

## **MRCT Project Report**

***Enhancing Respect for Research Participants,  
Safety, and Fairness in Multi-Regional Clinical Trials***

**Addressing the Globalization of Clinical Trials**  
**(March 18, 2010)**

## **About the MRCT Project**

Initiated by Pfizer, the Multi-Regional Clinical Trial (“MRCT”) Project began with a Summit Meeting in July 2009 to identify ways to enhance the planning and conduct of multi-regional trials and the integrity of these trials. The Project has involved experts from large and small companies, clinical research organizations (CROs), non-industry sponsors of research (such as participants from the National Institutes of Health), non-industry researchers and bioethicists, and others. The discussions have focused on opportunities to enhance research ethics, ensure respect for study subjects, strengthen fairness and equity in clinical trials, protect subject safety, and identify other opportunities to improve MRCTs involving the developing world.

At that initial Summit Meeting, four areas emerged as important to assess: *the ethical review process, the data and safety monitoring process, site selection and investigator team competence processes, and improving monitoring*. Later, a fifth area emerged involving *clinical trial agreements -- model provisions for MRCTs*. Pfizer recruited stakeholders to join working groups to address these areas and hired a project team from Education Development Center, Inc. (EDC) to manage the process.

In January 2010, the participants reviewed proposals from the various working groups. Attachment 7 to this Report contains the minutes of that second Summit Meeting. Attendees included stakeholders from AAHRPP, Amgen, Chesapeake Research Review, Inc., CISCRP, Duke University, Faster Cures, First Clinical Research LLC, Gates Foundation, Genzyme, GlaxoSmithKline, Harvard School of Law, Medical & Public Health, Huron Consulting Group, i3 Research, International the AIDS Vaccine Initiative, John Hopkins Carey Business School, KGH Advisors, London University, Manipal Acunova, Merck, the U.S. National Institutes of Health, Novartis, the Oswaldo Cruz Foundation, Parexel International, Partners HealthCare Systems, Pfizer, PRIM&R, Quintiles, RapidTrials, the Statistics Collaborative, the University of Hong Kong, United BioSource, the University Hospital, Kralovske Vinohrady, the University of Malawi College of Medicine, the University of Toronto, Vertex Pharmaceutical, & Western IRB, and others.

The proposals in this Report should be seen as *ideas-in-progress* -- the result of the Summit Meetings and Working Group discussions.

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## Table of Contents

<b>About the MRCT Project</b> .....	<b>ii</b>
<b>MRCT Participants</b> .....	<b>iii</b>
<b>Introduction</b>	
Rationale for the Project .....	<b>1</b>
Ethical Principles .....	<b>4</b>
Overview of Proposals and Their Relationship to Ethical Principles.....	<b>7</b>
<b>Work Group 1: <i>Enhancing Quality and Efficiency of Ethics Review</i></b> .....	<b>18</b>
<b>Work Group 2: <i>Enhancing Data and Safety Monitoring</i></b> .....	<b>26</b>
<b>Work Group 3: <i>Enhancing Site Selection and Investigator Team Expertise</i></b> .....	<b>34</b>
<b>Work Group 4: <i>Enhancing the Professionalism of Monitors</i></b> .....	<b>41</b>
<b>Work Group 5: <i>Transparency of Contract Provisions</i></b> .....	<b>49</b>
<b>Report Conclusion and MRCT Next Steps</b> .....	<b>55</b>
<b>References</b> .....	<b>57</b>
<b>Attachments</b>	
• Sample Ethics Section/Document to Accompany Protocols .....	<b>61</b>
• Proposed Tool (Draft) for Study Site Assessment .....	<b>63</b>
• Alternative Models for Managing Study Site Assessment .....	<b>68</b>
• Suggested Core Competencies for Investigators .....	<b>71</b>
• Core Competencies for Monitors Re: Informed Consent & Subject Protection.....	<b>73</b>
• Sample Questions Monitors Should Ask .....	<b>74</b>
• Minutes from the January 2010 MRCT Summit .....	<b>76</b>

# MRCT Project Report

## Introduction

### **Rationale for the Multi-Regional Clinical Trials (MRCT) Project**

The pharmaceutical and biotechnology industries contribute to the betterment of the human condition through the discovery, testing, commercialization, manufacturing, and distribution of new medicines that enhance health throughout the world. Historically, development activities have focused on regulatory approval in larger, well-developed markets, with more clinical development activities taking place in Western countries. However, that has been changing, with development now being done globally across numerous countries and regions, with these trials involving hundreds of investigators and thousands of patients in the Americas, across Europe, and throughout Asia.

Since 2002, the number of FDA-regulated investigators based outside the United States has grown by 15% annually. At the same time, U.S.-based investigators have declined by 5.5% each year (Getz, 2007). A recent estimate is that one-third of all Phase III trials being run by the largest 20 pharmaceutical companies are being conducted solely outside the United States (Glickman et al., 2009). Moreover, an increasing number of trials involve sites in Africa, Asia, South America, Eastern Europe and the Russian Federation as well as sites in the U.S. and Europe. As the U.S. National Bioethics Advisory Commission noted in its Report on Clinical Trials in Developing Countries (2001):

*Increasingly, scientists from developing countries are becoming more involved as collaborators in research, as many of the countries from which these investigators come have developed their capacity for technical contributions to research projects and for appropriate ethical review of research protocols. Although the source of funding for such collaborative research is likely to continue to be the wealthier, developed countries, collaborators from developing countries are seeking -- justifiably -- to become fuller and more equal partners in the research enterprise. Finally, the current landscape of international research also reflects the growing importance of clinical trials conducted by pharmaceutical, biotechnology, and medical device companies.*

There are obvious benefits associated with globalization. Placing more clinical trials around the world increases the speed of development programs, which is beneficial for patients as well as trial sponsors. It is estimated, for example, that in some therapeutic areas such as oncology, it would take 6 years to fill all of the currently recruiting trials using only U.S. sites versus about 2 years placing trials globally (Clark, 2009). Labor costs are also typically less in the developing world. More important, however, is the fact that it is increasingly hard to recruit patients for

clinical trials. Developing countries can provide sponsors with access to large numbers of patients, to patients who may not be concurrently using other medications (which can complicate the interpretation of research findings) and to patients who are not already enrolled in or being recruited for other studies. Moreover, developing countries also represent increasingly important markets for new medicines -- leading sponsors to want to invest in research there.

Faster speed for study completion brings therapeutics to patients sooner. Patients in the developed and developing worlds benefit from access to cutting edge investigational treatments, which otherwise might be years away from commercial availability. Within the developing world, a local community's medical and scientific infrastructure and overall economy can benefit from industry's investment in their scientific capabilities and health care systems. In short, industry-sponsored clinical trial activity can contribute to economic development in many regions and provide better accessibility of promising new medicines to local populations.

Despite the obvious benefits of clinical trial globalization, there are also ethical challenges, most notably related to the potential for, and opinions about, "exploitation." Concerns about exploitation exist regardless of the funding source(s). One of the most prominent examples was a set of sixteen perinatal HIV transmission studies, funded by non-industry sponsors, including the National Institutes of Health and the Centers for Disease Control in the United States, six governments, and the United Nations (Hawkins and Emanuel, 2008). Those trials came under criticism, because fifteen of the sixteen used placebo controls rather than the worldwide best standard of care (AZT therapy in common use throughout the developed world). Since these studies would have been unethical if done in the developed world, critics argued that the subject sponsors employed a double standard and that there was an obligation on the part of these sponsors to compare the new regimens against the worldwide best standard (Lurie and Wolfe, 1997 and Angell, 1997). Others, notably the then-head of the NIH and then-director of the CDC, disagreed. They argued on both scientific and ethical grounds that a placebo comparison was essential to address the needs of these impoverished countries (Varmus and Satcher, 1997).

International guidelines encourage the use of worldwide best standards for control groups and allow placebos only when strict criteria for exemption can be met, typically only if placebo is necessary for scientific validity and for short trials that do not involve a risk of serious harm – e.g. temporary discomfort (e.g., common headache), small deviations in physiological measurements (slightly raised blood pressure or a modest increase in serum cholesterol) (CIOMS, 2002 and WMA, 2008). However, other criticisms and concerns about exploitation continue (Hawkins and Emanuel, 2008 and Lavery et al, 2007).

Industry sponsors are aware that they bear an important responsibility to ensure respectful, safe and fair clinical trials in developing countries, and the MRCT Project is an effort to direct energy and resources toward addressing those challenges. Initiated at a Summit Meeting organized by

Pfizer in July 2009, the MRCT Project has been a multi-sector initiative, involving numerous pharmaceutical and biotechnology companies, non-industry research sponsors, such as representatives from the National Institutes of Health, clinical research organizations (CROs), independent Institutional Review Boards (IRBs) serving the global community, and academic bioethicists and scientists from major research universities.

The goal of the MRCT Project has been to identify actions that can be taken by industry research sponsors, and the CROs they work with, to ensure the highest possible ethical standards for multi-regional clinical trials. The MRCT Project built on many outstanding efforts ongoing around the world. For example, the World Health Organization, the Wellcome Trust, the Gates Foundation, the U.S. National Institutes of Health (through its Fogarty Program and its Department of Bioethics), the Foundation for Advancement of International Education and Research (FAIMER), among others, have programs that have developed a cadre of individuals with the training and expertise to sit on Research Ethics Committees (RECs, or what in the United States are called IRBs) across all regions of the globe. The Clinical Trial Transformation Initiative (CTTI), a relatively recent initiative spearheaded by Duke University, the U.S. FDA, and the U.S. NIH, and involving many industry participants, is focused on addressing opportunities for regulatory reform in the U.S. (FDA's policies for clinical trials) and conducting empirical research to inform policy development globally. The MRCT Project complements these other efforts, by focusing on specific actions that industry, individual trial sponsors and CROs, in collaboration with other clinical trial stakeholders, can take to improve their operations and to identify opportunities for building capacity within the countries where they locate their trials.

In September 2009, MRCT participants organized into four Work Groups, based on four essential areas identified at the July 2009 Summit Meeting as critical to research ethics infrastructure in culturally diverse and resource-poor environments. These groups focused, respectively, on enhancing:

- the efficiency and quality of ethical review,
- data and safety monitoring,
- site selection and investigator professionalism, and
- the training of site monitors who oversee the conduct of clinical trials.

More recently, a fifth Work Group was established to develop transparent options for contract provisions between sponsors and research sites on matters ranging from academic freedom of investigators to research participant and community benefits. Performance in all five of these areas must meet the highest standards if clinical trials are to be conducted safely and fairly and with respect for the individuals and culturally diverse communities volunteering to serve as research participants and research sites.

This report presents the proposals that emerged from the Work Groups between September and December 2009 and output from the January 2010 Summit Meeting. The proposals, which are still *works in progress*, have the potential for improving multi-regional clinical trials that involve developing world regions and advance the application of ethical principles to the design and conduct of clinical trials, generally. The following two sections describe some of the key ethical principles and provide an overview of how the MRCT Work Group proposals relate to these principles.

### ***Ethical Principles***

There is universal agreement that all research involving human participants should be guided by respect for persons, beneficence and justice (ICH-GCP/E6, 1996; CIOMS, 2002; WMA, 2008; National Commission, 1978, Nuremberg Code, 1947). However, when clinical trials are conducted in developing countries with more vulnerable populations and diverse cultures, there are additional challenges. The complexity is primarily due to differences in cultural values and generalized the lack of medical and scientific infrastructure. Ethical review, community involvement, robust data and safety monitoring, well-equipped research sites, and well-trained personnel can be obtained, but may be more difficult to ensure in such countries.

