Proceedings

MRCT Annual Meeting

28th November 2012 • 8:00 AM to 4:30 PM

Harvard Faculty Club • Cambridge, MA

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AGENDA

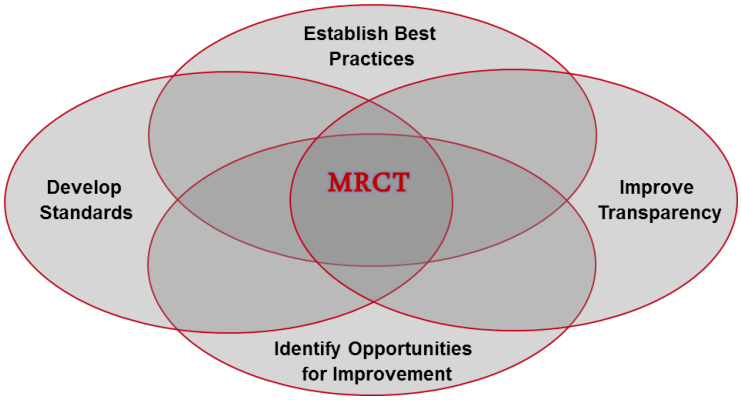
Time	Topic	Presenters/Moderator(s)
8:30 – 9:15 AM	MRCT Welcome and Introductions Agenda and Expectations Overview of Current MRCT Initiatives	Barbara Bierer Mark Barnes Rebecca Li
9.15 – 10:00 AM	Keynote Speaker Regulatory Perspective on MRCT Issues	Robert O'Neill
10:00 – 10:30 AM	Roadmap Project of Ongoing Clinical Initiatives by Consortia and Collaborative Groups	Pete Lyons Rohin Rajan
10:30 AM – 11:00 AM	MRCT Protocol Ethics Initiative Presentation and Panel Discussion	Susan D'Amico David Forster
11:30 AM – 2:00 PM	Global Regulatory Authority and Regional Stakeholder Presentations (Working lunch)	Agnes Klein Vijai Kumar Ockjoo Kim Evegny Rogoff Sabine Haubenreisser Ann Meeker-O'Connell
2:00 – 2:15 PM	Break	
2:15 – 3:15 PM	MRCT DMC/DSMB Initiative Presentation and Panel Discussion	Charles Knirsch
3:15 – 415 PM	MRCT Training Initiative	Natalie Rossignol
4:15 – 4:30 PM	Wrap-up/ Steps for moving forward	Barbara Bierer Mark Barnes Rebecca Li

INTRODUCTION

MRCT CENTER

Purpose: *To improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research.*

Objectives:



Establish Best Practices	To establish best practices of performance and to enhance the scientific and ethical conduct of multiregional research.
Develop Standards	To establish common, explicit, realistic and ethical standards for conduct of transnational research
Identify Opportunities for Improvement	To align practice with those standards and study barriers to alignment
Improve Transparency	To enhance predictability for the benefit of research participants, regulatory authorities, sponsors and researchers

Meeting Objectives

- Provide an update to all stakeholders regarding current initiatives and progress
- Engage regulators in the MRCT initiatives and mission
- Obtain feedback from regulators and stakeholders on MRCT ongoing and planned initiatives
- Collect survey data on potential new initiatives (please complete)

EXECUTIVE SUMMARY

A Regulatory Perspective on MRCT's and Potential Strategies to Synergize Initiatives

Robert T. O'Neill PhD, Senior Statistical Advisor to CDER, OTS, FDA

Dr. O'Neill discussed industry's increasing reliance on foreign clinical data. He also shared information about ongoing projects that might be of interest to the MRCT Project and suggested ways in which the groups might align.

Sponsors are increasingly relying on data from foreign clinical trials to support their marketing applications for new drugs and biologics. In a 2010 report the Office of the Inspector General (OIG) identified some of the challenges that inhibit FDA oversight of foreign trials. Missing from the report, however, was guidance on factors such as study planning, analysis, and interpretation that might help to overcome some of these challenges. Dr. O'Neill suggested that these may be areas of focus for the MRCT Project. For background he directed the group's attention to two documents that may be of use: the International Conference on Harmonization (ICH) – ICH E5, which established the framework for the conduct of foreign clinical trials and introduced the idea of a bridging study and the 2006 Q & A Appendix to ICH E5 (R1), which introduced the framework for a *simultaneous* multi-regional bridging trial and described how these studies might be planned, analyzed, and interpreted.

As the size and complexity of multi-regional trials increase so do the sources of variability in the estimates of treatment effect/response and other factors. Dr. O'Neill emphasized that potential areas of variability in regional and site outcomes should be evaluated as early as possible. He suggested several *a priori* planning concepts he feels are important for sponsors, regulators, and perhaps members of the Data Monitoring Committee (DMC)/Data Safety Monitoring Board (DSMB) to be aware of in the context of a multi-regional trial: sample size (overall and per region), expected variation in treatment effects, and potential sources of variability and/or systematic differences (e.g., the investigator, patients, study conduct, medical/clinical environment, and quality of the data). Dr. O'Neill commented that planning is an area that no one has taken ownership of and suggested that it may be a place for the MRCT Project to make an impact.

In his concluding remarks, Dr. O'Neill suggested the MRCT Project consider partnering with PhRMA's MRCT KIT program (See Appendix A for more information about their program), the Drug Information Association (DIA), and/or the Asia Pacific Economic Cooperation (APEC) regulators (through the APEC Harmonization Center [AHC]). In addition, he mentioned that both Pharmaceutical Statistics and the Journal of Biopharmaceutical Statistics have recently published Special Issues on the conduct of multi-regional trials.

Roadmap and Opportunity Analysis for Clinical Development Improvement Initiatives

Pete Lyons, MBA and **Rohin Rajan, PhD**, Deloitte Consulting presented the results of a Roadmap and Opportunity Analysis for MRCT. The objectives of the analysis were to:

- Determine potential opportunity areas for MRCT that are consistent with its unique organizational focus, mission and initiatives portfolio
- Highlight MRCT's differentiated position amongst other consortia active in clinical development
- Recommend MRCT's forward path as comprised of specific, targeted collaboration opportunities with other consortia and other stakeholders in the clinical trial enterprise

The analysis showed that at the initiative level, MRCT is clearly differentiated from other efforts across consortia and that its unique initiatives enable high-impact solutions for various clinical trial stakeholders and opportunities for collaboration with regional and global consortia. The analysis confirmed that MRCT initiatives are focused in highly concentrated high-level categories suggesting that there is a strong demand for solutions in these areas. At a sub-category level its' initiatives are aligned to complex and multi-faceted efforts that require requiring distinct and collaborative approaches. The path forward for MRCT will represent a continued effort to differentiate and collaborate in order to develop holistic approaches.

During the discussion that followed, there appeared to be consensus that it will be important for MRCT to establish synergy/collaboration among the higher levels of the various consortia to ensure that the relationships are ongoing so they can be effective in the early stages of the next generation of projects and not just confined to current efforts.

