Proceedings
Standardizing and Measuring PI and Site Qualifications for Conducting Clinical Trials Workshop

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AGENDA

Time	Topic	Presenters/Moderator(s)
8:30 – 9:00 AM	Welcome and Introduction to MRCT	Rebecca Li
9:00 – 9:15 AM	Agenda and Expectations	Barbara Bierer
9.15 – 10:10 AM	Panel 1: Summary of Current Initiatives in PI Standards and Certification External to MRCT	Adrian Otte
10:10 – 11:40 AM	Panel 2: PI and Site Requirements in Emerging vs. Developed Markets	Helmut Wolf Richard Peters
11:40 AM – 12:20 PM	Lunch	
12:20 – 1:15 PM	Speaker Series: Regulatory Considerations in Foreign Site Selection	Ann Meeker-O'Connell Fergus Sweeney
1:15 – 2:05 PM	Panel 3: Building the Infrastructure for Trials – A Focus on Regional Ethics Committees	Debasish Roychowdhury
2:05 – 2:15 PM	Break	
2:15 – 3:35 PM	Panel 4 Training Challenges in Emerging Markets and Potential Solutions	Craig Eslinger
3:35 – 3:45 PM	Wrap Up: Consensus & Discussion on Next Steps for MRCT	Rebecca Li
3:45 – 4:00 PM	Closing Remarks	Mark Barnes

MRCT Project 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; to foster respect for research participants, efficacy, safety, and fairness in transnational, trans-cultural human subjects research.

Current Initiatives

The MRCT Project has 4 ongoing initiatives (Appendix A). The purpose of this meeting was to discuss approaches to move forward with Initiative 1 and to discuss issues and guidance for and how to move forward on Initiative 2. Working committees have been formed for Initiatives 3 and 4 and these will be the subject of future meetings. Barbara Bierer, MD, Brigham & Women's Hospital, Harvard Medical School, and MRCT, stressed that the MRCT Project is not and does not plan on becoming an accrediting or certification agency. She suggested, however, that the broad range of stakeholders and the collaborative structure of the project make it an excellent agent to foster the development of standards/criteria for primary investigators (PIs) and sites involved in clinical research, as well as the methods to quantify those criteria.

Workshop Expected Outcomes

1. Consensus list of "key selection standards or criteria for sites and PIs"
2. Proposed methods to quantify the importance of these criteria
3. Recommendations for the MRCT Project's role moving these issues forward, which may include but are not limited to:
    - Initiate workgroups focused on specific projects related to the topic
    - Host annual meeting to serve as a forum for those working in the area
    - Provide a roadmap for coordination of current in-flight initiatives; document gaps and overlaps

EXECUTIVE SUMMARY

PANEL 1: Current Initiatives in PI Standards and Certification External to MRCT

The speakers in this session discussed current initiatives related to investigator training, why those efforts are important, and how the MRCT Project might help the groups already working in this area to interface. Ongoing projects from five groups were presented.

- The Hever Group has an ongoing initiative to assess the feasibility of developing a common set of standards for Good Clinical Practice (GCP) qualification and training and attaining agreement for mutual recognition of these standards among pharmaceutical companies. Benefits could include a reduction in training costs and faster study start-up.
- The Alliance for Clinical Research Excellence and Safety (ACRES) is currently pursuing a program to establish a network of professional clinical research sites that use the same standards, performance metrics, information infrastructure, and pharmacovigilance system. The initiative focuses on 4 critical domains: site development and operations support, safety and pharmacovigilance, quality management and systems improvement, and information systems management.
- The Association for the Accreditation of Human Research Protection Programs (AAHRPP) has developed 2 sets of standards for researchers and research staff. The first concentrates on research related issues (e.g., sound research principles, minimizing risk) and the second relates to issues of compliance (e.g., rules, regulations, reporting requirements).
- The Association of Clinical Research Professionals (ACRP) and Academy of Physicians in Clinical Research (APCR) have developed and independently validated 5 categories of proficiency for qualified investigators (ethics and subject protection; scientific concepts; subject care; operational excellence and regulatory compliance; and leadership and business management) and 3 levels of investigator research training and proficiency.
- The Health Improvement Institute (HII) has two projects focused on the accreditation of research sites: the Project to Harmonize Health Research Guidelines and a joint project with ACRES to develop an accreditation system for research sites. The intent is to develop a program that includes management mechanisms and validation surveys, provides for dynamic reporting/accreditation, and establishes a quality management

organization. Standards will be developed for facilities and management, investigators and staff, protection of human subjects, accrediting organizations, and site surveyors.

There was consensus that diversity of perspective and credibility are important assets that the MRCT Project brings to the table. Specific roles for the MRCT Project included assembling the roadmap for an overall certification program, acting as a catalyst to keep the program moving, promoting resource conservation by identifying duplication of effort, and helping to maintain awareness of and a balanced approach concerning what can be accomplished in developed versus emerging markets. Specific questions that the MRCT Project might address include whether the current model, in terms of the number of research sites, IRBs, and ECs, etc., is the best or whether consolidation or a more cooperative system would be more efficient and effective and better serve the needs of all the stakeholders.

Several gaps were identified among the current initiatives, including attention to the details, cost of the certification and accreditation programs, lack of metrics, and the need to expand the reach of the group to include more of an international perspective. It was agreed that there is an opportunity to address inefficiencies in terms of training, education, accreditation, and certification. Possible roles for the MRCT Project are to coordinate the development of standards and to look at the measures of performance, and to help address the issue of whether certification and accreditation should be mandatory.

PANEL 2: PI and Site Requirements in Emerging vs. Developed Markets

Overcoming the challenges of conducting trials in emerging and developing markets requires attention to factors as varied as the effect of history on the delivery of healthcare (a particularly important factor in Central and Eastern Europe), the lack of trial centers and laboratories that meet international standards, and the absence of a precedent or regulatory pathway for conducting trials, as well as trained personnel. Attention must also be given to existing cultural values. Several organizations have established programs to enhance their ability to conduct trials in these regions.

- Novartis has established a Clinical Trial Enabler Program based on education and training in 4 areas: drug discovery and development, designing and reporting clinical

trials, regulatory framework for clinical trials, and pharmacovigilance and risk management.

- The Pfizer Global Trial Placement Strategy uses a risk-based system to determine the level of support that will be needed to establish a clinical trial program. Countries are risk-rated with countries of higher risk receiving additional emphasis on relationship building with the sites and the staff.
- ViS Research uses a social networking approach that allows research centers to upload their disease specific profiles to the ViS social network. Local experts then use ViS algorithms to generate additional intelligence relative to the centers' location. The integration of these data allows for the creation of a complete map of clinical research infrastructure that can be used to match trial planners with research centers. Benefits include a reduction in the cost of the research center selection process.
- PATH has established several establish critical requirements for PIs and research centers. For the PIs these criteria include: education, training, experience in clinical research and in the disease area, being able to devote adequate time to the trial, and being willing to learn on the job. Critical requirements for research centers include having adequately trained, experienced support staff; adequate infrastructure and equipment, an adequate patient pool, and a trained, functional EC.
- The objective of Sanofi's Practical Roadmap to Clinical Investigator Certification is to create a standardized PI certification that is readily available, user-friendly, and affordable. The program rollout is expected to occur in the second quarter of 2012 at which point it will be offered to additional internal staff and PIs. The perceived benefit of increased certification with this program is an overall improvement in the quality of academic and clinical trials.

