clinical Investigation and the Association of American Physicians, is a fellow of the American Association for the Advancement of Science and the American College of Physicians, and served as the president of the American Society of Bone and Mineral Research.

He received his undergraduate degree *summa cum laude* from Columbia University and his M.D. *magna cum laude* from Harvard Medical School.

Jocelyn Ulrich, MPH, RAC, is Director, Scientific and Regulatory Affairs at PhRMA, where she supports PhRMA's policy advocacy strategies on clinical trials and innovative biologics and biosimilars. Prior to joining PhRMA, Jocelyn held positions at Pfizer and Human Genome Sciences in SOP development and implementation, clinical research management, and Medical Affairs.

She is a recognized expert in managing public-private research collaborations, and from 2011 – 2013 she led the Investigator-Initiated and Sponsored Research Association's (IISRA) Collaboration Forum, a cross-functional group that aims to establish best practices for research conducted in partnership with Industry and the NCI-funded Cooperative Groups.

Jocelyn is an active member of the Healthcare Businesswomen's Association (HBA) Mid-Atlantic Chapter, and has served as Chair of the Membership and Outreach sub-committee of the Mid-Atlantic Women in Science Committee since 2012. She received her MPH in Global Health Policy and Management from NYU.