Concerns about exploitation have been well-articulated through numerous academic publications (e.g., Lurie and Wolfe, 1997; Angell, 1997; Emanuel et al., 2004; Emanuel et al., 2008; Hawkins and Emanuel, 2008; Glickman et al, 2009; and Lavery et al., 2007) and media accounts. Nonetheless, there is agreement that:

- Investigational medicines should generally be compared against world-wide standards of care, wherever possible. Comparisons to placebo or local standards of care are generally not appropriate if the administration of placebo or a local standard of care poses a risk of serious harm to the participants;
- Study populations should be chosen carefully, with attention paid to whether the potential new therapy may benefit the population and with consideration as to whether the medicine will be made available to that population, if proven to have met the standards of safety and efficacy required by regulatory authorities;
- Individual research participants deserve to receive “fair benefits” for participating in research, which may consist of the associated medical care, post-trial drug access, or other benefits provided to them or, in some cases, their community;
- Trials should only be conducted where adequate infrastructure exists or can be developed to ensure an appropriate review of the protocol by a qualified ethics committee, and only with suitable data and safety monitoring, data collection and

study management. Where the infrastructure is absent, but the medical need for the trial is great, sponsors may need to work with local communities to help establish a qualified ethics committee or infrastructure for safety monitoring, data collection and study management.

The Guideline for Good Clinical Practice (GCP) established by the International Conference on Harmonization (ICH) provides a common framework for oversight and has been adopted by the United States, Japan, the European Union and many other nations (ICH-GCP, 1996). The U.S. Food and Drug Administration requires that all foreign studies adhere to GCP guidelines, and the Council of Europe will not recognize the results of trials, wherever conducted, if they violate the Council's Convention on Human Rights and Biomedicine (1997).

Despite the broad acceptance of ethical principles and regulatory standards, applying these criteria can be difficult. There are substantive challenges, as when parties disagree on whether a principle has been, or should be, met in a particular instance. There are also operational and educational challenges that impede the optimal implementation of a guideline in practice.

### **Substantive Challenges**

Substantive disagreement can center on whether a given study, either in its design or in its conduct, has reached an acceptable threshold and therefore met the principle. For example, the World Medical Association's Declaration of Helsinki (2008), states that "*At the conclusion of the study, patients [emphasis not in original] entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.*" (World Medical Association, 2008, Guideline 33). In contrast, CIOMS guidelines state:

*Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that ... the sponsor and the investigator must make every effort to ensure that ... any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community [Guideline 10]. ... "reasonable availability" ... will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge [Commentary to Guideline 10].*

Guideline 10, Council for International Organizations of Medical Sciences ("CIOMS") 2002.

Thus, the obligation of sharing of benefits of research is often dependent on "reasonable availability" and other trial-specific and population-specific factors. Indeed, reasonable

availability can itself mean many things, from simply registering a drug in a country so that it can be marketed to special drug access mechanisms to make the drug affordable.

As mentioned above, there is often great subjectivity in determining whether an ethical principle has been applied and how, and also when exceptions are reasonable, justified and appropriate. There is significant agreement that, as “*a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention* [CIOMS (2002) Guideline 11].” Sponsors, most ethicists, and other stakeholders may also agree that, “*In some circumstances, it may be ethically acceptable to use an alternative comparator, such as placebo or “no treatment”* but that those exceptions to the general rule need to be carefully justified (e.g., where there is no established effective intervention, where subjects would only be at risk of temporary discomfort; and/or where a comparator would not yield scientifically reliable results and the placebo would not pose an added risk of serious or irreversible harm. CIOMS, Guideline 11). Nonetheless, stakeholders sometimes disagree about whether and when control groups should receive a placebo control or a comparator therapy that constitute the local standard of care (rather than the worldwide best standard of care). (Temple and Ellenberg, 2000; Ellenberg and Temple, 2000). This issue is also positioned differently in the most recent version of the Declaration of Helsinki which advocates that “*Extreme care must be taken to avoid abuse of this [placebo] option*” (World Medical Association, 2008).

Applying ethical principles such as these to factual situations can be difficult, even where the principles are universally subscribed to, because parties will disagree about the scope of an ethical recommendation, the interpretation of that recommendation, or about what constitutes reasonable and justifiable exceptions. But the application of ethical guidelines is difficult in practice for another reason as well: guidelines can only go so far; if and when such principles are applied to different fact patterns and circumstances, only then can the principles be fully developed.

### **Operational and Educational Challenges**

To ensure change that “sticks,” it is usually necessary to change the day-to-day ways in which members of complex organizations approach their work. For example, scientists focus on identifying research questions and designing methods capable of answering those questions. Trial protocols describe how the experiment will be conducted, what the rationale is for the experiment, and how the risks and benefits are to be managed, but do not require that the investigator articulate how the study and protocol address specific ethical criteria. Some believe that if the investigator, or the sponsor, were committed to answering a set of questions about how the study design was chosen, and how site selection will be done, etc., then ethical issues would be addressed with greater focus and efficiency. Some of the Work Group proposals encourage this kind of thinking.

Another set of challenges are educational in nature and arise out of the need for a professional work force with the requisite skills to ensure scientific, operational, clinical and ethically reliable review and implementation of protocols. One recent study of 31 RECs in Africa found that 92% of the committees self-reported that they felt inadequately trained to properly review and monitor trials (Nyika et al., 2009). In a study of Australian clinical trial investigators, more than one-third (38%) reported that they could not claim that they understood good clinical practice principles and only 47% reported understanding serious adverse events and their reporting requirements (Babl et al, 2008). All of the MRCT Work Groups have proposed strategies to enhance the training and post-training performance of each of the key actors, whose behavior and skills are essential for optimal review and implementation of clinical trials: those who sit on RECs, those who sit on DMCs, clinical trial investigators, and monitors.

The purpose behind all of the proposals in this Report is to build a more robust research ethics infrastructure and therefore a more trustworthy clinical research endeavor worldwide. Figure 1 below presents the proposals recommended by each of the five MRCT Work Groups.

In evaluating these proposals, it is important to keep in mind how they relate to the MRCT Project's goals and ethical principles. Therefore, the next section explains more fully the relationship between the proposals and the ethical concerns that have impelled them. To articulate this relationship, we have found it useful to use the framework of principles articulated by Emanuel et al. in the *Journal of Infectious Diseases*, 2004 and used again by Lavery et al. in their casebook, *Ethical Issues in International Biomedical Research*, 2007. The following discussion and Figure 1 are therefore organized using the Emanuel et al. framework, which advocates eight ethical principles that should guide the design and conduct of all multi-regional clinical trials. These eight ethical principles are: collaborative partnership, social value, scientific validity, fair selection of study populations, favorable benefit-risk ratio, independent ethics review, informed consent, and respect for recruited participants and study communities (Emanuel, Wendler & Grady, 2000; Emanuel, Wendler, Killen and Grady, 2004; Emanuel et al., 2003, and Lavery, Grady, Wahl and Emanuel, 2007).

### ***Overview of the Proposals and Their Relationship to Ethical Principles***

Below, we give a flavor for the ways in which each of the MRCT Work Group's proposals aim to address the aforementioned eight ethical principles, all of which are central to the ethical conduct of clinical trials, especially when the trials are conducted in developing countries. However, this discussion is brief and is not intended to describe all of the proposals. For a more thorough description of each proposal and its corresponding rationale, please refer to the MRCT Work Group reports which constitute the main body of this Report. The goal of this section of the Report is simply to illustrate, with reference to some of the proposals, how such proposals relate to important ethical considerations.

**Collaborative Partnership.** This ethical principle calls on research sponsors to develop partnerships with local researchers and the communities where research is to be carried out. The principle is broad and intends to ensure a robust concept of partnership through a wide variety of means, such as mutual decision making about whether the health problem under study is important to a prospective participating community and whether recruited participants and communities will receive adequate benefits from participation. Many of the indicators of collaborative partnership relate to how fair a proposed study is likely to be: in other words, this ethical principle requires that sponsors relate to individuals and communities volunteering to participate in clinical trials as true partners who can expect to gain some benefits from their willingness to take on the risks of human research.

Several MRCT Project proposals aim to build more robust collaborative partnerships with prospective study communities. For example, Work Group One's Proposal 1.1 proposes that sponsors develop a common set of ethical questions common to large multi-regional clinical trials involving the developing world that could be addressed in a document accompanying the protocol and submitted to the RECs. The proposed document would include high-level information about the relevance of the research (the extent to which the disease being studied is a problem among the intended study population) and how recruitment and informed consent would be done. The document might also ask about the likely benefits that will accrue to prospective participants, such as whether or not post-trial drug access or post-trial care is planned (and if not, why it is not planned).

Given that parties will inevitably differ about a set of common ethical concerns and that in different protocols, different ethical questions will have more salience than others, the purpose of Proposal 1.1 is not to dictate specific answers to the questions. Rather, it seeks to encourage reflection and transparency about common ethical issues which tend to arise in multi-regional clinical trials and the inclusion of those answers in a document, where non-technical members of RECs can readily find them. This simple, but potentially useful change might ensure early attention to ethical considerations, possibly influencing study designs before protocols are finalized and/or facilitating comprehensive and timely ethical review by RECs.

Other examples of commitment to the ethical principle of collaborative partnership include Work Group One's Proposal 1.6, which calls for supporting the establishment of Community Advisory Boards. Work Group Three's Proposals 3.1, 3.2 and 3.3 all aim to enhance fairness with respect to the placement of studies where they are likely to offer benefits to the participants and their communities. Work Group Five aims to address concerns about whether some prospective research sites in the developing world, and their patients, would benefit from having access to more standardized provisions for contracts with research sponsors, in lieu of negotiating these on an institution- by-institution basis.

**Social Value.** As articulated by Emanuel et al. [2004], the ethical principle of social value is meant to ensure that there is likely going to be value to those individuals and communities who volunteer to undertake the risks of research participation, such as assurance that the disease under study is one of importance in that population. As noted above, Work Group Three's Proposals 3.1 and 3.2 call for a common set of ethical and quality criteria for selecting study populations and research sites, which, if adopted, would reduce the likelihood that studies occurred in locations simply because research participants were readily available, without also providing important social value to the community. Proposal 1.6, calling for greater use of and support for Community Advisory Boards (CABs), is another way to ensure participation of local communities. CABs can identify benefits they would want to see accrue to individuals and communities, help with recruitment, and help disseminate research findings at the end of a study.

**Scientific Validity.** No clinical trial warrants the assumption of risk by human volunteers -- if the trial is not capable of answering important/meaningful scientific questions. Therefore, to be ethical, studies must be scientifically valid, which in turns means that they must be carried out in responsible ways that ensure appropriate inclusion and exclusion recruitment criteria, data integrity, and analytic rigor.

All of the MRCT Work Groups have offered proposals that aim to enhance the professionalism of those individuals who play key roles in ensuring the scientific validity of the clinical research enterprise. Work Group One's proposals focus on building expertise among those who sit on RECs; Work Group Two's proposals focus on building competence among those who sit on Data Monitoring Committees (DMCs, or what in the United States are called Data and Safety Monitoring Boards or DSMBs). Work Group Three proposes steps to enhance the competencies of investigators and research coordinators. Work Group Four strives to enhance the professional development of monitors. Enhancing the professionalism of these key actors will simultaneously enhance the scientific, operational and ethical quality of multi-regional clinical research. Work Group Five seeks to secure the right of investigators to access the data from the trial and publish findings, consistent with modern notions of academic freedom and with reasonable accommodation to protect intellectual property.

**Fair Selection of Study Populations.** This ethical principle aims to ensure that sites are selected on justifiable grounds and not simply because of easy access to participants. Justifiable grounds include both scientific validity (the population provides an opportunity to study something of social value in a scientifically rigorous manner – see above) and ethical validity (e.g., if the investigational medicine is eventually demonstrated to have met the standards of safety and efficacy required by regulatory authorities, it will be available to the population). There should be special cautions to avoid the exploitation of vulnerable populations, including those with less political power and those who suffer from marginalization, stigma and poverty.