Protocol Ethics Working Group Phase 1 Report

Susan Callery-D'Amico, BSN, Reata Pharmaceuticals, Inc. and **David Forster, JD, MA, CIP**, Western Institutional Review Board, presented the Protocol Working Group's Phase 1 report in which they identify constraints that affect the ethical considerations in clinical protocols. The report addresses these constraints from two perspectives: those that impact the Institutional Review Boards (IRBs) and Ethics Committees (EC) who review the protocol and those that affect the study teams that develop them. It proposes a new section to the protocol that focuses specifically on ethics.

Several deliverables are in process.

- A protocol ethics template was drafted in November 2012 with a final version due January 2013.
- A draft document containing points-to-consider that will guide the user towards drafting a standardized protocol and informed consent form (ICF) ethics section was completed in December 2012. The final version is due January 2013.
- A web tool for an on-line decision tree and checklist that provides guidance at the main decision points during the design phase and allows users to populate sections within a prescribed template format has been evaluated. A draft for programming is expected in March 2013 with the final product being available June 2013.
- Development of a companion checklist for ECs to ensure that key ethics issues have been addressed is also scheduled for June 2013.

The rationale for adding a standalone protocol ethics review section is to ensure that as a protocol is being developed the appropriate issues are raised and a conscious decision is made on each item. In addition, the work group believes that this approach, when used with the checklist that is also in development, provides the appropriate level of information to the members of the EC/IRB as they make the decision on whether a trial may proceed.

This presentation was well-accepted. Comments from the regulatory and regional stakeholder panel were centered on whether this section could be implemented without additional burden to the reviewers, whether it is sufficiently flexible to be used in all types of clinical trials, and the need for training. Areas of the document the members of the panel thought may be either missing or not given sufficient attention were: conflict of interest arising from payments to the investigator, vulnerable groups, compensation for trial-related injury, and post-trial access and disclosure.

Global Regulatory Authority and Regional Stakeholder Presentations

Challenges in Multiregional Trials – From the Canadian Perspective

Agnes Klein, MD, DPH, Health Canada, discussed some of challenges with multi-regional trials from the Canadian perspective. She noted that some of these stumbling blocks can result from regional variability in clinical outcomes, ethics, populations, and statistical considerations while others stem from legislative and regulatory issues. Areas of particular concern include training and educational gaps (e.g., minimal or no training of personnel, and poor understanding of GCPs and the need to follow rigorous process) and poorly kept source records. Dr. Klein also noted that with multi-regional trials it is sometimes difficult to determine the degree to which and the form in which ethical processes are used.

Transition from an Excellent Clinician to a Competent Investigator: The Indian Challenge

Vijai Kumar, MD, Excel Lifesciences India, discussed how India is moving forward to increase trial capacity and what is still needed. He told the group he believes India needs to increase trial capacity, particularly in the tier 2 and 3 cities, and enhance competence at all sites through continuous training for all personnel involved in clinical trials (including community outreach). Dr. Kumar sees the training program as a collaborative effort among the regulators, industry, and academia through specialty associations/professional bodies. It should also include the identification of trainers and mentors. He suggested mandatory certification.

Several initiatives are completed or are ongoing. The Drugs Controller General of India (DCGI) has initiated GCP inspections and US, EMA, and Canadian regulators have played an active part in training the inspectors; joint inspections are not uncommon. A clinical trial registry has been instituted as has registration of ECs. India has also developed guidelines for compensation of trial related injury and within the last two years New Drug Approval Committees have been established for IND & NDA approval. The immediate issues for India include: training of DSMB members, converting more clinicians to competent investigators, and assistance in causality analysis to determine compensation.

Needs and Priorities in MRCT in Korea

Ockjoo Kim, MD, PhD, National University College of Medicine Korea, discussed the initiatives that have already been undertaken to increase Korea's competitiveness in clinical trials and what is being planned.

The National Enterprise for Clinical Trials (KoNECT) currently supports 15 regional trial centers and a human resource academy comprised of 19 educational centers that train ~5000 to 7000 students annually. A certification program was started in January 2012 for clinical investigators, clinical research associates (CRA) and clinical research coordinators (CRC). Certification has two levels: qualified (refers to competency) and certified (refers to expertise), and is based on completion of training, job experience and written exams. Certification is good for 2 years; education is required to maintain certification.

The 2020 Clinical Trial Future Creation Planning Group is currently working to strengthen Korea's regulatory competitiveness, establish strategic plans for medical device clinical trial development, enhance the clinical trials communication system, strengthen the clinical trials safety protection system, and strengthen clinical trial capability. Other recent initiatives include the establishment of a global leading clinical trial center consortium to serve as an early phase center of excellence and a clinical trial information center to provide patient education. Guidelines for evaluating clinical trials with women are being developed by the Korean FDA, which has also allocated significant funds towards clinical trials for children.

Clinical Trials in the Russian Federation: What are the features?

Evgeny Rogoff, Clinical Trials Control department, Roszdravnadzor of Russia, discussed the clinical trial environment in Russia. He noted that by law, clinical trials conducted in Russia can only be performed by the research sites registered in the official database of the Ministry of Health (currently~844, most in Moscow and St. Petersburg). Only a qualified person (an MD specializing in the area under investigation in the trial) with at least 5 years of professional experience in clinical trials area can serve as PI. Most PIs are GCP trained and fluent in English. Up to 90% of the clinical trial monitors have a healthcare background.

EMA Needs and Priorities Relating to Multi-Regional Clinical Trials

Sabine Haubenreisser, MSc, PhD European Medicines Agency Liaison Official Based at the FDA, discussed the EMA approach to multi-regional trials. Dr. Haubenreisser said that the two main issues for European Regulators are the acceptability of the trial (ethical standards, GCP compliance) and it's applicability to European populations and medical practice. For acceptability, the EMA relies on a recently published reflection paper, which stresses that reviewers must confirm that ethical principals have been respected in the protocol and in the conduct of the trial and that there has been compliance with GCP at every step for every clinical trial. The document makes it clear that these concepts must be proactively enforced at the planning stage and again at the assessment stage. For the issue of applicability, the EU regulators look to the framework established in the ICH E5 and ICH Topic E5(R1) Questions and Answers.

Dr. Haubenreisser noted that it is becoming clear that although intrinsic factors cannot be ignored, extrinsic factors are becoming increasingly important in the interpretation of differences in outcomes between populations of patients. Important points to be considered fall into three areas:

1. Medical practice (differences in co-medications and invasive procedures)
2. Disease definition (heterogeneous medical conditions, medicalization of some conditions, insufficient standardization and validation of scores and scales)
3. Study population (different inclusion criteria, life style, medical and social environment)

CDER Perspective: Enhancing Trial Quality and Efficiency

Ann Meeker-O'Connell, Office of Compliance, Office of Scientific Investigations, FDA, spoke about the CTTI Quality-by-Design Project, which was initiated to develop a set of high-level principles for building quality into trials and suggest a potential approach to prospective quality planning.