PANEL DISCUSSION: Moderators Helmut Wolf & Richard Peters

The discussion about certification centered on 2 questions: Is certification the right thing on which to focus? How can the effects of certification be evaluated? Several members agreed that certification might give sponsors and CROs additional leverage in enforcing standards agreed to in the contract. There was also some agreement that certification increased the PIs' and clinical research staffs' awareness of quality and compliance issues and by doing so may raise their

attention to these principles and thus lead to improvements in overall trial quality. The group agreed on the need to identify measures to assess the impact of PI certification and site accreditation. A related question involved how sponsors can adapt to the practicalities of conducting a clinical trial in various cultural environments and how to translate these differences, and their effect (or lack of effect) on quality for the regulatory agencies.

Caution was raised concerning pushing too hard for certification before more fully exploring the outcomes, cost, and implementation issues as doing so may make it more difficult to find PIs and sites to run clinical trials. Other areas of discussion included the need to maintain the integrity of sites once they have been certified and the possibility that more will be gained by working from the bottom-up (setting minimum standards for sites) versus the top down.

Speaker Series

In the Speaker Series section of the program, Ann Meeker-O'Connell, MS, from the FDA and Fergus Sweeney, PhD, of the EMA, discussed the regulatory considerations in foreign site selection. Ms. Meeker-O'Connell discussed the FDA's participation in the Clinical Trials Transformation Initiative (CTTI), a public-private partnership to identify practices that will increase the quality and efficiency of clinical trials by prospectively identifying the aspects of a specific trial that are "critical to quality", identifying important and likely risks in these areas, and tailoring the investigational plan and trial implementation to eliminate or reduce those risks. The CTTI project could help inform the MRCT Project in its efforts to develop standards for site selection as well as some of the general and specific performance metrics.

Fergus Sweeney, PhD, EMA, discussed these same challenges from the European perspective. He commented specifically on a recent EMA reflection paper that outlines a number of responsibilities for the sponsor with respect to site selection, oversight, data quality and control, and investigator selection, and for the study monitor with respect to initial/ongoing verification of the investigators qualifications, resources and adequacy of the facilities.

PANEL DISCUSSION

When asked whether investigator certification would affect their respective Agency's current thinking concerning site selection and whether it might reduce the perceived risk of a given site, Ms. Meeker-O'Connell responded that while the FDA is supportive of external efforts to develop standards or certification, they have not taken a position to endorse such efforts. The FDA is developing and piloting several risk models for selecting investigators for inspection and for identifying IRBs for surveillance inspections. Certification is one measure being considered for that model. With respect to risk based monitoring, Ms. Meeker-O'Connell pointed out that there is still no clear indication that certification can serve as a meaningful indicator of ongoing performance. Dr. Sweeney added that in his opinion, if you can use certification to increase the threshold of quality, it may help in other areas but it is unlikely to be recognized by the EMA.

PANEL 3: Building the Infrastructure for Trialists – A focus on Regional Ethics Committees

The focus of this discussion was the challenges and possible solutions for improving the quality of the ECs. Most of the discussion centered on training and education but there was also a suggestion that consideration be given to moving to a system of regional or national review and exploring the possibility of one protocol – one ethics review.

Opportunities for MRCT Project involvement in support of IRBs and EC include providing (and sustaining) education and training for the ECs. Most of the existing courses and other educational material that has been written for use by the ECs focus on the ethical principles that govern clinical research. There is a new manual that takes a somewhat different approach by addressing the intersection between the investigator and the EC in the context of conducting clinical trials. It focuses on trial design as a way of providing a framework for the ECs to use as they evaluate the risk/benefit of a protocol. The key concepts included in the manual are: ethics review and the science of clinical trials are integrally intertwined, ECs must know about the design of clinical trials to review them appropriately, and quality assurance of clinical trials is as important as ethics review.

Common challenges with respect to ECs in the emerging and developing markets include: failure to adhere the required regulations, differences in the interpretation of the applicable rules and guidelines, lack of comprehensive policies and procedures to guide practice, and ineffective communication. Opportunities for the MRCT Project to help the regional ECs meet their obligations could include the development of checklists and forms for meeting US regulatory requirements and country-specific guidelines (with tools) according to local laws/rules. To move these organizations to a more desired state of full regulatory compliance and increasing the number that are accredited will necessitate gaining a better understanding of the extent of the problem, increasing the incentive to be compliant, and developing internationally recognized standards. The MRCT Project can help to improve the quality of the IRBs and ECs by creating mechanisms for empirically understanding and comparing their performance worldwide, encouraging sponsors and CROs to allocate funds to IRBs/ECs at primary research sites, raising and allocating funds for IRB/EC improvement and subsidies for AAHRPP accreditation, funding research ethics conferences in high volume nations, and promoting training opportunities at organizations like WIRB and AAHRPP.

PANEL DISCUSSION: Moderator Debasish Roychowdhury, MD, Head of Oncology, Sanofi
Possible activities for the MRCT Project with respect to IRBs/ECS stemming from the panel discussion included:

- Inventory education and training programs, bioethics societies, universities with bioethics programs that exist in each country in each emerging market
- Link existing education and training programs with professional groups within countries that can deliver programs
- Explore partnerships with organizations like ACRP, the Canadian Association of Research Ethics Boards (CAREB), DIA, the Korean Association of Institutional Review Boards (KAIRB), and Public Responsibility in Medicine and Research (PRIM&R)
- Incorporate human subject protection principles and practice into GCP training for investigators
- Convene sponsors to pool resources around GCP training

PANEL 4: Training Challenges in Emerging Markets and Potential Solutions

There is a need for wide and equitable access to research and skill training in all regions and for all roles. Particularly important is training the sites in how to design and run trials (not just gather data) with a focus on developing transferable skills that promote sustainability. The speakers agreed on the need to establish standards and standardization of procedures and to engage the developing countries in the process, but concern was expressed the requiring accreditation would be a step backward in the goal to increase research in the emerging and developing countries because it would close off opportunity. There was a suggestion that before moving to requiring accreditation 2 questions should be answered: is there a connection between accreditation and improved quality and who benefits from accreditation?

Despite the variety of training sources (sponsors, CROs, universities, and specialized GCP training organizations) there remains some concern about the quality of the training, while access remains a problem in some countries (e.g., Russia). There was a suggestion that in addition to easier access through the use of web-based programs with 24-hour access, essential to improved training for investigators is the use of workshops and interactive exercises that promote discussion and transfer of knowledge. Specific training programs/aids were also discussed including virtual 3D training and collaboration using PPD 3D, a next-generation communications platform, offering a more realistic, engaging, and productive way to communicate that allows users to talk, send instant messages, view and interact with presentation and media content, record notes, and access the web from anywhere anytime. PPD 3D allows organizations to increase information distribution and collaboration across geographically disparate locations, accelerate the readiness of clinical trial teams by improving knowledge retention compared to on-site training, and reduce clinical trial management costs by eliminating travel and associated expenses. Job aids can also be useful to improve accuracy and consistency in data recording. A specific job aid that can be used to evaluate and assign causality for adverse events in clinical research was discussed.