Several MRCT Work Group proposals aim to ensure fair selection, including the call for CABs and high quality ethics review. In addition, Proposals 3.1, 3.2 and 3.3 from Work Group Three explicitly focus on the importance of choosing sites with appropriate populations for participating in the study, including locations that are reasonably likely to benefit from the results of the study. These proposals call on sponsors and stakeholders to agree upon and incorporate ethical principles into site selection, and to place sites at locations that meet those criteria.

**Favorable Benefit-Risk Proposition.** Obviously, all research should offer a favorable benefit-risk proposition or ratio (*if the potential risks outweigh benefits to participants, the social value must justify those risks*) before the study is approved (Emanuel et al., 2004, page 934)). In developing countries, it may be the community itself, through or in conjunction with the relevant REC, which should decide whether the risks are warranted and that assessment will vary, depending on the local context. For example, in an area where a disease is serious and endemic, the social value of the expected knowledge and agreement to post-trial access to proven therapeutics might warrant accepting greater risks than a community facing less dire health conditions (or where no post-trial medical care would not be available). Of course, the sponsor must also be comfortable with the risks posed by a given trial and product liability concerns may eliminate research that would otherwise be compelling for a local community and the relevant REC.

The proposals most relevant to the favorable benefit-risk principle are those Work Group One proposed related to enhancing the ethical expertise of REC members (1.2, 1.3 and 1.4) and to establishing CABs (1.6). While benefit-risk analysis is something that must be determined prior to study approval, it is also an ongoing concern because expected risks may change as a study unfolds over time and is monitored by a DMC. Therefore, Proposal 2.1 from Work Group Two is also relevant to this ethical principle which calls for the development of a training program for potential REC members.

**Independent Ethics Review.** Competent ethical review that is free of conflicts of interest is essential to a trustworthy research enterprise. Currently, much research in the developing world is vetted by an IRB in the research sponsor's host country and by local and/or national RECs in each of the host communities where the study will be conducted. Review by the host country is essential to ensure independence. Work Group One calls for developing models for increased use of regional or national RECs to avoid duplication and enhance efficiency, but also to ensure the higher quality of review that would be expected by having fewer RECs with greater experience and expertise.

Relevant Work Group One proposals regarding independent ethics review are: (a) Proposal 1.2, which advocates the accreditation of RECs; (b) Proposal 1.3, which calls for a grant-making initiative to support RECs as they move toward accreditation; (c) Proposal 1.4, which calls for sponsor support for training of REC members; and (d) Proposal 1.5, which calls for more regional or national models of review. Work Group Two's Proposal 2.1, which calls for the creation of apprenticeship programs to mentor DMC members, and Proposal 2.2, which recommends model charters for DMCs to help ensure accountability and transparency of DMC functions, are also important ways to improve the quality of independent review mechanisms.

**Informed Consent.** Voluntary, informed consent is one of the most longstanding ethical principles that ensures that research participants are respected as persons and are free to participate, refuse and/or withdraw from participation in human research. Special issues related to informed consent arise in the context of research in developing countries. For example, it is appropriate to be concerned about undue inducement, but such concerns must take into account the reality that many clinical trials, by their very nature, will offer benefits to study populations in resource-poor environments. A number of other informed consent issues come to the forefront in the context of the developing world. For example, many commentators argue that it may be wise and respectful to seek permission from village elders and other leaders to locate the study in a community, but that such permission should not replace individual study subject consent — even though members of the community may not themselves be comfortable with Western notions of *individual* consent. In the EU, individual consent would have to be obtained from each study subject for data from such a study to be used in support of a marketing authorization, under the Council of Europe 1997 Convention for the protection of human rights and dignity of the human being.

Work Group Four has four Proposals (4.5, 4.6, 4.7, 4.8) related to strengthening informed consent, by expanding site monitors' understanding of their importance and their skills in detecting optimal and sub-optimal informed consent processes.

**Respect for Recruited Participants and Study Communities.** Nearly all the ethical principles enumerated above stem from a desire to respect both individual participants and the communities that choose to participate in research. Too much weight is often placed on informed consent as the vehicle for ensuring respect, but other concerns -- such as confidentiality and the sharing of research findings -- are also important.

The Work Groups have identified mechanisms and initiatives that have the potential to foster professionalism among those who sit on DMCs, work as monitors, and serve as investigators and research coordinators. Work Group One proposes increased support for accreditation of RECs. These recommendations signal the importance of maintaining world-class standards for research participation protection, no matter where the research is conducted. In addition, the proposals aimed at ensuring fair selection of sites and study populations, assuring that ethical

considerations have influenced study design, and focusing on what the potential benefits of participation will be for both participants and communities provide other indicia of professionalism and respect.

In addition, Work Group Five's effort to develop consensus-based and transparent options for key contract provisions that relate to ethical issues (e.g., access to study data, publishing rights, participant benefits, addressing trial-related injuries) are also based on the principle of mutual respect. Such contract terms vary between sponsors and sites and across geographies. However, there are many useful reference points, such as basic provisions for access to study data after the trial for publication purposes, means for providing research-related health care for participants after study conclusion, post-trial access to proven therapeutics, and standards for addressing trial-related injuries. Not only do these provisions vary, but awareness of one's options, sophistication in negotiation skills, and realism also vary among all parties, especially when one side has more economic resources than another. By developing standard provisions, including variations that fall along a continuum, Work Group Five hopes to demonstrate respect for industry's local research partners and promote transparency and fairness in negotiations between both sides.

**Figure 1. Relationship between MRCT Proposals and Ethical Principles**

	Partnership	Social Value	Scientific Validity	Fair Participant Selection	Favorable Benefit-risk Ratio	Indep. Review	Informed Consent	Respect for Participants & Communities
<b>Work Group One: Enhancing the Quality and Efficiency of Ethical Review</b>								
1.1 Provide an ethics document with key questions/issues addressed to supplement the protocol, for certain trials, as appropriate.	✓	✓		✓	✓	✓		✓
1.2 Encourage accreditation of Research Ethics Committee (RECs) and human research protection programs.						✓		✓
1.3 Create a pool of funding and a grant application process to support REC accreditation.						✓		
1.4 Enhance continuing education for already-trained fellows and opportunities for mentoring of new REC members.	✓					✓		✓
1.5 Through a series of best practice case examples, high quality and efficient models of ethical review.	✓	✓				✓		✓
1.6 Promote the establishment of Community Advisory Boards	✓				✓	✓		✓

	Partnership	Social Value	Scientific Validity	Fair Participant Selection	Favorable Benefit-risk Ratio	Indep. Review	Informed Consent	Respect for Participants & Communities
<b>Work Group Two: Enhancing Data and Safety Monitoring</b>								
2.1	Develop a fellowship program for new DMC members.	✓			✓	✓		✓
2.2	Develop sample DMC charter(s).				✓	✓		✓
<b>Work Group Three: Enhancing Site Selection and Investigator Team Expertise</b>								
3.1	Adopt common ethical and quality criteria for selecting study populations and research sites.			✓				✓
3.2	Develop and measure the impact of using a Common Study Site Assessment Tool.			✓				✓
3.3	Evaluate/manage conflicts of interest associated with bundling responsibilities for site assessment & study management.			✓		✓		✓
3.4	To the extent legally permissible, share information on site and investigator quality.		✓					✓
3.5	Mount a rigorous study of the value of certification programs for investigators and study coordinators.		✓					✓

	Partnership	Social Value	Scientific Validity	Fair Participant Selection	Favorable Benefit-risk Ratio	Indep. Review	Informed Consent	Respect for Participants & Communities
3.6	Preferentially place trials at sites with investigator certification, and promote certification.		✓					✓
3.7	Verify the medical expertise of prospective investigators.		✓					✓
<b>Work Group Four: Enhancing the Professionalism of Monitors</b>								
4.1	Endorse a professional paradigm for monitors.		✓					✓
4.2	Establish recognized and expanded core competencies for monitors.		✓				✓	✓
4.3	Inventory existing monitor training programs and conduct gap analyses.		✓					
	Develop an educational framework with the characteristics of relevant, high quality professional education programs.		✓					✓
4.4	Encourage and reward monitor certification by preferentially using clinical research organizations and research sites that offer certified monitors.		✓					✓

	Partnership	Social Value	Scientific Validity	Fair Participant Selection	Favorable Benefit-risk Ratio	Indep. Review	Informed Consent	Respect for Participants & Communities
4.5 Develop greater clarity about the role that monitors have to play in enhancing informed consent processes.							✓	✓
4.6 Ensure that all monitor educational programs include a focus on the monitor's role in assessing and maintaining a high quality informed consent process.							✓	✓
Develop a kit of strategies and resources which monitors can use to enhance informed consent.							✓	✓
4.7 Develop a dissemination plan to promote the use of the kit by monitors.							✓	✓
<b>Work Group Five: Transparency in Contract Provisions</b>								
5.1 Publication Rights.			✓					
5.2 Confidentiality and Non-Disclosure.			✓					
5.3 Fair Benefits.	✓	✓			✓			✓

	Partnership	Social Value	Scientific Validity	Fair Participant Selection	Favorable Benefit-risk Ratio	Indep. Review	Informed Consent	Respect for Participants & Communities
5.4 Compensation for Trial-related Injury; Insurance & Indemnification.					✓			✓
5.5 Privacy and Data Use/Sharing.			✓					✓

## **Work Group One:** ***Enhancing the Quality and Efficiency of Ethics Committee Reviews***

### **Nature of the Challenge**

Both industry and non-industry sponsors of clinical research have the responsibility to ensure that clinical trials are performed safely and ethically, based on a strong and efficient process of independent ethical review.

Over the last decade, great strides have been made in building an ethical review system across the world. Although the system for such review varies by country, in many places and to varying degrees there are government regulations and infrastructure for human research protection at the research sites carrying out clinical trials. A central feature of all systems developed to ensure human research protection is the REC/IRB. Although only part of a total human research protection program, RECs are independent of sponsors and investigators and therefore play an essential role; they are the main line of defense against the launching of or continuation of inappropriate trials.

There are numerous research ethics training programs in existence through a variety of initiatives. The Fogarty Program and other institutes at the National Institutes of Health (NIH), the Wellcome Trust, and the Gates Foundation have all provided funding for research ethics capacity building. Numerous academic programs at major research universities in the United States, Canada, Europe and other countries, as well as the Department of Bioethics at the Clinical Center at NIH, and independent IRBs, such as Western IRB, have trained fellows from scores of countries. Working through its European and Developing Countries Clinical Trials Partnership (EDCTP), the European Union has funded grants for research ethics training in sub-Saharan Africa. The World Health Organization's Special Programme for Research and Training in Tropical Diseases (TDR) has launched The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), a public-private partnership to enhance the quality of ethical review in RECs around the world. There have also been very significant contributions from industry sponsors, including support for the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and long-term support of Harvard's two-year Clinical Trial Investigator Training Fellowship, which is funded by Pfizer and Merck, and covers both scientific and ethical topics for investigators-in-training. Work Group One is aware of the tremendous efforts that have been and are taking place. Work Group One's proposals are designed to support and build on this strong foundation.

At the same time, both within the developed and the developing world, there are recognized limitations on the systems for reviewing trials. Concerns center on efficiency (for example, the time it takes to get a protocol reviewed) and effectiveness (for example, the quality of the review and its ability to detect ethical problems) are well documented. Although these problems exist in

both developed and developing nations, there are additional special issues that may arise in the context of resource-poor environments with less existing infrastructure, both human and material.

First, in some places there may be minimal governmental regulations in place that would ensure that high quality ethical review occurs. Often sponsors address this problem by utilizing international guidelines and standards. Second, some local RECs may lack the same level of research and medical expertise one might expect to find in a well-developed region. Trial sites may also lack the most basic materials, such as locked cabinets or computers, and experienced study staff. Sponsors often address this by helping build the local infrastructure, by providing training or equipment, and/or by having their trial reviewed by multiple RECs (one for each region and/or site, and sometimes a REC in a developed country as well, even if the trial will not involve participants from that country). There are also different cultural attitudes that must be taken into account by deliberating RECs. For example, Western notions of individual informed consent may conflict with local concepts of community assent. Cultural attitudes toward women may pose special challenges both to issues of consent and other aspects of the study protocol.