Ms. Meeker discussed how prospectively identifying the aspects of the trial that are critical to quality and the important and likely intrinsic and extrinsic risks to those quality aspects allows the trial planner to adjust the investigational plan and its implementation to eliminate or reduce errors that could undermine the ability to draw conclusions from the trial results or meaningfully impact the subjects' safety.

Successful integration of quality into clinical trials rests on four areas:

- Focus on first principles: Why do we do clinical trials? To obtaining reliable evidence for decision-making
- Encourage broad engagement of stakeholders, including clinical investigators, patients, and regulators
- Identify and discuss the barriers to implementation early
- Be willing to pilot and refine Quality by Design (QbD) and Quality Risk Management (QRM).

The group and the panelists then discussed and raised questions about all of the presentations made by the global representatives. Mr. Barnes specifically asked the panel "What can MRCT do?" Following are some of the responses.

- Maintain a library or other resource to help planners identify differences in medical practices, privacy laws, etc., among various regions.
- Facilitate increasing the investigators' and academic community's awareness of the principles of QbD.
- Map the existing initiatives, training, and capacity building.

- Connect experienced clinical investigators with those who would like to perform clinical trials for mentoring.
- Education for the EC

DSMB Working Group Update

Charles Knirsch, MD, MPH, Pfizer, provided an update on the progress of the DSMB Working Group, which was formed to increase the engagement of experts from the emerging world on DMCs for multi-regional trials. To that end they have:

- Obtained agreement from the Fogarty Institute to solicit qualified Fogarty International Clinical Research Scholars & Fellows for the program, once regions are determined.
- Submitted a proposal to partner with the Society of Clinical Trials (SCT) to co-sponsor a one-day training workshop at the 2013 SCT meeting.
- Are currently identifying trials that are scheduled to be conducted in emerging countries, are in the pipeline to start in Summer/Fall of 2013, and would be appropriate to have apprentice DSMB members from emerging markets to serve on boards. Right now they expect 6-12 fellows to be trained in May and start participation in Spring/Fall of 2013.

There was significant discussion on the contents of the training program, which was very well accepted. Issues and questions mainly focused on how to lengthen the one-day workshop, expand the curriculum, and expand access to the training. Several potential partnerships and /or opportunities for collaboration were suggested, including PharmaTrain and the Clinical and Translational Research Awards (CTSA). There was also a suggestion that consideration should be given to conducting training sessions during appropriate congresses and meetings as a way to extend the program's reach.

PI Competence and Training Working Group Update

Natalie Rossignol, Bill and Melinda Gates Foundation, provided an update on the early progress of the Investigator Competence and Training Team, which met for the first time about two weeks ago and is building on work done during Phase 1 in 2010. Current projects include:

- Develop a draft minimum list of core competencies for PIs and clinical staff for discussion at a DIA roundtable forum in June 2013.
- Develop measurements of impact for training initiative outputs for discussion at a DIA roundtable forum in June 2013
- Review currently available GCP training materials; assess against proposed standards and identify the gaps (Due: December 2013)

MEETING SUMMARY

A Regulatory Perspective on MRCT's and Potential Strategies to Synergize Initiatives

Robert T. O'Neill PhD, Senior Statistical Advisor to CDER, OTS, FDA

Dr. O'Neill discussed industry's increasing reliance on foreign clinical data and MRCT's and the FDA's interest in these trials. He then shared information about other ongoing projects that might be of interest to the MRCT Project and suggested ways in which the groups might align.

Sponsors are increasingly relying on data from foreign clinical trials to support their marketing applications for new drugs and biologics. According to a 2010 report from the Office of the Inspector General (OIG)[1] ~80% of the marketing applications for drugs and biologics approved during 2008 relied on data from foreign clinical trials. During this same time period, however, the FDA inspected only 0.7% of these foreign trial sites. The report identified the following challenges to FDA oversight of foreign trials:

- the increasing number of early-phase trials being conducted outside the United States without Investigational New Drug (IND) Applications (thus without FDA knowledge)
- logistics
- the use of nonstandard formats for submission and the failure of sponsors to provide accurate and complete clinical study reports

Missing from the report, however, was guidance on factors such as study planning, analysis, and interpretation that might help to overcome some of these challenges. Dr. O'Neill suggested that these may be areas of focus for the MRCT Project. He discussed two documents important to the development of multi-regional trials that members of the MRCT Project should be familiar with: the International Conference on Harmonization (ICH) – ICH E5[2] Report and its 2006 Appendix.[3] The ICH-E5 established the framework for the conduct of foreign clinical trials and introduced the idea of a bridging study. In this 1998 report a bridging study was defined as: "…a supplemental study performed in the new

region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region." In other words the bridging study was sequential. However, when the 2006 a Q & A appendix was added to ICH E5 as clarification[3] the document took the bridging concept a step further by introducing the framework for a *simultaneous* multi-regional bridging trial and presenting a conceptual context describing how these studies might be planned, analyzed, and interpreted.

As the size and complexity of multi-regional trials increase, so do the sources of variability in the estimates of treatment effect/response and other factors. To adequately address these potential areas of variability, regional and site outcomes should be evaluated for dropout rate, differences in response rates, covariates, exposures, follow-up, and concomitant drugs all of which may be related to intrinsic (markers, gender, ethnicity) and/or extrinsic factors (recruitment patterns, medical support system, standards of care). With the availability of electronic records it is also feasible to evaluate individual patient records in more detail. Dr. O'Neill added that the Center for Drug Evaluation and Research (CDER) is considering aligning their inspection strategy with the review process in recognition of this complexity.

While differences in treatment effect are to be expected in multi-regional trials, too much heterogeneity is problematic and a proper evaluation must consider whether the treatment differences are real and whether they are systematic. To place the issue into context, Dr. O'Neill discussed several publications showing differential effects among multi-regional trial participants.[4-8] He suggested several *a priori* planning concepts that are important for sponsors, regulators, and perhaps members of the Data Monitoring Committee (DMC)/Data Safety Monitoring Board (DSMB) to be aware of: sample size (overall and per region), expected variation in treatment effects, and potential sources of variability and/or systematic differences (e.g., the investigator, patients, study conduct, medical/clinical environment, and quality of the data). Dr. O'Neill commented that planning is an area that no one has taken ownership of and suggested that it may be a place for the MRCT Project to make an impact. He offered some thoughts on what might be done at each stage.