PANEL DISCUSSION Moderator: Craig Eslinger, MS, MBA, PPD

There was general agreement that it's important for training to go beyond just learning the regulations. There should be more opportunities for interactive discussion-based training that

allows the participants to apply what they have learned. Training programs should include a needs assessment to ensure that the program fits the situation and student. It was suggested that the MRCT Project could help by organizing and prioritizing the training and education needs and identifying the resources that might collaborate in developing best training practices. Currently there is little emphasis on training and educating the kinds of people who are needed for the challenges of drug and device development in the future. The MRCT Project may be able to play a role in fostering the development of such individuals, perhaps in cooperation with PharmaTrain.

What can the MRCT Project do?

- Support sustainable emerging and developing country training (market may not work in developing countries to deliver training)
- ID opportunities for collaboration
- Support "best training" practices
- Support e-learning which may make training more cost-effective in emerging countries
- ID gaps in current training
- Enable training and competence to be built and delivered locally

MEETING SUMMARY

PANEL 1 Current Initiatives in PI Standards and Certification External to MRCT

While there are many high quality programs, overall, the current efforts at investigator training are inefficient, probably not fully effective, and not measurable in terms of meaningful outcomes. The speakers in this session discussed current initiatives related to investigator training, why those efforts are important, and how the MRCT Project might help the groups already working in this area to interface.

PRESENTATIONS

Summary of Current Initiatives in PI standards and Certification External to MRCT

Justin McCarthy, JD, Amgen

The Hever Group is a forum comprised of executive pharmaceutical R&D leadership established to address relevant issues facing the industry and to create solutions for addressing common challenges. The group recently established the Hever Initiative, a project focused on increasing the quality and decreasing the cost of clinical trials by building on the best practices that exist within the member organizations. At the moment there are 5 working groups. The Hever working group of most interest to the MRCT Project at the moment is evaluating shared site qualification and training. The objective of this group is to establish mutual recognition of good clinical practice (GCP) training and site qualification among pharmaceutical companies to improve the quality of clinical trial sites and accelerate study start-up. Each pharmaceutical company has its own GCP training program, and although they are good high quality programs, they are expensive and time consuming. This group is assessing whether it is possible to develop a common set of standards for GCP qualification and training and attain agreement for mutual recognition of these standards among the pharmaceutical companies. Were this to be achieved, the benefits would be a reduction in training cost and faster study start-up (as a result of investigators not having to be completely retrained each time they start a study for a different pharmaceutical company). Public launch of the Hever Initiative is expected later this month. The group has already begun outreach efforts to the other organizations and stakeholders such as the Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Clinical Trials Transformation Initiative (CTTI), and the Association of Clinical Research Organizations

(ACRO) to build awareness of their mission and to gather insights. In addition to its immediate charter, this group may be well-positioned to set the stage for a broader certification / accreditation program.

A Systems Solution to the Challenges of Globalization in Clinical Research
Greg Koski, PhD, MD, Alliance for Clinical Research Excellence and Safety (ACRES)

ACRES is a non-profit organization working to design, build, and operate a network of professional clinical research sites that use the same standards, performance metrics, information infrastructure, and pharmacovigilance system. The network will also be linked to a consortium of organizations that can provide expertise and knowledge resources as needed. Benefits of this approach include: confidence in quality and improved inter-operability and synergy. ACRES focuses on 4 critical domains: site development and operations support, safety and pharmacovigilance, quality management and systems improvement, and information systems management. The role of the investigator in all of these domains is central. ACRES ultimate goal is to establish *a global system for clinical trials, responsibly conducted according to the highest standards of safety, quality and efficiency*.

The Association for the Accreditation of Human Research Protection Programs (AAHRPP)
Marjorie A. Speers, PhD, AAHRPP

AAHRPP is a nonprofit association that offers accreditation to Human Resource Protection Programs (the Institution, Institutional Review Board [IRB] and Ethics Committee [EC], and the researchers and staff that together share the responsibility for clinical trials) that conduct, review, or manage research involving human participants. AAHRPP seeks to identify best practices, innovative practices, and programs that are operating at a higher level and which lead to excellent, ethically sound research that respects and protects human research participants. Of the standards that AAHRPP has developed, 2 are directly related to researchers and research staff. The first concentrates on research related issues such as do the investigators know when they are engaged in research, do they understand the principles surrounding sound research methodology, and do they understand ways to minimize risk in research studies? The second standard relates to

issues of compliance, for example does the researcher understand the rules and regulations regarding the research they conduct? Do they understand the reporting requirements? AAHRPP's primary focus is on subject protection. They do not currently require certification of investigators or research staff and, while they recognize the importance of education and training at the investigative site they do not offer either at the moment.

Summary of Current Initiatives in PI Standards and Certification External to MRCT: Association of Clinical Research Professionals (ACRP) and Academy of Physicians in Clinical Research (APCR) Initiatives

David Vulcano, LCSW, MBA, CIP, RAC, AVP & Responsible Executive, Clinical Research Clinical Services Group, Hospital Corporation of America (HCA) NOTE: Although now employed by HCA David Vulcano was speaking as Past Director/Chair of ACRP.

Over the past few years the staff at ACRP/APCR has been working to define competencies for clinical investigators. In a 2011 publication the APCR defined 5 categories of proficiency for qualified investigators: ethics and subject protection; scientific concepts; subject care; operational excellence and regulatory compliance; and leadership and business management. [1] This document is of particular interest to the current MRCT Project initiatives in that it focuses on the GCP principles that apply to investigators (versus the entire realm of GCP principles). It also outlines 3 distinct levels of investigator research training and proficiency. [2]

Recognition of independent certification can lead to cost savings on the part of sponsors, Clinical Research Organizations (CROs), and institutions that conduct clinical research by reducing training costs, eliminate repeated or unnecessary training and speeding study start-up. It may also increase the efficiency and effectiveness of regulatory agencies by allowing consideration for certification in their equations for risk-based monitoring programs. Although there is much variation among current certification programs, ACRP/APCR's products are the only ones validated by the National Commission for Certifying Agencies (NCCA) (the agency originally created by the U.S. Congress to differentiate legitimate certification products from those that are

just "certificates") and the only ones shown to correlate with improved outcomes in 2 independent studies. [3, 4]

Accreditation of Research Sites

Peter G. Goldschmidt, MD, DrPH, DMS, Health Improvement Institute (HII)

HII is a non-profit, research and educational organization dedicated to improving the quality and productivity of American health care by identifying leverage points through which it can demonstrate and pilot useful concepts. There are two ongoing projects of particular interest to the MRCT Project: the Project to Harmonize Health Research Guidelines and a project in conjunction with ACRES to research the development of an accreditation system for research sites. The objectives of the guidelines harmonization project are:

- to establish a sustainable mechanism to harmonize and maintain worldwide guidelines for the selection, design, conduct, and publication of various types of health research
- to develop metrics to assess the quality of research results and study success
- to promote the use of the guidelines and metrics use in policy decision-making, practice, education, and research itself

The intent is to develop an all-encompassing accreditation program that includes management mechanisms and validation surveys, provides for dynamic reporting/accreditation, and establishes a quality management organization to ensure that the accreditation program maintains credibility. Standards will be developed for facilities and management, investigators and staff, protection of human subjects, accrediting organizations, and site surveyors.

PANEL DISCUSSION: Moderator Adrian Otte, MB, BCh, FFPM

Questions for discussion: Perceived gaps and overlaps of initiatives? Areas of collaboration?