## **Proposals**

Sponsors can take a leadership role in ensuring optimal ethical review of global clinical trials by advancing each of the proposals below. These ideas are presented in a rough approximation of the order in which ethics issues are considered, starting with study and protocol design, then moving to submission for independent review, and ongoing REC performance. Despite this order, Work Group One wishes to note that Proposal 1.2, calling for accreditation of human research protection programs, was deemed to be of the highest priority and the most important of their recommendations.

**Proposal 1.1. Include an ethics section accompanying each/certain protocols (to help ethics committee review the proposal, as needed).** Work Group One envisioned a section with key ethics questions that sponsors should answer for all protocols (see draft included here as Attachment 1) or for certain types of protocols (such as those involving the developing world or certain types of trials involving vulnerable patient populations, etc.).

The questions should address issues identified as ethically salient in the conduct of trials in the global environment, such as whether the disease being studied is one prevalent in the country where the drug will be studied, whether post-trial drug access will be provided, what the sponsor's plan is with respect to minimizing risks to participants, etc. The purpose of such a section is not to dictate how the questions are answered or how the REC should decide the issues, but rather to ensure that sponsors consider these issues as they design the studies, and document how they handled them and why, in a common place in all protocols.

Many of the ethical issues that arise in the course of conducting clinical trials should be, and typically are, considered early on, while the study is still being designed and the protocol not yet finalized. It is nonetheless true that scientists designing studies think primarily of the scientific question and methods that are needed to answer that question without consistently focusing on ethical issues. When these ethics issues are grappled with “upfront” they may well influence the final design of the study and its protocol.

An ethics document can also facilitate more complete and timely REC review. REC members will know where to look to see how a standardized set of ethics concerns have been handled by the sponsor. When ethics problems arise in clinical research it can be because of the research design or some aspect of the trial agreements (e.g., regarding expanded medication access post-study, research-related injuries, consent) that should have been noticed in the review process. A standardized set of questions, and the REC’s realization that they can turn to that section during their deliberations, would facilitate review by the REC. It may also help to harmonize the perspectives of sponsors and RECs: rather than focusing independently on the science or ethics of the research, such a protocol section would assist both parties in recognizing their shared responsibilities for the ethical conduct of trials.

This proposal recommends that sponsors work collaboratively to design such a document and use it on a trial basis. Much remains to be ironed out. For example, the ethics section would have to work globally and for many kinds of trials, and it would be unwieldy to try to have different versions. The best approach might be to have a simple (plain vanilla document) that could be tailored to fit specific types of trials. The document would need to be simple enough and clear enough that sponsors would be willing to complete the document, in addition to the protocol and numerous other documents and filings required by regulators, research ethics committees, and existing sponsor SOPs. Work Group One therefore envisions a pilot study to assess the usefulness of the ethics document. Usefulness can be conceptualized along three dimensions: (1) the ability of the ethics section to create greater transparency regarding key issues that have been identified as central to trustworthy research, (2) the ability of the ethics section to advance preventive ethics (by encouraging changes early on in the study design that might not have been identified), and (3) in terms of its contributions to more efficient ethical review. *At the same time, there would be a downside to duplicating information that is already provided in the trial protocol (such as the consent process, recruitment procedures, special protections incorporated into the trial).* The pilot should thus also try to identify what information was most important, what was merely duplicative, and for which trials such a document is most useful (if any).

The results of such a pilot, if supportive, could then be used to advocate for broader acceptance and utilization, of a standardized ethics document.

**Proposal 1.2. Encourage accreditation of human research protection programs globally.**  
The goal of this proposal would be to strengthen the accountability and capacity of RECs

through the process of applying for, achieving, and maintaining accreditation. Accreditation seems to work. There is at least one study showing fewer deficiencies in FDA audits at those sites with accredited human research protection programs as compared to those without accreditation (unpublished presentation to the U.S. Secretary's Advisory Committee on Human Research Protections, October 27, 2009). Accreditation may enhance efficiency, by increasing trust in accredited RECs and thereby providing sites participating in multi-site trials with the confidence to delegate ethical review to a single, or smaller set of accredited RECs.

Any initiative aiming at accreditation of diverse RECs in other parts of the world should aim to learn from the experience of ongoing efforts, such as those by AAHRPP and by SIDCER (which runs a "Recognition Program" in two parts: full recognition and preliminary recognition, based on the degree to which candidate RECs meet specified criteria).

Work Group One saw the benefit of a tiered or staged process, which might culminate in accreditation, but that would also recognize the achievement of milestones along the way. However, the final accreditation process is structured and whatever entity administers it, RECs around the world will need assistance to meet these standards. The next proposal represents a strategy to enable RECs to take the necessary steps to meet uniform, worldwide standards of accreditation.

**Proposal 1.3. Create a pool of funding and develop a grant application process to enable RECs to apply for financial support to facilitate progress toward accreditation.** At least one sponsor has already begun providing funding for accreditation of some of its higher volume research sites. That could be extended industry-wide, through a pool of funding that could be established to which research sponsors (not just industry) would contribute and from which grants would be made to RECs globally. Such grants should be multifaceted and should support both the actual accreditation process (paying for staff to develop SOPs, complete the application and preparing for the site visit), as well as capital purchases necessary to ensure the infrastructure of the REC so that it can achieve accreditation. Grants could also be used to support basic and advanced training of REC members (see Proposal 1.4 below). Any REC in the world would be eligible to apply for funding. However one reasonable factor in considering whether or not to award a grant may be a particular REC's ability to review numerous trials and build on experience and capacity, as opposed to offering a small number of such reviews annually. (Regarding this point, see Proposal 1.5 below on the importance of developing more efficient review models.)

Close collaboration with the WHO, the NIH and major universities around the world could assist in achieving this recommendation, to advertise the availability of the grant program and to learn what their members (potential grantees) feel would be the most crucial use of the funds. Collaboration with SIDCER, which has created regional networks of REC members in 5 regions of the world (Asia, Africa, Latin America, North America, and Eastern Europe) might also work well.

**Proposal 1.4. Enhance continuing education for already-trained fellows and/or create mentoring opportunities for new REC members.** Many existing educational programs do an outstanding job in the short time in which they have to educate and mentor trainees. However, once fellows return to their home countries they are often left on their own to build local human research protection programs. This proposal would establish mechanisms to help ensure that already trained fellows in research ethics, of whom there are many, have the resources and support to maximize their full potential as leaders and ability to serve as mentors to others in their regions.

To promote more extensive continuing education opportunities, Work Group One suggests the following ideas.

**Proposal 1.4a. Survey already-trained fellows to determine what they see as their needs and what continuing education activities and resources would be most important to them.** In preparing its recommendations, Work Group One has held preliminary conversations with some of the existing fellowship program leaders, and it seems straightforward to compile a worldwide list of fellows who have “graduated” from recognized programs. A third party could take responsibility for constructing a survey capable of determining what these fellows see as ongoing needs, now that they are back in their home countries. The survey could also present an array of potential continuing education ideas (see Proposals 1.4b and 1.4c below for a tentative list) and ask fellows to indicate which would be most useful to them.

**Proposal 1.4b. Based on the survey input and on expert opinion from existing fellowship program directors, develop enhanced opportunities for the continuing education of already-trained leaders, who have returned to their home countries.** Work Group One recommends that continuing education focus on developing greater expertise in research ethics and on building systems for ethical review. Both require skills of leadership, team building, mentorship and management -- all appropriate topics for continuing education.

It would be impossible to transform the quality of clinical trial review globally without an investment of hundreds of millions of dollars, and thus sponsor support for pilot projects in one or two lesser developed countries would be more feasible. In one or two countries, promising pilot programs for continuing education could include:

- Regional research ethics meetings to bring practitioners together within a given area. Ideally, Work Group One envisions more partnerships with local NGOs and established in-country or region wide networks, so that the planning and sponsorship of the meetings themselves become a means of in-region or in-country capacity building;

- Grants, both for REC members to attend meetings and to organize bilateral site visits, would allow REC members in one location to learn from those in other locations, and could help build a broad learning community of professionals across regions; and
- Webinars could be used to strengthen links between experts and local research ethics leaders. They might focus not only on enhancing concepts that support better review or understanding of protocols, but also on leadership, team building, mentorship and management. Funds could support the “marketing” of such events to ensure participation of large numbers of attendees, as well as support to include well regarded experts. Since online learning assumes the availability of computers, the grant might also include computers and/or internet service for developing country sites that lack ready access to the internet. Alternatively, materials in printed form should also be considered for low resource regions that lack good internet access/connections.

**Proposal 1.4c. Offer infrastructure and strategies to enable already-trained fellows to mentor new REC members.** Here, Work Group One envisions a program that might be called “Fellows Mentoring Fellows.” Clearly, such mentoring is occurring informally now in some places, and more formally in others. For example, a grant from the Gates Foundation to the University of Toronto has enabled the hiring of fellows previously trained through the NIH Fogarty and Clinical Bioethics Center programs to participate in a mentored post-doctorate fellowship focused on research ethics in the developing world.

Much more, however, remains to be done. Therefore, Work Group One recommends developing strategies to encourage and support the cultivation of greater in-country expertise by fellows returning to their home countries. Potentially, an NGO might be well-placed to coordinate this, with support from sponsors and other stakeholders.

Many of the activities listed above in Proposal 1.4 could become a part of the Fellows Mentoring Fellows program -- if already-trained fellows reach out to new REC members and prospective members and involve them in those activities. In addition, there are other strategies that could be more specifically targeted to enlarge the relatively small inner ring of already-trained individuals. For example:

- Development of an application process, by means of which prospective mentees could be nominated to become a part of the Fellows Mentoring Fellows program; already-trained fellows commit to providing learning opportunities (in-person and/or over the Internet), while mentees commit to completing those activities;
- Establishment of a website (preferably the same site where the webinars described above are hosted), where already-trained fellows could be linked to local REC members and/or mentees. The site could contain biographies of the fellows, adding

prestige to their role and identifying issues they are most interested in focusing on; and/or

- Review and vetting of existing resources, which -- once screened -- could be posted on the website (or reached via hotlinks).

**Proposal 1.5. Through a series of best practice case examples, promote a worldwide trend toward more efficient models of ethical review.** The MRCT Project is, by definition, focused on clinical trials performed at multiple sites in various geographic regions, where the potential for ethics review redundancy and inefficiency is greater than if such a trial were to take place in only one location. Although there are conflicting arguments for how best to alleviate these concerns, there is probably not one right way to enhance efficiency, while maintaining (and improving) quality. Nevertheless, some best practices are emerging that demonstrate the power of more centralized models both at regional and country levels. To name just three, The Netherlands, South Korea and South Africa offer especially promising examples of systems that have successful centralized review mechanisms in place.

Work Group One proposes conducting a survey of highly regarded review systems and the development of case studies of how they are structured and operate. Once these “best practice” case studies are developed, the Work Group envisions disseminating them and developing a strategic plan for encouraging adoption and adaptation of these models in other parts of the world that could benefit from them.

Work Group One also notes that developing more regional and/or national models is not only a matter of efficiency but also of quality, as specialization usually enhances quality. By having a smaller number of RECs per country, and perhaps specialized ones for different types of protocols, it becomes more feasible to prepare an adequate number of individuals to serve as REC members and create a body of knowledge and skill that can more easily be maintained over time.

Work Group One recognizes that actions leading to greater centralization of ethics review can be controversial and that it may remain important to ensure some level of local community involvement. To respond to these concerns, the following proposal calls for support for CABs.