At protocol planning stage

- Be aware of and plan for heterogeneity/variation
- Decide in advance how much is too much
- Sample size the trial according to expected heterogeneity
- Choose sites (and investigators) with some prior information on performance
- Plan endpoints (e.g., composites) with knowledge of sensitivity to medical culture and health care environment

At the analysis stage

- Analyze and display results using models that account for site, country, and region
- Evaluate statistical interactions and use other tools to explore chance variation
- Evaluate intrinsic/extrinsic factor contributions and imbalances

Dr. O'Neill also presented several topics to be considered when planning for heterogeneity and developing analysis plans to deal with it:

- How and why are sites selected - What is known about investigator training
- Use of central statistical monitoring to identify outliers
- Rationale for number of sites per country/region and sample size per site
- What might the stratification be (not always obvious – country, region, size)
- When only a single large study may be conducted – raise the bar

He recommended several recent articles that present useful statistical analysis tools for the exploration of regional differences and methods that may be worth consideration in designing a multi-regional clinical trial[9-13] and suggested that, in addition to the standard monitoring, trial designers should consider inspection/audit strategies. He referred the group to Special Issues on the conduct of multi-regional trials that were recently published by Pharmaceutical Statistics[14] and the Journal of Biopharmaceutical Statistics.[15]

In his concluding remarks, Dr. O'Neill said that the MRCT Project should seek to partner with other groups already working in the area of multi-regional trials including PhRMA's MRCT KIT program (Appendix A), the Drug Information Association (DIA), and the Asia

Pacific Economic Cooperation (APEC) regulators (through the APEC Harmonization Center [AHC]).

Roadmap and Opportunity Analysis for Clinical Development Improvement Initiatives

Pete Lyons, MBA and **Rohin Rajan, PhD**, Deloitte Consulting

Mr. Lyons and Dr. Rajan presented the results of a Roadmap and Opportunity Analysis they completed following the September MRCT meeting. The objectives of the analysis were to:

- Determine potential opportunity areas for MRCT that are consistent with its unique organizational focus, mission and initiatives portfolio
- Highlight MRCT's differentiated position amongst other consortia active in clinical development
- Recommend MRCT's path forward including specific, targeted collaboration opportunities with other consortia and other stakeholders in the clinical trial enterprise

Methodology

Fifteen consortia (Appendix B) and 88 initiatives were profiled in detail. The consortia were classified by type (e.g., public-private, industry), longevity (e.g., date founded), sponsors, and geographic emphasis. The initiatives were assessed based on whether they had a strategic or operational alignment, their highest level of focus (e.g., trial operations), sub-focus areas (e.g., training related to trial operations), life sciences (LS) value chain focus area (e.g., clinical development), and timeframe (e.g., near-term, mid-term, long-term).

Results

- MRCT is one of 11 consortia with a specific global focus. Although a global focus does not completely differentiate MRCT from other consortia, it does provide an opportunity for a broader impact for MRCT's initiatives.
- MRCT is one of eight consortia with a focus on regulatory guidance, trial operations, and standards development. The high concentration of interest in these areas suggests a strong demand for solutions.

- MRCT's initiatives are aligned to three major sub-categories (standards guidance, trial operations training, and regulatory policy guidance). The significant concentration in terms of the number of initiatives for each of these sub-categories suggest that they are complex and multi-faceted issues requiring distinct and collaborative approaches.
- At the initiative level, MRCT is clearly differentiated from other efforts across consortia. Its unique initiatives (DMC/DSMB, PI and site training, protocol ethics, and a regulatory authority engagement initiative) enable high-impact solutions for various clinical trial stakeholders and opportunities for collaboration with regional and global consortia.
- MRCT participates across all of the possible beneficiary groups/stakeholders across the clinical trial enterprise.

Recommendations

Maintain a Differentiated Focus

- Strategic initiatives such as protocol ethics, should be translated into tactical steps to facilitate sponsor uptake via pilot programs.
- Build and expand on the Regulatory Authority Engagement Initiative for faster/deeper insights into policy changes at a regional level. Evaluate and expand into opportunity areas aligned with MRCT's mission and focus (e.g., operationally-focused regulatory guidance initiatives, data-sharing initiatives, and education-focused initiatives).

Collaborate to Create a Comprehensive Solution

- Evaluate partnership opportunities with TransCelerate (mutual recognition for site qualification) to expand training impact.
- Develop and incorporate output and lessons from Site Metrics efforts (CTTI) and Site Quality Informatics (ACRES) as needed for PI and site training.
- For DMC and DSMB training, engage in discussions with the Critical Path Institute (CPI) on predictive safety testing, e-patient reported outcomes, data submission guidance, and CTTI for expedited safety reporting.

A theme that arose during the Q&A portion of the presentation was the importance of establishing a mechanism for maintaining synergy/collaboration among the higher levels of the various consortia to ensure that the relationships are ongoing and thus can be effective in the early stages of the next generation of projects and not just confined to current efforts.

Protocol Ethics Working Group Phase 1 Report
Co-chairs: **Susan Callery-D'Amico, BSN**, Reata Pharmaceuticals, Inc. and **David Forster, JD, MA, CIP**, Western Institutional Review Board

Ms. Callery-D'Amico and Mr. Forster presented the Phase 1 report from Protocol Ethics Group, which has identified several constraints that affect ethical considerations in clinical protocols. These constraints are evidenced in two areas: those that impact the Institutional Review Boards, (IRBs) and Ethics Committees (EC) who review the protocol and those that affect the study teams that develop them.

1. Limitations on the current systems for reviewing trials regarding:
    a. Effectiveness - quality of the review and ability to detect ethical problems
    b. Efficiency – time for protocol review
    c. Expertise - in some regions, local ECs lack the level of expertise or sufficient resources required to review complex protocols
2. Lack of a rigorous methodology by which study teams developing protocols can ensure that all ethical issues have been considered and addressed.

Status of Deliverables

Deliverable	Issue Addressed	Status
Protocol ethics template section	2	A recommendation to expand the protocol ethic section was posted to the FDA docket in May 2012 Draft completed 11/27/12 Final version 1/16/13

Points-to-consider document to guide the user towards drafting a standardized protocol and informed consent form (ICF) ethics section	2	Draft completed December 2012 Final version 1/16/13
On-line decision tree and checklist that provides guidance at the main decision points during the design phase and allows users to populate sections within a prescribed template format	2	On-line web tool evaluated Draft for programming March 2013 Final available June 2013
Companion checklist for ECs to ensure that key ethics issues have been addressed	1	June 2013

The group considered 13 points of importance to the development of an ethical protocol in preparing the points-to-consider document and the protocol template (Appendix C) and an outline of the new section was provided to the meeting attendees for comment.

Mr. Forster noted that the working group intends this section to be a standalone section of the protocol and that they are not going to "take a stand" on any particular question. He stressed that the rationale for the document is to ensure that when a protocol is being developed the appropriate issues are raised and a conscious decision is made on each item versus the issue being overlooked. In addition, the work group believes that this approach, when used with the checklist they are developing for the EC/IRB, provides the appropriate level of information to the members as they make the decision on whether a trial may proceed.