There appeared to be consensus that diversity of perspective and credibility are important assets that the MRCT Project brings to the table. Specific roles that were mentioned included assembling the roadmap for an overall certification program, acting as a catalyst to keep the program moving, promoting resource conservation by identifying duplication of effort, and helping to maintain awareness of and a balanced approach concerning what can be accomplished

in developed versus emerging markets. Specific questions that the MRCT Project might address include whether the current model, in terms of the number of research sites, IRBs, and ECs, etc. is the best or whether consolidation or a more cooperative system would be more efficient and effective and better serve the needs of all the stakeholders.

The group identified several gaps among the current initiatives. None of the initiatives appear to be looking at the cost of the certification and accreditation programs and how it might be reduced or offset. On a somewhat related topic there was some concern raised that there is insufficient attention being paid to the positive effect of the training on outcome (the studies that were shown were retrospective and based on the absence of a negative outcome), how effectiveness could be measured, and how often sites should be evaluated. There was also a request to expand the reach of the group to include more of an international perspective to gain the perspective of those countries that are well ahead of the United States and Europe and to identify barriers in those countries that might not be as far along.

There is an opportunity to address inefficiencies in terms of training, education, accreditation, and certification. Possible roles for the MRCT Project to are to coordinate the development of standards and to look at the measures of performance, and to help address the issue of whether certification and accreditation should be mandatory.

The following are the specific areas for MRCT Project involvement that appeared to have group consensus:

- Demonstrate the value, cost/benefit of PI certification/accreditation
- Define the accreditation program/system roadmap and path for execution (not standard setting)
- Identify barriers and gaps that an overarching PI accreditation/certification would face on a global and regional scale
- Evaluate the correlation between the increasing number of sites and IRBs and efficacy of clinical trial quality and execution
- Act as pre-competitive enabler to bring various stakeholders to the table as a means to collaborate on certification/accreditation standards

- Define metrics to stratify investigators and determine associated mentoring approaches
- Define the operational levers, metrics and statistics to enable a visual dashboard of PI challenges/issues/risks and enable real-time intervention
- Evaluate best practices across US/North America and the rest of the world and align expectations on a global scale

PANEL 2: PI and Site Requirements in Emerging vs. Developed Markets

PRESENTATIONS

Novartis Clinical Trial Enabler Program

Helmut Wolf, MD, Novartis

The move toward conducting clinical trials in emerging markets has been driven by a number of factors. Among these are cost savings, the practicality of conducting drug trials in areas that are most likely to need them, and, probably most importantly, ensuring that emerging market unmet medical needs are appropriately represented in pharmaceutical development programs. In truth the decision to conduct trials in emerging markets is not a choice, it is a business imperative. Such a course is not without risk, however, both from internal factors such as staffing and choice of country and sites but externally in terms of limited ethical oversight (e.g., IRB not adequate, poor understanding of informed consent, etc.), inadequate investigator experience (limited infrastructure, underestimation of the workload and administrative burden) and inadequate regulatory support and control. The Novartis Clinical Trial Enabler Program was established to reduce the external risk of initial trials in emerging and developing countries by engaging the affected parties along with experienced experts from neighboring countries in the planning process. The program was initiated in Malaysia in 2011 and is based on education and training in 4 areas: drug discovery and development, designing and reporting clinical trials, regulatory framework for clinical trials, and pharmacovigilance and risk management. Critical requirements for PI and site competency include:

- Company Internal: Hire adequately trained staff, ensure high quality guidance from global functions, cooperate with experienced CROs and site management organizations (SMOs) if required, to give full support to PI and site staff
- Site Selection: Ensure that the PI receives full support from peers at the site, from the IRB and regulatory bodies, has access to the right patients, understands framework of clinical research and development (especially their role in multinational/multicenter trials) and is aware of the ethical requirements, workload, and data quality requirements.

Principal Investigator and Site Requirements in Central and Eastern Europe

Dana Leff Niedzielska, CEO, August Research

Central and Eastern Europe (CEE), loosely defined as the former Warsaw bloc countries and former Soviet Union, has 3 characteristics that are important to understand in the context of clinical trials:

- historically the provision of health care was centralized around disease-specific, specialized hospitals and the systems today still reflect this organization
- internally these large hospitals operate as independent clinics/departments with department heads as key decision makers and with less power held by the hospital administration
- there is little threat of malpractice/litigation for errors in provision of care

This environment impacts clinical trials conducted in the CEE in 3 ways: site infrastructure (mostly insufficient equipment maintenance and certification), study team organization (teams are selected by the PI and 20% to 30% of the teams are inappropriate in terms of having the necessary support for maintaining study documentation and keeping timelines), and patient documentation (no emphasis on proper record keeping).

Data support that quality is there from these sites, but it is being achieved at the cost of extra work, extra time, and extra money. Creation of a global trial site certification process would improve the quality of trials in these facilities (patient records may have to wait for E-health reporting), save time, and reduce study cost. The sites could also use their certification for marketing purposes to increase the number of trials they conduct and as justification for higher fees.

Pfizer's Global Trial Placement Strategy

John Oidtman, Pfizer

Pfizer is committed to significantly increasing the number of patients participating in clinical trials in emerging markets and has implemented measurable goals to ensure that this happens. To support this goal the company implemented tools and processes that the internal site selection team could use to optimize trial placement. A systematic site selection strategy was also developed to increase trial quality. Using that strategy, countries are rated by risk based on prior experience across factors such as past clinical trial volume and performance, gross domestic product, literacy, stability, medical/business relevance, and the strength of existing Pfizer operations/infrastructure. Each country is then assigned to one of 4 risk quartiles.

Countries at the high end of the risk structure (more risky) receive additional emphasis on relationship building with the sites and the staff. One vehicle for this is a program called INSPIRE (Investigator Networks, Site Partnerships, and Infrastructure for Research Excellence), which focuses on building key relationships and establishing high performance and high quality sites by providing funding and training to help the sites manage their clinical trials more effectively. Other tactics included establishing community advisory boards, ECs, training, site accreditation, and site partnership. A question the MRCT Project could help to answer is how the outcomes of these efforts should be measured, beyond meeting the target goal in terms of numbers.

Mapping & Sharing Disease-Specific Feasibility Analytics

Fabio Thiers, MD, PhD CEO, ViS Research Institute

Trial planners have difficulty locating the information they need about research centers and the global locations in which they operate. At the same time research centers find it time-consuming and difficult to identify and present their capabilities to trial planners. The information needed by both parties to move forward is multidimensional, complex, scattered, and in some cases non-existent. The ViS Research Institute enables easy access to a complete map of clinical research

infrastructure through a web-based platform that integrates disease specific analytics from the country level all the way to what is inside the research sites.

Analytics is the discovery and communication of meaningful patterns in data. ViS uses a web-based process called collaborative analytics to integrate location analytics with center analytics. Research centers upload their disease specific profiles (e.g., personnel, expertise, capabilities) to the ViS social network and local experts use ViS algorithms to generate intelligence relative to the centers' location (e.g., epidemiologic and infrastructure data). The integration of these analytics allows for the creation of a complete map of clinical research infrastructure that can be used to match trial planners with research centers. Direct benefits of the system include a reduction in the cost of the research center selection process for both trial planners and research centers. The ViS platform also provides for a common understanding of the disease specific requirements for clinical research infrastructure for the research centers, while providing communication and collaboration tools for the clinical research community.