**Proposal 1.6. Promote the establishment of CABs to ensure authentic community involvement and the cultural acceptability of a prospective clinical trial for a given venue.** CABs are different from local RECs. CABs, which already exist in a variety of places, are intended to provide community insight into the likely acceptability of the proposed protocol for that community, based on its interests, needs and customs. CABs can help both their own communities and the sponsors that wish to conduct trials in those communities. They can assist sponsors by anticipating the likely local challenges prospective research protocols may face, consulting on development of the protocol, local education about the research, the informed

consent process, collection of data and samples, and dissemination of research results. They can also help build community support for the proposed study, and by helping with recruitment. CABs can be used to help involve and protect community interests by, for example, advocating for fair benefits for the community. Most importantly, CABs can provide the local community with a clear avenue for conveying concerns about research proposals that lack cultural acceptability. The membership of a CAB is up to the sponsor, but often would involve community leaders from ethnic, religious, or business groups in the community.

CABs are used before a trial begins, but they can convene either at the same time that ethical review is ongoing or immediately after a protocol has received REC approval. CABs may also meet periodically, while the research is ongoing, to be apprised of how things are going and to serve as a point of communication between local investigators and the community.

Work Group One believes that if we are to move toward more regional or national models of ethics review, the maintenance of local involvement through CABs would be an excellent means for ensuring authentic community engagement. A grant program could help develop CABs in areas where greater community involvement would be beneficial.

## **In Conclusion**

Sponsors, researchers, their institutions, patients and other stakeholders have strongly aligned interests in ensuring the protection of human research participants and fairness to the communities volunteering to serve as research sites. The long-term success of clinical research would be enhanced if all stakeholders could align around these shared interests and develop one or more of these proposals.

## **Work Group Two:** *Enhancing Data and Safety Monitoring*

### **Nature of the Challenge**

Safety monitoring in clinical trials in the developing world, like all safety monitoring, requires recognizing signals of harm as early as reasonably possible and acting appropriately when a signal arises. Ideally, the action should protect the participants in the trial in a way that maintains the scientific integrity of the trial itself. Such monitoring often relies on a Data Monitoring Committees (DMC). The U.S. Food and Drug Administration (US FDA, 2006) has promulgated guidance for the establishment and operation of DMCs, some of which are independent in the sense used by ICH, within the context of clinical trials undergoing regulatory review for products to be used in the United States. This guidance has not been routinely adopted worldwide. The European Medicines Agency (EMA, 2005), the International Conference on Harmonization (ICH/E9, 1998), and the World Health Organization (WHO, 2005) have also offered suggestions for DMCs.

DMCs discharge their duty to study participants by reviewing ongoing data from clinical trials and making recommendations to the sponsor or steering committee which, in turn, reports to each local IRB and REC. In developing countries that lack a strong central health agency, the RECs sometimes serve a quasi-governmental purpose assuming certain roles otherwise performed by the government itself and making decisions about the trial. In such cases, the relationship between the DMC and the REC is particularly sensitive. In some countries, local and national ethics committees are themselves directly involved in the monitoring of the safety of subjects in trials.

Some DMCs, especially in Phase III trials, monitor not only the safety, but also the efficacy of treatments with a view to stopping a trial early if the data show no convincing evidence of benefit or clear evidence of futility. (Note that the meaning of “futility” differs depending on the type of trial. On one hand, a trial that is studying a new medical product or intervention may stop for futility if the data to date strongly indicate that continuing the trial will not lead to a demonstration of benefit. On the other hand, a trial that is investigating a product already in use may stop for futility if the current data indicate that continuing the trial will not lead to a finding that will influence practice.)

Highly competent DMCs, whether independent of the sponsor or including staff from the sponsoring organization, are essential for the protection of human research participants. Underperforming DMCs can harm participants in trials and the trials themselves. Injudicious decisions to stop a clinical trial prematurely may disrupt an entire development program, potentially depriving society of a promising new therapeutic agent. Conversely, failure to stop a trial when the data shows convincing evidence of harm or ambiguous evidence of benefit may

jeopardize the well-being of participants in the trial and may deprive the reallocation of finite resources to more promising development programs.

The various ways in which different sponsors (e.g. government or international agencies such as the NIH and the WHO, non-governmental organizations such as the Wellcome Trust and some Gates Foundation-funded groups, and life sciences companies) deal with safety and efficacy monitoring can be inconsistent, leading to confusion among the investigators, the RECs and the DMCs. Documents describing data and safety monitoring plans for specific studies may exist but, because of confidentiality, are often not shared among sponsors. Greater clarity and harmony among sponsors with respect to their policies for when to use a DMC, what expertise the DMCs' members should have, and how the DMCs should conduct their activities would improve the effectiveness of DMCs. Expectations for safety monitoring in the developing world must not, however, be expected to be a carbon copy of such monitoring in the developed world. For example, in the developing world, the interpretation of abnormal laboratory values is almost impossible if normal standards from North America or Europe are utilized. A working group recently published a position paper on DMCs as they relate to work in Africa that addressed the increase in funding for clinical studies of diseases endemic in resource-poor countries. The demand for DMCs within Africa and the shortage of skilled personnel led to a capacity-building effort that resulted in a summary relevant for Africa. Additional work is needed to take this effort to scale and extend to multi-regional trials in Africa and other developing countries.

The complex relationship and overlapping responsibilities of the DMC, the sponsor, the investigators, the RECs, and the relevant government agencies requires that all involved in the trial understand and respect their own roles and the roles of others. In particular, members of DMCs require training not only in their own responsibilities, but often in basic principles of randomized clinical trials as well. Only training the DMC members is not sufficient, for DMCs can only function well if the sponsor, investigators, and DMC members have a common understanding of the purpose and goals of the DMC.

Too often investigators learn about Good Clinical Practice (the regulatory "how-to") without a firm foundation in the underlying principles of clinical trials (the scientific "why"). Methods need to be developed to facilitate data collection in a way that is both efficient and accurate. Training of investigators in what constitutes an "adverse event" and a "serious adverse event" as well as the distinction between "mild," "moderate," and "severe" events will aid in data collection. Investigative teams should be taught what DMCs and their members need to learn how to assess interim data and how to report, when to report and to whom to report their recommendations. In particular, they need to understand what data may become available to the study sponsor and the investigator during the course of a specific trial. Further, investigators need to be aware of their obligations to report such events to the sponsor's drug safety team, for inclusion in periodic safety reports or risk management plans.

## Relationship between DMCs and RECs

DMCs and RECs have complementary roles in ensuring that the design and conduct of the study conforms to established ethical principles for biomedical research. This section of the Report briefly outlines the regulatory relationship between DMCs and RECs, in order to provide a context for the recommendations of Work Group Two. While the regulations deal with trials in the United States and trials carried out under ICH guidance, we include this section here because the principles articulated for Europe and the United States are relevant to trials in the developing world.

Unlike U.S. regulations [45 CFR 46.111 (a) (6) (DHHS) and 21 CFR 56.111 (a) (6)], the ICH – GCP Guideline E6 (ICH-GCP/E6) is silent on the requirements of REC review, other than the need to review investigator qualifications, the consent document, and payments. Nonetheless, most RECs use criteria for approval similar in principle to the regulations of the FDA/DHHS. Provisions to monitor the data collected are essential for all clinical trials evaluating safety or effectiveness of medicines. In many clinical trials, DMCs conduct such monitoring.

In order to evaluate whether a research plan's provisions to monitor the data collected will ensure the safety of subjects, the REC needs to know:

- Who will be monitoring the data;
- What data will be monitored;
- How quickly and how often will the data be monitored;
- What analyses are planned; and
- What stopping rules, if any, are in place.

Statements in protocols saying that a DMC will monitor the study data do not provide the REC with sufficient information to address the above issues. Instead, the DMC charter should describe the DMC's role in monitoring safety. Then, if sponsors provide the DMC Charter or equivalent information to the REC, it should have enough information to determine what the DMC's role must be to ensure the safety of participants during the conduct of the trial. The RECs must understand that DMCs typically review aggregate data on safety at periodic intervals. Depending on the size of the trial and the charge to the specific DMC, the DMC may or may not review individual serious adverse event reports on a real-time basis. The DMC Charter for an individual trial will describe the obligations of that specific DMC with regard to safety monitoring.

U.S. regulations also mandate that clinical trial protocols include information that describes how unanticipated problems involving risks to subjects or others will be promptly detected and communicated to the RECs. The regulations also require that RECs have written procedures in place that are designed to ensure prompt reporting of such problems by the REC to the sponsor. In practice, however, most REC procedures simply describe what investigators should report promptly to the REC. This process can be effective in single center trials; however, it is often

cumbersome and confusing in multi-center trials where a more effective approach would utilize a centralized process for reporting unanticipated problems.

Many DMCs review adverse events and they report them to sponsors which, in turn, report them to regulators and to RECs. General adoption of this approach would obviate the need for investigators to report any adverse event to the REC. ICH-GCP guidelines indicate that RECs should have written procedures for investigators to report changes or new information that increases subjects' risks or affects the trial's conduct. This guideline is similar to the FDA/DHHS's "unanticipated problems involving risks to subjects or others."

## **Goal**

The purpose of Work Group Two is to build the capacity of DMCs, especially those serving for multi-regional trials that involve the developing world, so that they can effectively monitor the safety and efficacy of trial.

This section of the Report describes the Work Group Two's proposal for implementing two focal projects: (1) developing a training program for potential DMC members and (2) developing a sample DMC Charter directed to studies conducted in the developing world to adapt to their own needs.

**Proposal 2.1. Develop a training program for potential DMC members.** This proposal aims to increase training opportunities for individuals capable of serving on DMCs, especially scientists and experts from the developing world. Such a program would continue over time so that the group of trained experts would grow in specialization and expertise. While, ideally, DMCs should be composed of members who are familiar with the operation of such committees, Work Group Two recommends that, in the absence of a large number of experienced experts in this area, individuals from the developing world might be included in the DMC despite their lack of specialized training to help the DMC balance risks and benefits in a manner relevant to the particular setting of such trials. Such inexperienced DMC members would have to undergo their training at the same time as serving as DMC members. This proposal includes the following two steps:

*Conduct a Survey.* The first step in the process would be to design and implement a survey of current practices related to DMCs in the developing world. In the developing world, some DMCs have little or no access to unblinded data in ongoing trials; even if they request access to such data, in some cases they receive access to the data only if the sponsor agrees. Additionally, in the developing world, some DMC members may be more closely tied to the investigators than would be considered ideal. The opinions of members of the Work Group Two on this issue come from specific experiences rather than from a scientific assessment of current practices. Therefore, Work Group Two recommends collecting data to better understand those current practices. Such

a survey could be sent to industry, government, and not-for-profit personnel who manage or participate in trials in the developing world.

A survey might also try to take a census of current DMCs to characterize their composition (who and what disciplines are represented on the DMC) and experience (what the members experience has been previously in industry, on previous DMCs, as an investigator, etc.) across sponsors and types of trial. Notably, many of the problems that Work Group Two has identified are not particular to the developing world.