Questions from the members of the global regulatory and regional stakeholder panel revolved around several themes:

- Whether the EC and IRB now have to take additional time to compare the contents of the new section with the actual contents of the protocol. (Ockjoo Kim)
- Whether there is a risk that the IRB reviewers will only read this section.
- The concepts expressed in the proposed document should also be used by the protocol writers when they write the protocol. This type of thinking should be

implemented throughout the protocol, including the hypothesis. (Ockjoo Kim; Sabine Haubenreisser; Agnes Klein)

- The documents need to be flexible enough to be applied to different types of trials (e.g., multiple therapeutic areas, both pharmaceutical and investigator initial trials, controlled vs. non-controlled or historical controls, regional differences, etc.). (Ann Meeker-O'Connell; Agnes Klein; Salvatore Alesci)
- It is important to guard against the unintended consequences of developing this type of document such as language. For example: What does appropriate mean? How is adequate defined? Some parameters/specificity may be needed. (Ann Meeker-O'Connell; Salvatore Alesci)
- This issues raised here could form the basis for a training initiative for both protocol developers and ECs. (Agnes Klein)
- How does this fit with and take account of regulatory requirements without becoming an additional burden that could slow the review process. (Salvatore Alesci; Barbara Bierer)

There were some areas of the document that members of the panel thought may be either missing or not given sufficient attention in the new document:

- Conflict of interest that may arise from payments to the investigator. (Ockjoo Kim; Vijai Kumar; Evgeny Rogoff)
- Vulnerable groups – perhaps should be a separate section. (Ockjoo Kim; Sabine Haubenreisser; Agnes Klein; Evgeny Rogoff))
- Compensation for trial-related injury. Guidelines are currently being developed for India. (Vijai Kumar)
- Inducement for individuals to enroll. (Agnes Klein)
- Focus groups should be conducted before this is implemented. (Vijai Kumar; Sabine Haubenreisser)
- Post-trial access is a clear obligation in countries covered by the European Medicines Agency (EMA). (Sabine Haubenreisser)
- Post-trial disclosure of treatment is also a clear obligation for the EMA. A timeline would be useful. (Sabine Haubenreisser)

- Does the EC itself have the right level of competence, the correct mandate, and the appropriate level of independence to accomplish their task? May not be appropriate for this group but needs to be considered. (Sabine Haubenreisser)
    - In Russia there are no strict regulations about the activities of the ECs. There is an initial review only – nothing ongoing. Right now this is all under the Ministry of Health (MOH). A system of local ECs independent of the MOH needs to be created. (Evgeny Rogoff)
    - Concerning the competence of the EC. The growth of studies in regenerative medicine was offered as an area that required specialized training for the EC to make decisions about the quality of the protocol. It's questionable as to whether the PI (who is currently responsible for this training) is the right person to train the EC. (Vijai Kumar)
- Training will be required both for the individuals drafting this section and the people reviewing it. (Ann Meeker-O'Connell)
    - Training should be shared with industry and the regulators not left to the sponsor alone. (Sabrina Haubenreisser)
    - The training should be scalable (Barbara Bierer)
- Disclosure on Clinicaltrials.gov should be added to the disclosure section. (Ann Meeker-O'Connell)
- A cogent preamble is needed to explain the purpose of this section. (Barbara Bierer)

Offers of Assistance

- Vijai Kumar offered to make a connection with India's New Drug Ethical Committee to facilitate the focus groups in India.
- Sabine Haubenreisser offered to assist with contacts in the EU to take the entire concept further. She suggested that APEC would be a good contact to move forward globally and that the Regulators Forum at the annual ICH meeting might be an appropriate forum for feedback.
- Ann Meeker-Connell suggested there might be synergy with Quality of Design Project within CTTI which is intended to promote critical thinking and cross-functional discussion at the time of trial design.

Global Regulatory Authority and Regional Stakeholder Presentations

Challenges in Multiregional Trials – From the Canadian Perspective

Agnes Klein, MD, DPH, Health Canada

Dr. Klein noted that there is a broad range of challenges with in multi-regional trials. She noted that some of these challenges are the result of regional variability in the state of the art and science, clinical outcomes, ethics, populations, and statistical considerations, and/or changing approaches to trial design and analysis. Other challenges stem from legislative and regulatory issues associated with differing levels of flexibility in the interpretation of legislation, different philosophical approaches to market authorizations, and differences in the standards of clinical/medical practice.

Canadian regulations require that all those participating in the conduct of trials be adequately trained. Although Health Canada engages in some voluntary training and educational activities and there is a GCP Inspection Program, the ultimate responsibility for training lies with the study sponsor. In Dr. Klein's experience the educational and training gaps uncovered during the Good Clinical Practice (GCP) inspection generally involve minimal or no training of personnel, and poor understanding of GCPs and the need to follow rigorous processes. Inspection may also uncover poorly kept source records and challenges/concerns with electronic data capture systems.

With respect to ECs, there is a current trend in Canada toward developing centralized Research Ethics Boards (REBs). Health Canada mandates special ethical considerations for the conduct of clinical trials, in the analysis of the studies, and concerning the clinical applicability of the results as they concern sub-populations such as women, pediatrics, and the elderly and very elderly. However, when thinking about multi-regional trials, Dr. Klein noted that it is difficult to determine the degree to which and the form in which ethical processes are used.

Transition from an Excellent Clinician to a Competent Investigator the Indian Challenge

Vijai Kumar, MD, Excel Lifesciences India

India has an excellent reputation for the conduct of quality trials. Outside of the US, it has the largest number of US FDA inspected manufacturing facilities. Since 2005, when these inspections first started, 30 sites have been inspected in 10 therapeutic areas. All 30 inspections were data audits; none resulted in official action being initiated and none involved informed consent related issues.

Physicians in India are very well trained and experienced in patient care and considered competent in basic and other areas of medical research. Most are somewhat naïve in terms of pharmaceutical industry sponsored research, however, and dedicated efforts for a nation-wide training program are taking shape to improve this situation. Dr. Kumar believes that what is needed in India is increased capacity, particularly in the tier 2 and 3 cities and enhanced competence at all sites through continuous training for all personnel involved in clinical trials (including community outreach).

He sees the training as being focused on the three sections of each trial and offered his insight on what that training might include. In the pre-trial phase the focus should be on developing a reliable patient database and projections for enrollment, the EC submission and approval process, site set-up, workload and manpower estimate, recruitment and retention strategies, and contractual and commercial obligations. Once the trial is underway, the focus should shift to patient identification, the consenting process, screening and randomization, active follow-up, quality and timely documentation, how to manage unscheduled visits and safety events, and the monitoring process. Post-trial training should focus on study closeout and archival. Dr. Kumar sees the training program as a collaborative effort among the regulators, industry, and academia through specialty associations/professional bodies. It should also include the identification of trainers & mentors and certification should be mandatory for participation.

The Drugs Controller General of India (DCGI) has already taken the initiative in several areas to improve the confidence of the global community in the standard of clinical trials in

India. The GCP inspection has been started and regulators from the US, EMA, and Canadian have played an active part in training the inspectors; joint inspections are not uncommon. A clinical trial registry has been instituted as has registration of ECs. There are now guidelines for compensation of trial related injury and within the last two years, New Drug Approval Committees (NDAC) for IND & NDA approval have been established.