PI and Site Requirements in Asia and Africa

Sonali Kochhar, MD, PATH NOTE: Although now working with PATH, Sonali Kochhar provided an example as the past Medical Director with the International AIDS Vaccine Initiative.

Clinical research in developing countries is complicated by a variety of social (stigma attached to certain diseases), cultural (mistrust, recruitment of volunteers), and economic (trial site capacity, country scientific capacity development). The partnership between IAVI and the Indian Ministry of Health and Family Welfare for the conduct of the first AIDS Vaccine trials in India is a good example of how addressing these issues can increase trial success.

At the time this trial was initiated there were no vaccine trial centers or laboratories of international standards and no precedent or regulatory pathway for conducting such trials in India. In addition, the PIs were pre-selected by the government and the trials were the subject of intense media scrutiny. 2 vaccine trial centers of excellence were established by renovating and equipping existing centers and initiatingthe necessary trial support services. Since many of the center personnel were not experienced in international clinical research, extensive training was

conducted. All of these efforts were standardized with existing clinical research centers to ensure comparability of results. Care and treatment guidelines for trial participants were formulated through national consultations, an arbitration board was set-up and medical insurance was offered to volunteers for the duration of trial. Three Phase 1 trials were ultimately conducted.

Using this experience and feedback from investigators involved in vaccines and drug trials from advanced and recently developed centers in remote areas of Africa and Asia, the following critical requirements for PIs and research centers have been suggested. For the PIs these criteria include: education, training, experience in clinical research (including conducting international trials with external sponsors); experience in the disease area (the ability to provide adequate medical care to study participants including the management of serious adverse events); being able to devote adequate time to the trial; and being willing to learn on the job. Critical requirements for research centers include having adequately trained, experienced support staff; adequate infrastructure and equipment (e.g. water, electricity, internet, computers, clinic/dedicated hospital beds, labs with accredited and calibrated equipment, emergency medical equipment, incinerator, IP storage, administration, data management, document storage, archival and referral facilities); an adequate patient pool, and a trained, functional EC.

Practical Roadmap to Clinical Investigator Certification
Richard Peters, MD, PhD VP, Sanofi

Dr. Peters discussed a joint Sanofi-ACRP initiative: Practical Roadmap to Clinical Investigator Certification, which grew out of Dr. Peters' participation in the November MRCT meeting. The objective of this initiative is to develop a program to support a standardized PI certification that is readily available, user-friendly, and affordable. The program is based on the principles that individuals requesting the certification should lead by example, the process to achieve certification should be as free of risk as possible, and there should be financial support for investigators. A pilot program is currently underway at Sanofi whereby internal staff in the clinical group are becoming certified using the ACRP certification program. Risk reduction is achieved through training and the current expectation is that financial support for the

certification exam will be included in the research grant. The program is currently in the training phase. Certification testing is expected to take place in November/December of this year and will be followed by an evaluation during the first quarter of 2013. The program rollout is expected to occur in the second quarter of 2013 at which point it will be offered to additional internal staff and PIs. The perceived benefit of increased certification with this program is an overall improvement in the quality of academic and clinical trials.

PANEL DISCUSSION: Moderators Helmut Wolf & Richard Peters
Questions for discussion: Which requirements are testable/measurable and how? (The following questions were not discussed: Which are the high impact requirements? How can we assist sites in developing countries meet requirements?)

The discussion about certification centered on 2 questions: Is certification the right thing on which to focus? How can the effects of certification be evaluated? Several members agreed that certification might give sponsors and CROs additional leverage in enforcing standards agreed to in the contract. There was also some agreement that certification increased the PIs' and clinical research staffs' awareness of quality and compliance issues and by doing so may raise their attention to these principles and thus lead to improvements in overall trial quality. With respect to measurement it was pointed out that the focus of measurement should not be on what's easy to measure but what is meaningful to measure and it was suggested that this might be an area to which the MRCT Project could bring some clarity. The group agreed on the need to identify measures to assess the impact of PI certification and site accreditation. Some of the outcome measures mentioned during the discussion were patient enrollment, deviations, serious and continuing noncompliance, audit outcomes (scheduled or not), and errors. A related question involved how sponsors can adapt to the practicalities of conducting a clinical trial in various cultural environments and how to translate these differences, and their effect (or lack of effect) on quality for the regulatory agencies.

Most members of the group said that they were aware of "high performing sites" but no one could define how that designation was quantified. One suggestion was that the quality of a center goes beyond training and education; that it is a reflection of the commitment level of the PI and

that even in the absence of a direct connection between outcomes and certification, being willing to undergo certification could be a marker of commitment. Another important factor is aligning the interests of the institutions in which the investigators perform their research with the expectations of the sponsor. Caution was raised, however, concerning pushing too hard for certification before more fully exploring the outcomes, cost, and implementation issues. Doing so may make it more difficult to find PIs and sites to run clinical trials. It may also be important to evaluate the differential benefits of on-site versus on-line training programs and formal programs versus mentoring, as the reality is that no one method will be possible for all sites. Other areas of discussion included the need to maintain the integrity of sites once they have been certified and the possibility that more will be gained by working from the bottom-up (setting minimum standards for sites) versus the top down. A similar approach could be taken with the PIs.

The following were identified as potential testable and measurable requirements during the panel discussion:

- Noncompliance
- Audits
- Patient enrollment within a given timeframe
- Level of education/training/experience
    - Risk Based Monitoring factors (deviations, event error rates, patient intervention timeline)
- Markers of investigator commitment at high-performing sites vs. others
- Determination and alignment of interests at the institution level
- Eliciting value of certification vs. mentoring
- Effects of raising/adapting the study minimum standards for sites and PIs
- Able to devote adequate time to trial
- Experience conducting international trials with external sponsors
- Disease area, medical care and SAE management experience
- Prior PI track record
- Number of support staff and infrastructure
- Effectiveness of EC

SPEAKER SERIES: Regulatory considerations in foreign site selection

Ensuring Sites Meet Regulatory Requirements

Ann Meeker-O'Connell, MS, FDA

The increasing complexity of clinical trials, the number of sites required for each study, and the turnover among clinical investigators have combined to present a series of challenges in the selection of sites for clinical trials. In addition, with the expanding global footprint of trial conduct we now have a need for global agreement on what makes an investigator and/or a site "qualified" (both generally and for a specific study) and how performance should be evaluated to ensure that both the PI and the site continue to demonstrate competence. It is also true that, in some cases, the regulatory framework or perceptions about regulatory requirements may inadequately reflect evolving models of trial conduct and may unintentionally introduce inefficiency.

Overcoming these challenges requires a focus on "what matters" and in the case of regulatory issues, an understanding of the difference between FDA regulations, which are legally enforceable requirements and FDA guidance, which represents current thinking. It is also important to assess FDA regulations and guidance in the appropriate context. For example, for foreign studies not conducted under an Investigational New Drug Application (IND) the requirements differ based on whether the data in question are being used to support an IND or a marketing application or as the sole basis for marketing approval. Another area of misunderstand is the FDA's role in site and investigator selection. In general, FDA regulations do not cover site selection either with respect to qualification or how the selection should take place. Neither do they cover the selection of investigators except for the requirement that the PI must have knowledge of key regulations concerning human subject protection (HSP) and GCP.