*Design a DMC Fellows training program.* The second step would be to design the training program itself. The designers of the program should consider the following issues for the participants (“Fellows”):

- A. Which general principles should govern DMCs? While specific practices may vary, sponsors, investigators, and DMCs should develop a general consensus concerning the goals of these committees with particular reference to issues in the developing world;
- B. Who should be trained? Work Group Two recommends training clinicians, statisticians, ethicists, and community representatives, as well as those members of industry and government who structure and oversee DMCs. REC members might be trained so that they more clearly understand the relationship between RECs and DMCs. Work Group Two suggests that individuals from the developing world be over-represented among those trained in order to build capacity for data and safety monitoring within the developing world. Those trained from the developed world could be those who are likely to be involved in trials with a developing world component, although in order to ensure compliance with standards the knowledge of those who have been trained should be tested to confirm the effectiveness of the training;
- C. What should be the role of the Fellows in DMCs? Work Group Two suggests that Fellows in the training program not necessarily be voting members of DMCs, but that they should attend all sessions (open, closed, and executive) of meetings and be subject to the same obligations regarding confidentiality as voting members. The designers should discuss whether the Fellows should be observers or fully involved in discussions, voting or non-voting; potentially those questions could be left to the trial sponsor to decide;
- D. How many Fellows should participate in a DMC?;
- E. Who should pay? Sponsors (industry, NCO and/or government) should be encouraged to pay for the Fellows’ expenses. The designers of the program should consider whether Fellows should receive payment for their time or not;
- F. Whether and how to train industry and government representatives? Often individuals from industry and government oversee the implementation of DMCs without ever having attended a DMC meeting. Therefore, Work Group Two recommends that the designers of the training

program discuss whether, and the extent to which, individuals from industry and government should be encouraged to attend DMC meetings as part of their training;

- G. How should DMC members be trained? There is a need for a broader capability to train DMC members. Work Group Two recommends that an entity with appropriate expertise and standing develop a program for training potential DMC members. Such training should focus on the roles and responsibilities of DMC members, generally, as well as on basic competencies in research design and statistical analysis. Training novices in these general areas should not be a replacement for the inclusion of experienced members on all DMCs;
- H. How can the access to information about DMCs be improved? Some of the academic work on the ethical issues related to DMCs, and indeed more generally to all aspects of DMCs, could be placed on the internet (possibly with the WHO) to help build capacity and improve knowledge about DMCs;
- I. How can video training be used to improve DMC training? Work Group Two suggests applying for funding to create video training sessions for DMC members and for investigators and steering committee members who must work with DMCs;
- J. Would certification improve the use of DMCs for multi-regional trials? Some members of Work Group Two recommend developing a certification process for potential DMC members. In their view, potential members should be able to demonstrate basic understanding of the tenets of clinical trials, especially randomized trials, and to show that they understand the role of DMCs. Certification should include demonstration of potential members' ability to evaluate ongoing data. Others in Work Group Two have noted the difficulty of defining uniform standards. The value of Certification for DMC members may require further review; and
- K. What training about DMC responsibilities should investigators and coordinators receive? Work Group Two agreed that investigators and coordinators should be trained in the principles underlying the DMC for the particular trial in which they are involved. They should understand why the DMC is needed in the trial and they should be aware of the composition of the DMC.

*Implementation and duration.* This two-step proposal will require, first, the development and implementation of a survey to gain information about current practices. An inventory of types of trials currently being performed will be necessary and a questionnaire will have to be developed. If adequate resources are available, this phase should take about six months.

The actual development of a training program would be more complicated. At the same time the survey is being designed and conducted, a pilot training program can begin with various organizations informally assigning Fellows to newly formed DMCs. If a network of such sponsors and Fellows is formed, the Fellows and chairs can report back to the planning group

with a brief summary of the experience thus far. These actual experiences can then be used to develop a more formal program.

A formal training program would warrant cooperation among many groups. The standards for DMCs in various companies differ considerably and differ from DMC practices at the NIH (where the practices vary from institute to institute) which in turn differ from practices in other countries and with respect to standards for the use of DMC used by NGO sponsors. Once data are collected about the current practice for DMCs in the developing world, and the experience in the pilot training program shared (in a way, of course, that preserves confidentiality of the trials themselves), a planning committee can develop a training program.

*Metrics.* Success of the program may be difficult to measure. Simple metrics, such as number of Fellows and disciplines from which they come, would allow some basic measures of success. More complicated qualitative measures could attempt to assess the quality of the experience gained by the participants in the program.

A simple metric that could be used for this would be a straightforward before-and-after assessment. If the survey phase of the project includes a characterization of the prior experience of the members of each DMC, a post-program assessment can include a similar characterization after the first year and then again after the second year of the training program.

*What industry can do to help.* The success of this program depends on industry's willingness to share information about the operations of their DMCs and their cooperation with and support for such a training program.

**Proposal 2.2. Develop a sample DMC Charter directed to studies conducted in the developing world.** Each DMC operates under a charter which may vary in length, specificity, and content. The shortest ones are about one to two pages; the longest ones are 20 to 30 pages. Work Group Two proposes establishing a committee to create a sample charter, or at least sample language to include in a charter. Several sample charters are publicly available, but none of which deals specifically with issues related to the developing world to the best of the Work Group Two's knowledge.

Work Group Two agreed on the following principles:

- A. DMC charters should include a description of how the subject DMC's recommendations will be handled. Work Group Two agreed that the DMC should report information to the principal investigator, the steering committee, or the sponsor; that person or committee should report information to the RECs, as needed. The DMC should not report information directly to the RECs;

- B. Protocols for trials should include the DMC charter or at least information describing the process of data and safety monitoring to allow RECs to determine whether the protocol includes adequate provisions for monitoring the data to ensure the safety of subjects as required by Federal regulations in the U.S. or comparable laws/regulations in other jurisdictions;
- C. The DMCs and the RECs should be trained so that both groups understand that the DMCs role vis à vis the REC is to identify new risks and then inform the sponsor of such risks so that the investigators and IRBs can be informed of them. A “newly identified risk” is either:
- *A harm not already listed in the investigator’s brochure;*
  - *A harm listed, but occurring at an unexpectedly high frequency; and/or*
  - *A harm listed, but occurring at an unexpectedly high intensity.*
- D. A DMC and REC exercise to align the roles and responsibilities of DMCs and RECs would be valuable, to make formal recommendations related to communication to IRBs from sponsors after a new risk is identified, and provide an actionable decision to RECs that obviates investigators and RECs from assessing individual SAE reports in real-time.

A committee charged with forming a charter could collect charters in use by industry and government and create a template. Of particular interest would be sample charters from trials performed in the developing world, particularly those from trials run by the WHO. Industry can initiate this by setting up a process to begin sharing charters with a committee charged with developing a sample charter or common elements.

Success and timing will depend on the willingness of sponsors to share their charters in order to develop such a document. Such a process may take time because of sponsors’ natural preference for their own charter, and because the charter is often part of sponsors’ SOPs. Thus, the committee may instead opt to propose elements that such a charter should contain. Long-term success could be measured by the breadth of adoption of such a model charter or recommended elements.

#### **\*A Note on Terminology**

This section of the Report uses the US FDA’s term “Data Monitoring Committee” or “DMC” to refer to the committees that review interim data from clinical trials. The United States National Institutes of Health and many academic groups often use the term “Data Safety Monitoring Committee” (DSMC) or “Data Safety Monitoring Board” (DSMB) for the same type of committee. The ICH uses the term “Independent Data Monitoring Committee” (IDMC) to refer to DMCs that are “independent” of the sponsor of the trial. Other names are sometimes used for committees that monitor ongoing data from clinical trials.

## **Work Group Three:** ***Enhancing Site Selection and Investigator Team Expertise***

### **Nature of the Challenge: Ethical Interests in Ensuring High Quality Performance**

Many sponsors have embraced globalization for clinical research because it offers a faster, lower-cost platform for gathering safety and efficacy data on investigational medicinal products and provides an ability to increase scientific collaborations with physicians to treat unmet medical needs outside of the developed world. In doing so, it is essential that sponsors ensure that sites are selected appropriately in terms of ethical concerns and have the infrastructure and expertise to deliver scientific and operational quality. Work Group Three's proposals for enhancing multi-regional clinical trials focus on practical measures that sponsors can adopt to better assure appropriate global site selection, including the appropriateness of the population to be recruited as well as the training and education provided to investigators and site personnel.

We discuss the recommendations pertaining to site selection first, followed by the recommendations related to the training of investigators and site personnel.

### **Site Selection**

Before a sponsor approaches an investigator or a site about participation in a study, a number of critical decisions are made within the sponsor organization, including decisions on the study design and where and how the study will be implemented. The decision-making process sets the stage for downstream activities that have significant consequences for the overall study costs, timing, quality and ethics.

Once a draft protocol is shared among those parties who will conduct the study, the transition from the "design of the protocol" to "the implementation of the protocol" is set in motion. It is at this juncture that a "Study Feasibility," a term commonly used in industry sponsored trials, is undertaken. Confirmation that the study design is consistent with the capabilities, the standards of medical care and practice, and the resources at the study site should be a prerequisite for site selection. Typically such studies focus primarily on the ability of the prospective site to yield a sufficient number of suitable research participants and other operational concerns and questions about regional infrastructure.

Work Group Three seeks to broaden the traditional concept of Study Feasibility to include not only the likelihood that large numbers of subjects can be recruited at reasonable cost, but also an assessment to ensure that the site is appropriate from an ethical perspective. Since Work Group Three recommends assessing potential sites on ethical criteria as well, this group prefers the term "Study Site Assessment" to "Study Feasibility," and hereinafter, will refer to the former rather than the latter.

Since Study Site Assessment sets the stage for all downstream operational decisions regarding a protocol, and for the ethics of choosing appropriate study populations, it is essential that sponsors choose an appropriate mechanism and business model, allot the necessary time, select adequate samples and sources of information, and ask the right questions during the Study Site Assessment process. For example, the following are some of the questions that Work Group Three recommended should be considered:

- Is the disease prevalent enough among the potential study population in this country to warrant experimental human research (i.e., is there going to be relevance of the study to this population)?
- Does the sponsor offer sufficient benefits (e.g., post-trial drug access) to the study population in light of the risks they are being asked to assume? What are those benefits?
- Is the comparison appropriate (e.g., is the drug under investigation being compared to worldwide best standards or a local standard?) Is the choice of comparison group defensible? On what grounds?
- If the medicine is approved, will the sponsor make it commercially available and accessible in the countries in which the research will be conducted?
- What mechanisms exist at the country and local levels to ensure protection of human subjects?
- Are there other significant ethical/scientific concerns?

The above should be assessed periodically throughout the development lifecycle for an investigational medicinal product, and adjustments made when necessary.

In an effort to assess the quality of the Study Site Assessment process, Work Group Three conducted a small survey among sponsors to assess variation in approaches and content during typical assessments now ongoing. The findings from just a small sample of companies demonstrate that within and across the companies, inconsistencies exist with respect to:

- The experience and skill of the entity overseeing the assessment process;
- The sample size upon which decisions are based;
- The use of external data to supplement “opinions” of investigators; and
- Time for the internal team to complete feasibility.

Furthermore, this brief survey revealed certain unintended consequences of holding study teams (medical monitor, project manager, and study manager) accountable for the completion of the assessment. In addition to overseeing the assessment process, study teams are typically responsible for final selection of the site and for study conduct. In an effort to meet critical

timelines, study teams may abbreviate and/or omit key steps in the assessment process and move right into the site selection process without realizing that circumventing a full assessment might compromise the longer term ethical and business considerations.

**Proposal 3.1. Sponsors should formulate, adopt and publicly commit to a common ethical and quality framework for selecting study populations and sites.** Ethical concerns will pertain to a range of issues, beginning with an assurance that the disease to be studied occurs within the prospective study population and extending to the prospects that experienced and independent ethics review is available. Quality issues include such things as whether there are highly competent investigators and research coordinators available, as well as the nature of the health care infrastructure in the country. Determining the full range of criteria that should be met before site selection is finalized is an activity that will require time and effort and will have to be vetted across industry and CROs. However, once such criteria have been defined, Work Group Three envisions the development of a tool, described in the next proposal, for ensuring that the agreed-upon criteria are actually used in practice. Attachment 3 contains a description of models for including ethical and other criteria in Study Site Assessment Processes.

**Proposal 3.2. Develop and measure the impact of a common Study Site Assessment methodology -- to identify countries and sites that meet the ethical, scientific, and business criteria.** The purpose of the tool would be to bring potential issues to the forefront and assess them explicitly (e.g., Does this population suffer from this disease? Will there be post-trial drug access?) Issues such as investigator and site certification status (see Proposals 3.5 and 3.6) could be incorporated to ensure that all sponsors are working to raise the bar. In addition to assuring the “right set of questions are answered,” Work Group Three also recommends that the sampling methodology include third party validated data, whenever possible, as opposed to current processes. A draft Study Site Assessment Tool is attached (see Attachment 2).