Much progress has been made. The immediate issues for India include:

- Training of DSMB members (perhaps as observers in global studies or through a train the trainer program)
- Converting more clinicians to competent investigators
- Assistance in causality analysis to determine compensation

Needs and Priorities in MRCT in Korea

Ockjoo Kim, MD, PhD, National University College of Medicine Korea

In the Asia Pacific Region, Korea is the second most active country conducting clinical trials, especially Phase 1 and Phase 2 trials. The National Enterprise for Clinical Trials (KoNECT) was established in December 2007 with support from the Korean government, academics, and related business industries to meet the increasing demands for clinical trials and to raise national competitiveness by fostering necessary human resources, developing core technology, and building a solid infrastructure to become a global clinical trial hub.

KoNECT currently supports 15 regional trial centers and a human resource academy comprised of 19 educational centers. A certification program was started in January 2012 for clinical investigators, CRA and CRC. Certification has two levels: qualified (refers to competency) and certified (refers to expertise), and is based on completion of training, job experience and written exams. Certification is good for 2 years. Continuing education is required to maintain certification. Suggestions to improve the certification program include expansion to other professionals, online testing, provision of study aids, etc. Open questions concerning the program include the fact that there are no controlled studies to confirm the effectiveness of the systems and no direct correlation between certification and

performance, career development, salaries, etc. Follow-up needs include updated databases on open positions, salaries, and satisfaction indices, and the need to conduct a survey on the actual performance of certified individuals.

The2020 Clinical Trial Future Creation Planning Group has set five issues and tasks through which they intend to improve the Korea's competitiveness in the conduct of clinical trials.

- Strengthen regulatory competitiveness
- Establish strategic plans for medical device clinical trial development
- Enhance the clinical trials communication system
- Strengthen the clinical trials safety protection system (APPENDIX D)
- Strengthen clinical trial capability

Other recent initiatives for clinical trials in Korea include:

- KoNECT/Ministry of Health and Welfare (MOHW) - Global Leading Clinical Trial Center Consortium and early phase center of excellence focused on global unmet needs
- Korean FDA (KFDA), Korean Association of IRBs (KAIRB) – participants outreach program, a clinical trial information center for patients
- KFDA Guidelines for evaluating clinical trials with women are being developed
- KFDA funds for clinical trials for children (5.5 million for 2012)
- Promotion of GCP and research ethics education at various levels (e.g., medical schools, graduate schools, GCP, CITI Korea, KAIRB –KFDA joint symposium (2012)

Clinical Trials in the Russian Federation: What are the features?
Evgeny Rogoff, Clinical Trials Control Dept. Roszdravnadzor of Russia

Russia has a mostly urban dwelling population of ~143 million. Clinical trials are characterized by high recruitment, low drop-out rates, and good quality data. By law, clinical trials conducted in Russia can only be performed by the research sites registered in the official database of the MOH (currently~844 most in Moscow and St. Petersburg) and

only a qualified person (MD specializing in the area under investigation in the trial) with at least 5 years of professional experience in clinical trials area can serve as PI. Most PIs are GCP trained and fluent in English. Up to 90% of the clinical trial monitors have a healthcare background.

The initial dossier for submission of a clinical trial must include the application letter and fee, copies of the clinical trial protocol, investigator brochure, and informed consent form (in English & Russian), copies of the case report form and insurance certificate, a list of participating clinical sites, the CVs of the PIs, and any patient-related documents. Insurance is mandatory for all trial participants, should be issued by a Russian company, and should cover the entire period of the trial. Submissions are reviewed in parallel by the Federal State Institution Scientific Center for Expertise of Medical Products of the MOH (scientific review) and the Ethical Council of the MOH (ethics review). Both must approve and the approval time is one month. No approval can be granted for clinical trials of medical devices and equipment, trials without the definite goals to evaluate a medicine, and/or trials involving vulnerable patient groups (e.g., under-aged patients, military and law-enforcement personnel, convicted individuals, pregnant women). Following study start reports of serious adverse events (SAE) and suspected unexpected serious adverse reaction (SUSAR) are submitted to the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (ROSZDRAVNADZOR).

EMA Needs and Priorities Relating to Multi-Regional Clinical Trials
Sabine Haubenreisser, MSc, PhD European Medicines Agency Liaison Official Based at the FDA

Between 2005 and 2011 almost 900,000 patients were enrolled in ~70,000 pivotal trials in 106 countries. Approximately one-third of these patients were from Europe and one-third were from North America; one-quarter were from the rest of the world, with recruitment increasing over time in these areas, particularly in the Asia/Pacific and Central and South America Regions. The increasing number of clinical trials being conducted outside of the European Union (EU) raises questions on the part of the European Regulators in terms of

the acceptability (ethical standards, GCP compliance) and applicability (to European populations and medical practice) of the trial results.

In April 2012 the EMA published a reflection paper on the ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/European Economic Area (EEA) and submitted in marketing authorization applications to the EU Regulatory Authorities.[16] No new legal requirements were instituted. The theme throughout the paper is that at every step for every clinical trial there must be confirmation that the ethical principals have been respected in the protocol and in the conduct of the trial and that the GCP compliance has been proven. The document makes it clear that these concepts must be proactively enforced at the planning stage and again at the assessment stage. Sponsors are advised to seek guidance when writing the protocol and there is a provision for the Committee for Medicinal Products for Human Use (CHMP) to seek expert advice in difficult situations.

The EMA is implementing the practical steps set out in the reflection paper and further developing policy and process where needed (e.g., assessment of dossiers, European public assessment report (EPAR), access to ethical expertise for CHMP). As with other projects the EMA will work with international partners on training, capacity building, opportunities for joint inspections, and information sharing (as permitted within the confines of confidentiality arrangements). For the issue of applicability the EU regulators will look to the framework established in the ICH E5[2] and ICH Topic E5(R1) Questions and Answers.[3]

Dr. Haubenreisser noted that it is becoming clear that although intrinsic factors cannot be ignored, extrinsic factors are becoming increasingly important in the interpretation of differences in outcomes between populations of patients. In this context the EMA regulators can refer to a reflection paper from 2009 that discusses the extrapolation of results in clinical studies conducted outside EU to the EU-population.[17] The paper is based on a number of files for which the interpretation of the data for EU had been difficult. Important points to be considered fall into three areas:

1. Medical practice (differences in co-medications and invasive procedures)

2. Disease definition (heterogeneous medical conditions, medicalization of some conditions, insufficient standardization and validation of scores and scales)
3. Study population (different inclusion criteria, life style, medical and social environment)

Since these factors will impact the regulator's decision whether certain clinical trials conducted outside EU are relevant to EU and/or whether additional trials may be required, the recommendation is that there should be a prospective analysis of potential extrinsic/intrinsic factors before conducting a clinical trial. Any potential complications should be discussed with the Agency so that they may be addressed early on.