Another area of particular interest for the MRCT Project is financial disclosure with respect to site selection. The FDA requires financial disclosure under 21 CFR Part 54 for foreign studies conducted outside of an IND and which either FDA or the applicant relies on to establish efficacy or in which a single investigator makes a significant contribution to the demonstration of

safety. However, individuals involved in site selection should consider that the Justice Department has an interest in financial considerations in the selection of foreign sites as well by way of the Foreign Corrupt Practices Act, and may be looking at site selection from a different context.

The FDA is participating in the Clinical Trials Transformation Initiative (CTTI), a public-private partnership to identify practices that will increase the quality and efficiency of clinical trials by prospectively identifying the aspects of a specific trial that are "critical to quality", identifying important and likely risks in these areas, and tailoring the investigational plan and trial implementation to eliminate or reduce those risks. An initial finding from one of the CTTI working groups showed a strong connection between site selection and study feasibility and quality. The CTTI project could inform the efforts of the MRCT Project in its efforts to develop standards for site selection as well as some of the general and specific performance metrics.

Perspective: Investigator Selection
Fergus Sweeney, PhD, EMA

Between 2005 and 2010 more than 750,000 patients were involved in pivotal clinical trials at 57,363 clinical sites in 90 countries. Such statistics make it clear that trial site selection is a global exercise requiring sponsors to manage clinical trials across multiple countries and regions while taking into account the challenges to harmonization brought on by differences in language, standards of medical practice, and regulatory requirements.

In April 2012, the EMA published a reflection paper on ethical and GCP aspects of clinical trials conducted outside of the EU/EEA and submitted in marketing authorization applications to the EU Regulatory Authorities. [5] In that paper they state that it is the sponsor's role to decide on the trial location, that the sponsor is responsible for ensuring that each site has oversight from an appropriate EC, and that the necessary applications are made to the EC and regulatory authority. Further, the paper states that where infrastructure, oversight, or personnel are not adequate, the trial should not be performed unless the sponsor can ensure that these inadequacies are mitigated. Specific responsibilities for the sponsor in terms of data quality and control, and site and

investigator selection, and for the study monitor with respect to initial/ongoing verification of the investigators qualifications, resources and adequacy of the facilities are included in GCP. Also included in GCP are the procedures for reporting and preventing recurrence of deviations to or failure to comply with the protocol, standard operating procedures, GCP, or applicable regulatory requirements.

In choosing a clinical research site, sponsors should anticipate local issues (e.g., language, culture, vulnerable populations, access, facilities, medical culture, and the availability and quality of IRBs/ECs), establish priorities, and analyze and manage the risks. As part of study oversight, poor-performing and non-compliant sites should be closed. The protocol should be amended when necessary (versus waiving the inclusion criteria) and there should be procedures in place to manage emerging issues. The goal should be the selection, training, and management of investigators and sites that perform studies in accordance with ethical and data quality requirements, and who are able to contribute adequately to the research and to ensure that subjects/patients participating in trials are fully protected – wherever the trial takes places.

PANEL DISCUSSION

Questions for discussion: What are the current challenges in this area? How can we best collaborate to assist sites?

The speakers were asked whether investigator certification might affect their respective Agency's current thinking concerning site selection and whether it might reduce the perceived risk of a given site. Ms. Meeker-O'Connell responded that although the FDA has historically been very supportive of external efforts to develop standards or certification, they have not taken a position to endorse such efforts largely due to concern about adopting a program over which it does not have control. They do consider AAHRPP certification during the IRB inspections, however, and they are also developing and piloting several risk models for selecting investigators for inspection and for identifying IRBs for surveillance inspections. One of the measures being assessed, particularly for the IRBs, is whether or not they have certification. With respect to risk based monitoring, although certification could be one of the measures considered, Ms. Meeker-O'Connell pointed out that there is still no clear indication that certification can serve as a

meaningful indicator of ongoing performance. That may change if such a connection can be established. Dr. Sweeney added that in his opinion, if you can use certification to increase the threshold of quality, it may help in other areas but it is unlikely to be recognized by the EMA. In terms of the site, the question is- who's holding the certification. What happens if they leave and what happens if there are personnel changes on the study. Noting that there are many standards that are mandated in the medical world, Mr. Vulcano asked what would need to be done in this circumstance to make certification of sites and investigators accepted. Ms. Meeker-O'Connell responded that it would be useful to have longitudinal data to show a connection between the criteria used to select investigators and continued performance in a way that takes into account all of the potential factors (certification, education, training, GCP, etc).

The benefits of having a trained cadre of investigators and sites (whether certified or not) should go beyond adherence to regulation. They should extend to enabling the investigators to develop a clear understanding of trial design and methodology such that they are not only capable of conducting a trial well but can provide feedback to improve future trials and design well thought out trials of their own.

PANEL 3: Building the Infrastructure for Trialists – A focus on Regional Ethics Committees

Independent Ethics Committee Qualifications and Competency

Marjorie Speers, PhD, AAHRPP discussed Independent Ethics Committee Qualifications and Competency.

In most countries, an ethics review is a necessary condition to conduct a clinical trial. ECs are integral partners in the conduct of a clinical trial and they are the only entity with the sole responsibility of protecting human subjects. Too often ECs are overburdened and inefficient, have poor access to training and education, and generally lack the capacity to conduct sound ethics review and when the EC review is deficient, site performance and trial quality is compromised. Given its importance in the conduct of a quality trial and the fact that the responsibility to obtain EC approval lies with the site, it is reasonable that the quality of the EC be a factor in site selection.

Most of the existing courses and other educational material that has been written for use by ECs focus on the ethical principles that govern clinical research and the way these principles are carried out. Dr. Speers discussed a recently published manual that takes a somewhat different approach by addressing the intersection between the investigator and the EC in the context of conducting clinical trials. It focuses on trial design as a way of providing a framework for the ECs to use as they evaluate the risk/benefit of a protocol. [6] The key concepts included in the manual are: ethics review and the science of clinical trials are integrally intertwined, ECs must know about the design of clinical trials to review them appropriately, and quality assurance of clinical trials is as important as ethics review. Opportunities for MRCT Project involvement in support of IRBs and EC include providing additional education and training but more importantly in sustaining these programs.

Dr. Speers also suggested that the current model of multiple EC reviews needs to change as there is no good evidence to show that requiring multiple reviews adds value or that it protects research subjects. Further, she suggested that consideration should be given to moving to a system of regional or national review and exploring the possibility of one protocol – one ethics review.