**Proposal 3.3. Evaluate and compare the benefits and shortcomings of a centralized study site assessment model vs. individual project team site assessment.** Evaluate the economic, ethical, operational and scientific benefits of decoupling study assessment from final site selection and other study-related responsibilities of teams. To accomplish this, interviews should be conducted with members of sponsor organizations (executive, manager, staff and investigator) that deploy different models for completing study site assessments. The outcome would be a report on the issues, costs and alternative organizational models capable of avoiding negative consequences of the current structure.

**Proposal 3.4. Share information on site quality to ensure industry-wide visibility on country-specific (and possibly site-specific) quality issues, as legally permissible, and collaborate to improve selection of high quality sites.** Fundamental to any collective initiative that industry supports to improve the ethical, scientific and operational conduct of clinical trials is the willingness to transparently share information. Sponsors must ensure that they identify problems with research quality at the site level, work to resolve those problems, and avoid using inadequate or inappropriate investigators or sites. Developing ways to share such information in accordance with competition, defamation/libel, and privacy laws, would represent an unprecedented collaboration on the part of research sponsors, but one that could potentially increase the ability to protect human subjects. Information about local sites should not be seen as proprietary (since most, if not all, sponsors become aware of these sites), but rather information that can be used collaboratively and responsibly to protect patients and the research enterprise. All such information would need to be factual in nature to reduce the risk of any defamatory allegations being made -- where an investigator's or site's conduct has failed to reach an objective standard.

### **Training of Investigators and Site Personnel**

Industry sponsors, human research participants, and the public need assurance that clinical trials are run by experienced and competent professionals, in an ethical manner, and at well-qualified sites that have the necessary resources to ensure human research protection. A lack of quality threatens subjects and the reliability of the trial data. Clinical trial investigators and research coordinators are at the front lines for ensuring the ethical conduct of clinical trials.

The trial investigator is the leader of the team and bears the major responsibility for reliable data collection, fidelity to the protocol, effective and ethical research participant recruitment, and safety of human research participants. The research coordinator shares in these responsibilities, and has day-to-day responsibility for their implementation. Ensuring the highest professional standards for this research team is essential. Yet worldwide, there is tremendous variation in the skills and experience of both investigators and coordinators, and staff turnover at sites can dilute organizational competence even further.

Prior to conducting their first clinical trial, many physician-investigators and their study coordinators receive no more than a brief exposure to the specific protocol they are implementing, and have little or no background in research design or in research ethics. As competent physicians, they may believe that they have all the necessary skills to conduct clinical trials, perhaps due to involvement with clinical trials during residency. However, without exposure to and understanding of the process of drug development, they may not know that there are specific drug development activities and regulations, research methods, site and data management skills, and responsibilities for protection of human research participants that they may not have.

Lack of adequate training and support for clinical research site personnel can threaten research integrity. Therefore, both industry's interest and the public's interest would be well-served by the development of mechanisms to improve and validate the capacities of investigator teams and sustainable professionally run research sites.

Various programs have been developed to increase investigator team expertise. For example, the American Academy of Pharmaceutical Physicians and Investigators (APPI) offers a certification which is about to receive accreditation from the American National Standards Institute (ANSI). For decades the Association of Clinical Research Professionals (ACRP) has offered certification programs for research coordinators, as does the Society of Clinical Research Associates (SOCRA). Both the APPI and ACRP programs are harmonized to ICH/GCP-based examinations. SOCRA offers a generalist exam that is not job-specific, and therefore, not harmonized to the ICH/GCP exams. There are also masters and doctoral degree programs now available for advanced training for physicians, which could be more widely utilized. For many, if not all of these, the cost of scaling such programs to tens of thousands of investigators and tens of thousands of study coordinators and site personnel needs to be managed. Large sponsors may be able to adopt these programs for high volume numbers of investigators and study coordinators, potentially at much lower costs than are presently available to individuals.

If industry is to endorse, promote, and possibly subsidize investigator certification, evidence to more definitively establish the correlation between investigator certification and improvements in the efficiency and quality of the research must be provided. For this reason, as we discuss below, a study is being recommended by Work Group Three to add to industry's understanding of the benefits that certification offers.

**Proposal 3.5. Study with greater rigor the value of certification programs for enhancing the knowledge, skills and performance of investigators and research coordinators.** To date, one study has attempted to assess the value of investigator certification, but such study looked at a very small number of investigators and was U.S.-centric, in that, the outcome variable was deficiencies on FDA audits. In contrast, there is a need for larger international studies, capable of comparing knowledge and skill outcomes of certified versus noncertified investigators.

A randomized controlled trial could compare certified and non-certified investigators on a variety of outcome measures, such as regulatory observations, data quality issues, the incidence of compliance issue(s) at individual sites, and/or negative monitoring reports. However, since the number of certified investigators is currently very small, another way to begin to examine this issue that would be relatively quick and more modest in cost, would be to assess the working knowledge of currently active investigators -- relative to what a group of knowledgeable peers has determined is the appropriate knowledge base for clinical trial investigators. Such a study could use the currently available CPI examination from ACRP, as a knowledge assessment tool for investigators working in global study sites, academic medical centers, specialty centers (e.g.,

oncology and children's hospitals) and community-based private clinical research networks. Performance on the examination, taken cold, could be analyzed in relation to the type and extent of training and experience of those taking the exam. The results would form the basis of policy recommendations regarding training and qualifications of investigators for both sponsors and regulatory authorities, and would promote adoption of a more professional paradigm in clinical research.

**Proposal 3.6. If (and only if) validation of the effectiveness of certification in improving investigator quality is demonstrated, industry should preferentially place trials at sites that offer certified investigators (and consider other ways to promote certification).** For example, industry should consider the following ways to encourage certification:

- advertise the importance of certification;
- provide financial assistance to investigators and research coordinators in resource poor environments, so that they can attain the certification (current cost of APPI certification, as an example, is \$895 USD for nonmembers); and/or
- encourage a process for accrediting sites as a whole.

**Proposal 3.7. To ensure a global standard of medical competence, CROs and sponsors should seek verification of the medical expertise of prospective physician-investigators.**

A critical point in selecting competent and reliable investigators, especially in a developing country context, is to make sure, first and foremost, that the sponsor is able to consistently identify and choose well-qualified physician-investigators.

Sponsors can educate a competent physician in how to be an investigator; but a physician with perfect research regulatory knowledge who lacks basic clinical competence cannot and should not be used as an investigator. One interesting strategy is to ask investigators to demonstrate that they have passed a test such as the Foundations of Medicine/NBME examination (which many medical schools in the developing world require of their graduates). However, the Foundations of Medicine/NBME exam is not the only possible screening tool. The important point here is that some criteria be used to assure that the on-the-ground investigators know what they are doing clinically before they are charged with enrolling subjects and administering investigational medicines and other interventions.

## **In Conclusion**

Many of the suggestions Work Group Three has made, particularly regarding certification, likely will increase costs both for sponsors and for investigators, at least in the short term. There is a shortage of investigators world-wide, and data suggest that the costs that investigators assume when agreeing to conduct trials are poorly compensated by sponsors. Therefore, in order to implement these recommendations, further study is necessary to ensure their feasibility and cost-

effectiveness. Going forward, we must keep our sights on the need for greater professionalism, while honestly grappling with issues of efficiency, feasibility and cost.

Adoption of these standards, through agreement, and hopefully the use of a common tool, by both industry and non-industry sponsors would greatly mitigate the potential for exploitation. Once adopted, a mechanism for ensuring that these principles guided actual decision making would be required. The three recommendations in regard to training of investigators and site personnel are intended to set a baseline standard for appropriate education in regard to planning, implementing and conducting clinical research trials that meet ethical and regulatory requirements on a global basis. The core competencies required at investigational sites should be recognized and established through appropriate experience, education or certification programs. A degree of assurance that these core competencies have been acquired should be established and refreshed as necessary. A preliminary set of core competencies are included herein as Attachment 4.

Ultimately, the action steps outlined here, in combination with other recommendations emerging from the other MRCT Work Groups, could lead to the establishment of hundreds of accredited sites worldwide, where industry could mount a trial, assured of its scientific and operational quality, efficiency, and ability to protect human research participants.

## **Work Group Four:** ***Enhancing the Professionalism of Monitors***

### **Nature of the Challenge**

Monitors (also called Clinical Research Associates or CRAs) perform an essential role in the oversight of clinical trials. The International Congress on Harmonization's Good Clinical Practice standards (ICH-GCP/E6, 1996) defines the primary purpose of trial monitoring as ensuring that:

1. the rights and well-being of trial participants are protected;
2. the reported trial data are accurate, complete and verifiable from source documents; and
3. the conduct of the trial is in compliance with the currently approved; protocol/amendments, with GCP, and with the applicable regulatory requirements.

Compliance with ICH GCP is often interpreted as requiring intensive site monitoring, but the following paragraph should be noted:

*“The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during and after the trial; however...central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified” (ICH-GCP/E6, 1996, 5.18.3)*

Despite these standard purposes, the role of a monitor has traditionally varied based on the type of trial, the sponsor's concerns, and the geographic location. The monitor's responsibilities can range from straight forward tasks, such as tablet counting and validating source documents to much more complex activities, such as evaluating the appropriateness of recruitment and informed consent. The Association for Clinical Research Professionals (ACRP) has conducted survey-based job analyses for monitors and documented wide variation in their roles and responsibilities.

Monitors require multiple skills, including, but not limited to, extensive knowledge of clinical trial conduct (ICH GCP), a strong understanding of national and international regulatory requirements, operational and logistical sophistication, and deep understanding of the ethical principles that must guide research with human subjects. Monitors are also finding that the scope of their role has been extended to include tasks such as drafting and customizing subject screening scripts, developing recruitment plans, evaluating budgets and contracts, setting-up

electronic systems and processes (EDC and E-diaries), and facilitating interactions between the sponsor, site staff and third parties (RECs, vendors, labs, pharmacovigilance and endpoint adjudication groups). Some protocols require rigorous problem solving skills. Failure to master this broad body of knowledge, and to develop the skills necessary to identify and act on problems, may jeopardize data integrity, subject safety, regulatory compliance and successful completion of a clinical trial. Lapses at even one site may place an entire multi-center study at risk.

The range and complexity of the tasks required of monitors, as well as the risks associated with poor performance, mandate rigorous training. An opportunity is missed when the role of the monitor is too narrowly defined. Monitors, as the “eyes and ears” of research sponsors, have a unique opportunity to enhance the protection of research participants globally. To expand their skills in these areas, they must acquire an acute sensitivity to the ethical issues that may arise during study conduct. For example, current practice related to informed consent is too often confined to reviewing forms for the appropriate dates and signatures. If monitors were fully trained in the ethical principles that necessitate voluntary consent, they would likely develop a deeper appreciation for consent as a process, rather than a form. As a result, their ability to contribute to process improvements and to effect needed changes might be vastly enhanced.

In order to cultivate a broader sense of responsibility and professionalism, Working Group Four developed a set of recommendations, which it is hoped could ultimately help develop more highly qualified monitors. To achieve this end, Work Group Four divided into two groups. One was comprised of all work group members and it focused on one area, ripe for improved monitoring: informed consent. The idea is that to professionalize monitors and build research ethics infrastructure in the developing world, there are important challenges to take on with respect to improving informed consent, and monitors are well-placed to help meet those challenges. The second group focused on the broader issue of enhancing the professionalism of monitors. Recommendations from the latter group are presented next, immediately followed by the report and recommendations related to informed consent.

### **Enhancing the Professionalism of Monitors**

This subgroup believes that research sponsors can play a leadership role by enacting the following proposals:

**Proposal 4.1. Endorse a professional paradigm.** The importance of certification for monitors is not universally recognized or appreciated. If research sponsors prioritized and expected minimum training competencies in monitors, over time, high quality educational programs would become more readily available globally and the overall number of highly skilled monitors would increase.