CDER Perspective: Enhancing Trial Quality and Efficiency
Ann Meeker-O'Connell, Office of Compliance, Office of Scientific Investigations, FDA

Within the CTTI, there has been a change in how quality in a clinical trial is defined from thinking in terms of the *absence of any error* in data that has been collected to the *absence of errors that matter*. Ms. Meeker-O'Connell defined errors that matter as those that undermine the ability to draw conclusions from the trial results or errors that meaningfully impact the subject safety. She noted that traditional clinical trial monitoring and auditing approaches are not suited to preventing these types of errors and may not readily detect systemic errors. In her opinion, the best tool to avoid these errors is a well-designed and articulated investigational plan. Planning for a quality trial allows the trial planners to prospectively identify the aspects of the trial that are critical to quality as well as the important and likely intrinsic and extrinsic risks to those quality aspects. Once this has been done it becomes possible to tailor the investigational plan and its implementation to eliminate – or reduce the impact of – errors that matter.

Ms. Meeker-O'Connell believes it is both possible and necessary to develop a set of general principles about what really matters in clinical trials—i.e., what do we really need to get right to ensure reliability of results and patient protection? The CTTI Quality-by-Design Project was initiated to do just that. The goals of the project are to produce a draft document

outlining the high-level principles for building quality into trials and one potential approach to prospective quality planning. The draft document will be tested in a series of workshops with hands-on exercises involving different therapeutic areas and product types, various stakeholders, and different functional lines and then refined and published along with the case-studies and lessons learned.

There is no regulatory requirement for sponsors to use a Quality by Design (QbD) or Quality Risk Management (QRM) approach in their trials. While there is also no single "right way" to implement them, trials using this design are more likely to be successful if the approaches are sufficiently flexible, not unduly burdensome, and not just "another layer" added to existing practices. Successful integration of quality into clinical trials rests on four areas:

- Focus on first principles: Why do we do clinical trials? To obtaining reliable evidence for decision-making
- Encourage broad engagement of stakeholders, including clinical investigators, patients, and regulators
- Identify and discuss the barriers to implementation early
- Be willing to pilot and refine QbD and QRM

Following the global presentations there was an active discussion.

- There appeared to be support for the concepts of QbD and QRM but there was also a sense that industry had mixed experiences in the past with the regulatory agency and the inspectors and sometimes felt 'burned". This feeling is particularly strong on the safety side. The Avandia RECORD Study was raised as an example.
- Encouraging the discussion of what might be a "deal breaker" in a study early in the planning phase was seen as a big plus, but time needs to be put into the IND process for this type of conversation and for an international study there needs to be international buy-in to the concept.
- Dr. O'Neill questioned whether there was a difference between the type of training that is being conducted and the type of training that is needed and suggested that a

disconnect between these two areas may lead to organizations/personnel operating at cross-purposes or at least without full understanding of the overall goals.

Mark Barnes asked "What can MRCT do?"

- Instruct academic research about the rigor that is required in clinical trials that are done for regulatory purposes. (Agnes Klein)
- Maintain a library or other such resource to help planners identify differences in medical practices, privacy laws, etc., among various regions. (Ann Meeker-O'Connell)
- Facilitate increasing the investigators' and academic community's awareness of the principles of QbD. (Ann Meeker-O'Connell)
- Mapping of the existing initiatives, training and capacity building (Sabine Haubenreisser)
- Capacity building and site training (Ockjoo Kim)
- Connect experienced clinical trialists with those who would like to perform clinical trials for mentoring (Vijai Kumar)
- Education for the EC (Evgeny Rogoff)

DSMB Working Group Update

Charles Knirsch, MD, MPH, Pfizer

Dr. Knirsch provided an update on the progress of the DSMB Working Group.

Project Impact: Increased engagement of experts from emerging world on DMCs for multi-regional trials.

Project Goals/Progress:

1. Identify qualified DSMB members from the developing world
   Progress –obtained agreement from the Fogarty Institute and they would solicit qualified Fogarty International Clinical Research Scholars & Fellows for the program once regions are determined.
2. Educate and train DSMB members for trials in the developing world.

Target Audience: Investigators, ethicists and statisticians who have never served on a DSMB or need a refresher

Progress – Have submitted a proposal to partner with the Society of Clinical Trials (SCT) to co-sponsor a one-day training workshop at the SCT meeting (May 17, 2013, Boston)

(APPENDIX E)

3. Apprentice DSMB members from emerging markets to serve on boards.

   Timeline: 6-12 fellows to be trained in May and start participation in Spring/Fall of 2013

   Progress – Currently identifying appropriate trial (i.e., trials that are scheduled to be conducted in emerging countries, are in the pipeline to start in Summer/Fall of 2013, and would be appropriate to allow fellows to participate).

There was significant discussion on the contents of the training program. Areas that the group felt might be missing or need additional focus:

- This needs to be done in the US as well. (Robert O'Neill)
- Wherever this is implemented the issue will be identifying the right individuals – medical schools may be a good source. (Robert O'Neill)
- There is good reason to have individuals sit on the DSMB in a non-voting capacity (perhaps more than once) before they become full-members. (Norman Goldfarb)
- There is a gross understanding of the amount of training that is needed to become competent in this area. This is not a one-day course it's a multi-year commitment. (Robert O'Neill)
- How would the entry and "graduation" from this type of program be managed? What are the qualifications?
- DSMB members should be certified. (Robert O'Neill)
- There is some concern about privacy on the part of the DSMB members. In part this may reflect anticipation of legal ramifications stemming from their decisions in the future. (Paul Knirsch)
- Important to differentiate the various roles within the DSMB (e.g., Chair, statistician) in the training.

- Conflict of Interest should be added to the topics.
- A possible efficiency measure might be to have DSMBs on the program level; however, there has been some reluctance to do this in the past so the cons would have to be seriously considered.
- There seems to be confusion surrounding the communications flow to the various stakeholders (e.g., investigator, sponsor, EC). Stopping rules seem to be very inconsistent and confusing. These items should be added to the curriculum; the morning session is too light. The material is dense and takes time to absorb. (Norman Goldfarb; Robert O'Neill)

Potential partnerships/opportunities for collaboration

- PharmaTrain in the EU might be a possibility for collaboration.
- The World Health Organization (WHO) published guidelines for the establishment and functioning of data and safety monitoring boards in 2005.[18] These may be useful.
- There may be an opportunity to partner with the Clinical and Translational Research Awards (CTSA) (Barbara Bierer)
- Consideration should be given to conducting training sessions at appropriate congresses and meetings as a way to extend the programs reach.

In summarizing, Barbara Bierer said that there appeared to be consensus that this is an area of unmet need but the some individuals felt that a one-day workshop is insufficient. She mentioned that there are plans to conduct a mock-DSMB as part of the training.