Possible activities for the MRCT Project with respect IRBs/ECS stemming from the panel discussion included:

- Inventory education and training programs, bioethics societies, universities with bioethics programs that exist in each country in each emerging market
- Link existing education and training programs with professional groups within countries that can deliver programs
- Explore partnerships with organizations like ACRP, the Canadian Association of Research Ethics Boards (CAREB), DIA, the Korean Association of Institutional Review Boards (KAIRB), and Public Responsibility in Medicine and Research (PRIM&R)
- Incorporate human subject protection principles and practice into GCP training for investigators
- Convene sponsors to pool resources around GCP training

Building the Infrastructure for Trialists: A Focus on Regional Ethics Committees
Delia Wolf, MD, JD, MSCI, CIP, Harvard School of Public Health (HSPH)

Studies that are sponsored either by the US government or US companies are required to follow US regulatory requirements for IRBs, however, it is often that case that despite agreeing to abide by these regulations local investigators fail to adhere to them because they are either unfamiliar with the regulations, the regulations conflict with local culture or belief, and/or there is some local resistance to meeting applicable US regulatory requirements. Challenges also arise with respect to interpretation of the applicable rules and guidelines. This latter situation often stems from differences in the definition of terms as well as the functions, operations, and scope of the IRB and Regional EC. Other challenges occur as a result of a lack of comprehensive policies and procedures to guide practice. These can lead to failure to implement/enforce existing policies, and/or discrepancies between policies and practices. Finally, lack of effective communication among regional ECs in multicenter trials can impede the review and approval process and lack of communication between REC and investigators can affect site performance (e.g., can lead to non-compliance). Opportunities for the MRCT Project to help the regional ECs meet their

obligations could include the development of checklists and forms for meeting US regulatory requirements and country-specific guidelines (with tools) according to local laws/rules.

The Current State of IRB/EC Performance and How to Improve It

Nicholas Slack, MBE, Western Institutional Review Board *(*WIRB*)*

Components that determine the quality of an IRB are the level of understanding the IRB and supporting staff have of their purpose and function (knowledge), how well they translate that knowledge into actual practice (operations), and the degree to which they operate without being influenced by internal and external pressures and have processes in place to manage conflict of interest should they occur (independence). To a greater or less extent there are deficiencies in all 3 of these areas within most IRBs. The most common deficiency of knowledge is that the mission of the IRB/EC is likely equated only with scientific review with little to no awareness of the regulatory criteria for approval. The source of this deficiency is primarily the limited training and education that is available to IRB/EC members. Operationally, many IRBs/ECs do not have SOPs, which leads to lack of consistency, poor record keeping and data tracking and in many cases there are no procedures for assessing submissions for completeness. Deficiencies in these first 2 areas can result in a blurring/misunderstanding of the lines of separation resulting in the IRB/EC being unduly influenced by investigators, officials, and/or sponsors and CROs.

In the US, and even more so internationally, the number of IRBs/ECs that can be considered not only regulatory compliant but approaching best practices (exemplified by AAHRPP) is small compared with the majority, which are largely defined by fragmented knowledge, poor operations, and a lack of independence. Moving these organizations to a more desired state of full regulatory compliance and increasing the number that are AAHRPP accredited will necessitate overcoming several obstacles. The first step is to gain a better understanding of the extent of the problem. At the moment it is unclear how many IRBs/ECs there are internationally, how well they are operating, and to what extent they are in compliance. Barriers to improvement exist on several levels. There is little incentive to be compliant since government oversight is lacking and sponsors and CROs are not demanding change. Limited information sharing and the absence of internationally recognized standards both contribute to inefficiencies. Most

importantly, there are likely too many IRBs/ECs and they lack too many of the necessary resources to move toward the desired future state.

The MRCT Project can help to improve the quality of the IRBs and ECs by creating mechanisms for empirically understanding and comparing their performance worldwide (e.g., perhaps audit a number of IRBs and compare results?), encouraging sponsors and CROs to allocate funds to IRBs/ECs at primary research sites, raising and allocating funds for IRB/EC improvement and subsidies for AAHRPP accreditation, funding research ethics conferences in high volume nations, and promoting training opportunities at organizations like WIRB and AAHRPP.

PANEL DISCUSSION: Moderator **Debasish Roychowdhury**, MD, Head of Oncology, Sanofi
What are the current challenges in emerging markets? What high-impact opportunities exist for the MRCT Project to guide and assist in this space?

Dr. Roychodhury commented that he believes clinical research is under siege and is somewhat in retreat. He noted that much of the clinical research that is being talked about today is highly prescriptive but there is a spark missing. While agreeing that the sites, IRBs/ECs, and investigators are important targets for improvement he suggested that not much is being done around what he referred to as the *eco-system* that encourages human research − the policy regulators, patient groups, and the media. He asked the group to think of how the MRCT Project could help to "…bring back the spark, the sense of purpose, and the joy of clinical research and create researchers who want to make a difference."

There was a brief discussion of *scope creep* with IRBs/ECs especially around safety monitoring outside of the US and Western Europe, why that is happening and what might be done to refocus these groups on their primary tasks. The consensus of the group was that for the most part this is a training and education issue. The discussion moved on to why there has not been a stronger movement toward requiring accreditation given that the deficiencies discussed are fundamental to the operation of the IRB/EC and given that AAHRPP has programs that could correct them. It was suggested that a further incentive for accreditation might be that it would allow the regulatory agencies to differentiate between accredited and non-accredited sites with respect to

regulatory oversight. It is obvious that there is insufficient funding for the regulatory agencies to oversee all of the existing sites. The percentage of sites that are audited is too small and not likely to increase with the current emphasis on budget reduction. Including accreditation status as one of factors used to decide whether and how often to audit a site, would allow the regulatory agencies to realize a benefit in terms of efficiency and effectiveness since they would be able to focus their attention on sites that are more likely to be at risk. It was also suggested that while the regulatory aspect of accreditation is important, a more powerful effect of accreditation is accountability. Another area in which the MRCT Project could assist with respect to IRBs/ECs is determining which variables distinguish high- and low-performing ECs.

PANEL 4: Training Challenges in Emerging Markets and Potential Solutions

Training Challenges in Emerging Markets and Solutions
Trudie Lang, PhD, University of Oxford

Contrary to what some perceive the research site staff in most emerging and developing countries are competent, well educated, and highly committed. The populations of these countries are, however, very much underrepresented in research, and as a result there is a lack of scientific evidence to drive improvements in public health. If the goal is to impact the major and local public health issues in these countries, there needs to be need more and better trials at more varied trial sites. In particular there is a need for trials that will drive changes in health practices. Dr. Lang referred to these as "disease management trials."

There is also a need for wide and equitable access to research and skill training in all regions and for all roles. Particularly important is training the sites in how to design and run trials (not just gather data for a specific protocol). This type of training is valuable because it provides a set of skills that are transferable and it promotes sustainability. It should include open access training and resources for GCP and Good Clinical Laboratory Practices (*GCLP*).

Standards and standardization of procedures are important to quality. We should work toward establishing them and engage the developing countries in the process. However, accreditation is different and including it in the site selection process would not be a benefit in developing countries. Two questions should be answered before proceeding along this path – is there a connection between accreditation and improved quality and who benefits from accreditation. In Dr. Lang's opinion requiring accreditation would be a step backward in the goal to increase research in the emerging and developing countries because it would close off opportunity.

Current Situation in Russia

Anna Ravdel, Synergy

Although counted as a developing country Russia has been on the clinical trial maps for 20 years. At the moment, research site staff in Russia can receive GCP training from study sponsors, CROs, universities, and specialized GCP training organizations but the variability in the length of the classes (a few hours to a few days), the environment (face-to-face, online) and the motivation of the student make it difficult to assess how well the classes meet their objectives. Despite the different sources for training, access remains difficult. Invitations to the investigator meeting generally do not include the support staff and much of the training can only be conducted online. Russia is a large country, there are few cities that offer this type of training and it is difficult for many investigators to take off the 2 to 3 days required to travel and take the course. Lastly, although the courses offered by foreign providers are often very good, they often miss local specifics. Essential to improved training for investigators is the use of workshops and interactive exercises that discussion and transfer of knowledge among investigators. Team member training could be accomplished by inviting them to the Investigator Meeting. Alternatively interactive GCP courses could be develop and offered in the evening using webinars, Skype, etc.