PI Competence and Training Working Group Update

Natalie Rossignol, Bill and Melinda Gates Foundation

Natalie Rossignol provided an update on the early progress of the Investigator Competence and Training Team, which met for the first time about two weeks ago. The group is working from a list generated from the Phase 1 work in 2010. (APPENDIX F for detail on the suggested competencies)

PI Competence Issues Identified in the Phase 1 Report

1. Tremendous variation in skills and experience of PIs and coordinators worldwide; lack of adequate training and support can threaten research and data integrity; first time PIs and coordinators may have little background in research design or ethics.
2. Training programs are not typically modified or tailored to suit specific regional (geographic) or cultural requirements.
3. Lack of metrics to establish correlation between PI certification or training and improvements in the quality and efficiency of clinical research.
4. Lack of guidelines for core competencies that must be obtained by investigators prior to conducting clinical research.

Initial List of Deliverables

Deliverable	Issues Addressed	Timeline
Develop minimum training standards (list of core competencies) for PIs and clinical staff	1, 4	June 2013 Draft for discussion at DIA roundtable forum in June 2013
Review currently available GCP training materials, assess against proposed standards and identify the gaps	1,2	December 2013
Develop a web-repository of training materials that meet minimum standards to be open-access	1, 4	December 2013
Determine measurements of impact for training initiative outputs.	3	June 2013 Draft for discussion at DIA roundtable forum in June 2013

Following are some of the points raised during the discussion of this presentation.

- There seems to be quite a bit of diversity in terms of knowledge testing with respect to delivering training around GCP. It might be interesting to better

understand in what instances testing of knowledge is and is not necessary. (Craig Lipset)

- There are some related initiatives, more in terms of efficiency gains such as standardizing GCP training, so that it can be taken once and not for every trial. (Geoff Garabedian)
- Thought should be given to how to incorporate case studies into any training program. (Ann Meeker-O'Connell)
- An appropriate source to identify the FDA's priorities for investigator and site staff competence would be recently published reports. The information may take time to uncover but could be very useful, particularly for context. (Ann Meeker-O'Connell)
- This is problem with multiple layers because of the differing responsibilities of the individuals. Most of the investigators are also seeing patients so their time is very limited. This means that the training of the trial coordinators becomes even more important. (Geoff Garabedian)
- A goal of this program should be to find a small number of training programs that would be acceptable to all sponsors.
- The important part of training is not how well someone tests but how well they internalize the information and how they perform. Have the group considered the possibility of risk based (experienced based) training, e.g., as part of monitoring the study, the monitor identifies individuals who have clearly not internalized the training and who need additional training, then makes recommendations at that point.
- Ultimately, the idea would be to have a dynamic accreditation process that takes advantage of quality risk management.

The following groups were suggested as potential partners:

- Innovative Medicines Initiative (IMI; EU)
- Korean Network Clinical Trials (KoNECT; Korea)
- Inter America Foundation for Clinical Research (IAFCR; Latin America)
- Clinical Trials Transformation Initiative (CTTI; US)

- International Institute for the Safety of Medicines (ii4SM)
- Metrics Champion Consortium (MCC)
- Quintiles and the edX program at Harvard for web-based training

Mark Barnes closed the meeting by reviewing some of the presentations from today's meeting. In particular he discussed how Robert O'Neill's presentation had brought to light the existence of a set of scientific design issues that precede the implementation and operational issues that MRCT has focused on but which have not been considered in MRCT's agenda. Mr. O'Neill's presentation made it clear, however, that there may be a role for MRCT either in training or establishing principles for the design of transcultural/transnational studies that would make it possible to anticipate and hopefully prevent later problems with the analysis and interpretation (or collection) of the data. It is also becoming apparent that MRCT may be an appropriate forum through which international groups might share information.

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APPENDICES

Appendix A: PhRMA's MRCT Kit Programs

Appendix B: Consortia Evaluated in the Roadmap and Opportunity Analysis

Appendix C: Areas to Be Considered When Developing Ethical Protocol

Appendix D: Korea Comprehensive Plan for Clinical Trials (2012 – 2020)

Appendix E: Proposed Course Outline for DSMB Training Workshop

Appendix F: Suggested Core Competencies for Investigators (From Phase 1 Report)

APPENDIX A: PhRMA's MRCT KIT program

1. Issues when endpoints/time points/etc. differ between health authorities (C. Girman)

Different Regional requirements	**Potential Handling in MRCT**
Different clinical endpoints as primary/co-primary	Pre-specify different primary or co-primary hypotheses in protocol, and describe separately in study report
Different time points for primary endpoint	Pre-specify different time points in primary hypothesis for different regions as long as blinded trial duration extends to longer duration. If analysis done at earlier time point, need to consider later time point as supplemental information, or account for interim look. Need to ensure trial integrity because of earlier unblinding.
Different non-inferiority margins	If trial size is sufficient for both margins, pre-specify different margins for different regions in protocol; describe separately in report.
Different analytic populations or methods	Pre-specify differences in protocol and describe separately for different regions in report.
Different study designs	Depending on magnitude of differences, can handle minor differences in MRCT by pre-specifying in protocol.

2. Considerations when defining "region" (Y. Tanaka, C. Mak)
   - Region does not necessarily have to be geographical or political.
   - Different factors should be considered depending on therapeutic area/disease state.
   - "Region" should be pre-defined (with justifications).
     - How these definitions are accounted for in the study design should be noted with the pre-definition
     - How region will be analyzed should be pre-specified in the planning stage (stratification, consistency method should be integral in the design).

Factors	**Rationale**
Race and ethnicity	Surrogates for genomic issues and therefore a supposedly homogenous, W.R.T. drug effects, group
Medical practice	Encompasses practices of treating a patient including local medicines, hospital treatment
Human Development Index	Surrogate for ability to provide and have access to the "latest" developments in health care (Adult literacy, GDP, Education, life expectancy)
Disease Epidemiology	Goes to the differing characteristics of the

	disease (including genomics/biomarkers) which are reflected by many of the issues on this list. Provides the background information that can indicate where disparate characteristics occur that will affect the planning, analysis and execution of the clinical trial.
Geographic proximity	The traditional idea of a region, yet still very fluid.
Geopolitical/Institutional	Health Authority driven
Culture	Broad term to encompass common health practices, ethics, and behaviors that impact on a clinical trial that arise within a common culture.

3. Consistency (H. Quan, J. Chen)
    - Ideally, all regions should be treated identically in the consistency definition.
    - Overall sample size plays a key role in examining consistency, and in fact it may not be possible to partition the regions to achieve desired power depending on the number of regions and the definition of consistency. Keep # of regions small.
    - Don't conclude inconsistency without attempting to understand why.
        - Multiplicity issues
        - Further exploratory analyses :Baseline characteristics, medical practice, and other intrinsic/extrinsic factors that may confound the results
        - Totality of the data/evidence
            - Overwhelming vs marginal overall effect
            - Consistency in other important endpoints and subgroups
            - External data (e.g., same class, same patient population, etc.)
    - Hill's criteria

4. Survey of PhRMA companies and MRCT practices (N. Scott):
    - Greater, region independent, standards to guide the conduct of all trials
    - Greater cross-regulatory collaboration to align:
        - Therapeutic area specific requirements
        - Safety data requirements
        - Logistics of drug import/export