Only accredited sites can participate in clinical trials and only investigators with 5 years of clinical trials experience can serve as PI. There are currently 557 accredited sites in Russia, mostly in the central cities. These sites are overwhelmed, while the potential of the remote sites' is not being fully utilized. A possible solution to increase the number of sites and PIs is to organize a system/course to develop PIs that uses remote education with practical seminars and participation in clinical trials as a study team member. Participation/cooperation among the study sponsors, educators, and sites is essential for such a system.

Virtual 3D Training and Collaboration

Glenn Wise, BA, PPD-TIPS

PPD 3D is a next-generation communications platform for life sciences organizations, offering clinical research teams a more realistic, engaging, and productive way to communicate with colleagues and clients around the world. Users can talk (the program is integrated with voice over IP; VOIP), send instant messages, view and interact with presentation and media content, record notes and access the Web from anywhere. Participants have a sense of virtual presence and have the ability to break-out into smaller groups for enhanced collaboration. Using PPD 3D organizations can increase information distribution and collaboration across geographically disparate locations, accelerate the readiness of clinical trial teams by improving knowledge retention compared to on-site training, and reduce clinical trial management costs by eliminating travel and associated expenses. The training and learning materials can be accessed 24/7 from anywhere allowing users to enter and leave as needed. Benefits include simple and effective knowledge transfer, higher engagement, and cost reduction.

Training

Shelia Clapp, MBA *fhi360*

For data to be valid and high quality, it must be consistent, accurate, timely, and complete; anything less results in low quality reporting. Data collection must be also be consistent, concise, and compatible to ensure generalizability

"A job aid is a repository for information, processes, or perspectives that is external to the individual and that supports work and activity by directing, guiding, and enlightening performance."—Rossett and Gautier-Downes from A Handbook of Job Aids. [7] Use of a job aid to evaluate and assign causality for adverse events in clinical research can increase the investigator's confidence and the accuracy of the safety profile of treatment interventions under study, and reduce variability in data collection. The job aid provides context for investigators to consider the relationship between the adverse events and study drug using clear consistent language for each of the 5 possible assignments. For studies using multi-site data collection this

approach increases the probability that multiple investigators will interpret and apply data the same way.

The job aid can be introduced at an investigator meeting through the use of scenarios that provide an opportunity for the investigators to discuss the rationale behind their choices. Ongoing training can be provided at site visits by assessing trends. Challenges to implementation include the variation in experience, expertise, and knowledge (including familiarity with the safety profile of the drug) among the investigators, a misunderstanding of the role of assigning causality, inadequate pre-study preparation and turnover. It is important to communicate to all involved that the purpose of the job aid is consistency in interpretation, not to encourage or discourage any specific assignment. NOTE: Ms. Clapp discussed a specific job aid designed by Salim Abdool Karim, MD, PhD.

GCP/GCLP – Achieving and Maintaining Clinical Excellence

Kim Havens, RN, PPD

Although there is not one solution to all of the issues discussed today, from the discussions it seems obvious that the training component is critical − in part to "get people on board" and in part, because (particularly ex-US) training is valued. Mr. Havens discussed a partnership between PPD and the National Institutes of Health (NIH) to conduct 14 regional training events over a 4 year period during which they trained over 3000 site staff. Eleven of the programs were in sub-Saharan Africa. The metric for success was a reduction in deviations shown on the monitoring reports. He suggested this approach may be appropriate for clinical investigator training.

PANEL DISCUSSION Moderator: **Craig Eslinger,** MS, MBA, PPD

Question for discussion: What high-impact opportunities do we have in the pre-competitive collaboration space?

It is important for training to just learning the regulations. There should be more opportunities for interactive discussion-based training that allows the participants to apply what they have learned. Training programs should always include a needs assessment to ensure that the program

fits the situation and student. It was suggested that the MRCT Project could help by organizing and prioritizing the training and education needs and identifying the resources that might collaborate in developing best training practices. For example, under the auspices of the Innovative Medicines Initiative, 26 European Universities have collaborated to create a program called Pharma Train. They have assessed what it takes to train people for every level of the clinical research enterprise and have developed curriculum requirements and standards for certification. The program is being expanded as a global initiative in colleges and medical schools. A distinction of this program is that it is focused on education vs. training. Currently there is little emphasis on training and educating the kinds of people who are needed for the challenges of drug and device development in the future. The MRCT Project may be able to play a role in fostering the development of such individuals perhaps in cooperation with PharmaTrain.

What can the MRCT Project do?

- Support sustainable emerging and developing country training (market may not work in developing countries to deliver training)
- ID opportunities for collaboration
- Support "best training" practices"
- Support e-learning which may make training more cost-effective in emerging countries
- ID gaps in current training
- Enable training and competence to be built and delivered locally

In closing Dr. Barnes said that he was a bit more sanguine than some of the other participants concerning investigator certification – not because it is a sufficient condition for making sure that trials are done well but because it is at least a necessary condition for trials to be done well – that people know the regulations and understand the requirements. However, in reference to Dr. Lang's comment about how certification will affect the developing world, he suggested that whatever course is chosen the spirit must be one of inclusion vs. exclusion. Dr. Barnes reminded the group that his job with the MRCT Project and that of Drs. Bierer and Li were to help the members of the group do their jobs better, so that we all can have better research and so that the subjects in the developing economies can have better protection. What the MRCT Project needs

from the attendees at today's meeting are very specific ideas about what can be done so that we can all do it better together rather than individually.

Rebecca Li, PHD. Mark Barnes, JD, and Barbara Bierer, MD thanked the participants and closed the session.

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APPENDIX A. Current MRCT Initiatives

1. **Investigator Competence**

   Impact: Improved investigator/monitor quality and regulatory compliance

   - Develop a standardized training and certification program for investigators and other study staff
   - Broaden the traditional concept of study site feasibility to include a site "ethics assessment"

2. **Regional Ethics Committee (EC) Support**

   Impact: Stronger REC accountability, quality and increased REC capacity

   - Support assistance, training and guidance for research ECs (focus on emerging countries)
   - Ensure the REC infrastructure for trials promotes human subject protection

3. **Data and Safety Monitoring**

   Co-Chairs: Janet Wittes, President, Stat Collaborative; Charles Knirsch, VP of Global Medical Research, Pfizer

   Impact: Increased protection of participants

   - Develop best practices for data and safety monitoring boards (DSMBs)
   - Educate and train DSMB members for trials in the developing world, and qualify new DSMB members from emerging markets

4. **Protocol Ethics Guidance**

   Co-chairs: Susan D'Amico, AVP Compliance, Reata Pharma; David Forster, Chief Compliance Officer, WIRB

   Impact: Increased transparency regarding ethics in the protocol, ICF and study design

   - Develop a standardized protocol/ICF ethics section
   - Derive an "ethics" checklist to guide the team at the study design stage
   - Develop a system for evaluation of ethical issues at the program level
   - Ensure that there are global perspective, regional-specific sections