**Proposal 4.2. Establish a comprehensive set of recognized and expanded core competencies for monitors.** Given the wide range of monitors' roles and responsibilities, it will be important to identify and articulate the competencies that monitors should be expected to develop. While it is crucial to have a strong working knowledge of ICH/GCP, the research community must be able to state which other areas of expertise are required as a prerequisite for the appointment of an individual to the role of monitor. Additional competencies for monitors, within an enhanced professional paradigm should include, for example:

- Familiarity with the ethical guidelines that govern the conduct of research,
- Effective communication skills that enable monitors to appropriately handle inadequacies with senior staff members at the site, when necessary,
- Appreciation of, and responsiveness to, the unique cultural perspectives and stakeholder interests of prospective research participants, local communities, governments, and ministries of health in the culturally diverse settings where trials are held.

**Proposal 4.3. Inventory existing training programs and conduct gap analyses.** There are many training programs for monitors around the world; some are offered in-house by pharmaceutical companies, others by CROs, and still others by independent professional organizations, such as ACRP. There are also a number of smaller independent organizations specifically focused on monitor training who serve the pharmaceutical industry and CROs. For example, Work Group Four easily identified 5 such groups in India, and there are probably many more in that country alone.

Despite this plethora of training avenues, very little is known about the quality of these programs. We therefore recommend developing a worldwide inventory, organized by regions of the world.

The goal is to create a vetted list of high quality educational programs, so that when sponsors know they want to conduct a protocol in a given region, they can assess or even require potential monitors to have received training in one of these programs.

A methodology for the gap analyses will have to be developed and a trusted third party should be called upon to carry it out. At a minimum, two analyses should be conducted:

- (1) current curricula (including the content, scope of the learning objectives) should be compared against the core competencies identified in Proposal 4.2 above; the purpose of this analysis is to ensure that *what* is being taught aligns with the roles, responsibilities and core competencies characteristic of experienced and skilled monitors.

(2) An individual or organization with educational expertise should review existing curricula and training programs in terms of their instructional methods; the purpose of this analysis is to determine *how* monitors are being educated and whether those methods are likely to equip the monitor to perform the robust professional role expected of them.

**Proposal 4.4. Develop an educational framework stipulating the characteristics of high quality professional education programs.** Once the inventory and gap analyses are concluded, a third party should work with stakeholders to develop a blueprint defining the components of optimal educational approaches. There is room for variation in educational approaches, but some elements are clearly going to be important to include in any approach. For example, while there is undoubtedly a need for computer-based training models, if we expect high level performance, professional education of monitors should also include practice in discerning problems that are often obscured, situation-based training, role-playing and mentorship. Monitors who have little or no experience should work alongside more experienced monitors, so that they can be exposed to more expert performance across the different types of engagements -- from site qualification through study close-out. In other words, there is no substitute for experiential learning.

There are already some instances of best practices -- examples of high quality monitoring education -- that can serve as models for others. Through the inventory and gap analysis, these best practices will be identified and they will help to inform the final framework to emerge from this process.

Work Group Four has not yet addressed how to encourage the dissemination and uptake of this framework, but we recognize that thought should go into designing strategies for encouraging adoption. More work is needed on this.

**Proposal 4.5. Encourage and reward professional certification.** While there will be many routes to gaining the requisite skills, ultimately the educational path should culminate in a certification process that ensures that the skills have been mastered. Such a system should also include methods for reaffirming monitors' skill sets through, for example, continuing education credits and periodic re-certification.

ACRP has developed a two-tiered certification program -- one for novices that assesses for a minimum set of competencies and another for more experienced monitors, which represents a higher level of skill. Since it is our understanding that ACRP serves mainly North American and European audiences, additional work is needed to make this certification financially and logistically accessible to monitors working in other regions. There is also a certification program offered by the Society of Clinical Research Associates (SOCRA), and one offered by TDR, a Special Program for Research and Training in Tropical Diseases, sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO). The TDR certification program is

specifically designed for clinical research professionals, including monitors, working in developing countries. These programs need to be assessed and compared, so that sponsors can better appreciate the value that such programs may offer.

We also note that at least one pharmaceutical company has already created a certification program for its own monitors, or those whom its CROs hire, which they believe meets or exceeds ACRP's program.

One of the challenges is determining how to evaluate the added-value of certification programs. We support the development of new methods of assessment, but in the mean time, monitor certification -- as a hallmark of professionalism -- should be encouraged. Another challenge is cost. Certification costs could be covered by the vendors and CROs seeking certification for their staff, by individual research sponsors, or by pooled funds across industry. Greater acceptance of certification of monitors could clearly eliminate redundant training programs and unnecessary re-training of monitors (e.g. of monitors who have already completed highly regarded programs). Therefore Work Group Four recommends further evaluation of possible efficiencies, recognizing that individuals may have worked across various companies during their careers and good programs already exist.

### **The Role Monitors Can Play in Enhancing the Informed Consent Process**

Informed consent, the internationally recognized foundation of participation in human research, is an ongoing process critical to human research participant protection. Unfortunately the understanding and application of the informed consent process varies throughout the research community and there is a need to strengthen the process globally.

Principal investigators have accountability for oversight and execution of the informed consent process for all subjects enrolled at their center. Study sponsors have trial oversight accountabilities and deploy resources and approaches to support the training and performance of investigators. However, monitors -- as representatives of the sponsors -- also have a crucial role to play. Monitors must be able to assess the quality of the informed consent process and work with investigators to strengthen that process. This should be done early in the process, i.e. during the Pre-Trial Assessment (PTA)

There are many factors involved in determining what constitutes an appropriate consenting process that site monitors should consider when working with investigators and site staff including:

- Requirements of the protocol and the REC;
- Local cultural attitude towards research;
- Local cultural attitude towards community assent versus individual consent;

- Western regulator attitudes towards obtaining the individual consent of a study subject;
- Doctor/patient relationship;
- Time allowed for subject review and decision making;
- Comprehension level of each individual subject;
- Expertise of the site staff involved in the process, methods of information delivery (video, paper, brochures etc); and
- Intentions of the sponsor regarding the use of the data generated and the locations at which such data will be held (particularly – with respect to European data protection laws).

The goal of these recommendations is to identify strategies and resources to help monitors enhance the informed consent process. Specific recommendations are as follows:

**Proposal 4.6. Develop greater clarity about the nature, scope and importance of an optimal informed consent process and the role monitors have to play in this regard.**

Investigator site monitoring and evaluation should focus on building the capacity of site staff to communicate with study subjects and improve the outcome of the informed consent process, rather than enforcing overly rigid procedures.

The objective of Work Group Four is to provide practical guidance to monitors and site staff overseeing trial conduct that will allow them to:

- Better educate themselves and their sites on the importance of thorough informed consent;
- More effectively engage the investigator and site staff, through both interviews and training, to improve the overall understanding and implementation of the consenting process;
- Create suggestions for improving potential subject comprehension;
- Understand and articulate the ethical consequences of an improperly conducted process;
- Develop methodology to monitor compliance with the protocol's requirements for the informed consent process;
- Develop methodology to monitor compliance with the IRB/REC requirements for the informed consent process;
- Develop methodology to verify that the research and medical records appropriately record how the consent process was executed and any deviations from that process, and
- Review withdrawal of consent by a study subject and the need for re-consenting when the risk: benefit ratio changes, or additional use of that study subject's personal data is contemplated.

**Proposal 4.7. Ensure that all monitor training programs include a focus on the monitors' role in assessing and maintaining a high quality informed consent process.** Please see Attachment 5 to this Report for Work Group Four's initial articulation of monitor competencies regarding informed consent and human subject protection. Although a robust informed consent

process is a cornerstone of all human research, the methods used to monitor and evaluate informed consent should be kept in perspective. Not all research involves the same degree of risk or burden for the study subjects. The monitoring approach should be influenced by each study's design and the risks and burdens to study subjects. Some study populations are considered vulnerable due to age, gender, socio-economic status, or physical, mental, or emotional state and thus require special consideration in the informed consent process. Therefore, not all of the following suggestions below will be appropriate for all studies. Nevertheless, educational programs can enhance the role that monitors play in informed consent, if they:

- Begin with training for monitors on the informed consent process, both initial and ongoing. This training could be done remotely but should involve simulation or role-play based training;
- Examine the role of the monitor during the pre – trial assessment and the initiation visit. This should focus on discovering the site's current process and reinforcement of the ideal;
- Suggest that the investigator and site staff demonstrate the informed consent process;
- Develop a series of open ended questions for monitors to utilize in order to gain a better understanding of the site's overall knowledge and execution (see Attachment 6);
- For emerging markets or vulnerable subject populations, the monitor training should include an assessment of the obstacles to obtaining a truly "informed" consent. These hazards include, but are not limited to, the current healthcare system, linguistic differences, local culture, alternative treatments and characteristics of the disease under study. If the study involves high risk, recommend that all attempts to have a patient advocate present during the consent process be made;
- Propose that subjects bring the consent with them at every visit and document discussions that occur such as review of the current visit's procedures, the next visit's procedures, and relevant safety risks. Sites should document at each study visit that the consent was discussed and the subject's willingness to continue was established;
- Suggest that the site provides a highlighter to each subject so they can mark statements or areas they have questions on as they read through the consent form;
- Include a mock consent process as part of the training provided by the sponsor to an investigator at an investigator meeting;
- Suggest that the investigator and site staff demonstrate the informed consent process;
- Suggest that the IRB/REC specify the informed consent process requirements;
- Suggest that sponsors address the informed consent process in the protocol; and
- State the subject's ability to withdraw consent and terminate participation in the clinical trial at any time without suffering any penalty.

**Proposal 4.8. Develop a kit of strategies and resources which monitors can use to enhance informed consent in the field and throughout the trial.** Some of the materials in this kit might also include resources for direct use by the study subjects.

For example, the use of a “Speaking Book” can be an aid in the education of potential subjects, especially those with limited literacy. They have been used to help low-literacy subjects in Africa understand clinical trials and also the informed consent process (Kloiber and Duncan, 2008).

**Proposal 4.9. Elaborate how this kit can be disseminated so that it is widely adopted by monitors serving various regions of the world.**

- Establish links to the kit on sponsor websites accessed by representative monitors;
- Establish partnerships with training and certification organizations to make the kit available for all monitors preparing for certification and as a resource following certification; and
- Create training videos (possibly be posted on “*You Tube*”-like websites).

## **Work Group Five:** ***Transparency of Contract Provisions***

### **Nature of the Challenge**

As Glickman and colleagues point out (2009), the variance in contracting practices for global clinical trials contributes to the complexity and delay associated with large-scale multi-regional clinical trials. They proposed adopting standard contract language for clinical research agreements and, in particular, standard provisions related to confidentiality, to increase transparency and efficiency in the contracting process, thereby reducing transaction costs and, presumably, increasing the degree of protection afforded to participants.

Although these problems arise in research conducted in developed countries, there are particular challenges to contract standardization for multi-regional clinical trials in developing regions of the world. The variance in laws and requirements among different regions must be accommodated in any attempt at standardization. Additionally, the power differentials that are always present in any contract negotiation have special implications for the ethics and efficiency of the research, in part because the gap between the expectations of research sponsors and sites in the developing world may be more pronounced than when research sponsors contract with sites in well developed regions, and sites or the countries where they are located may have unrealistic demands. Conversely, because of the disparity in resources and the corresponding incentives sites and countries may have to participate in lucrative research at any cost, there is concern that a site in the developing world may agree more readily to terms that are inconsistent with established research principles, based on financial need. The goal of Work Group Five has been to identify the development of options for contract terms for certain key provisions recognized as being particularly contentious in the negotiation process, and/or which raise particular concerns regarding the rights granted, and respect afforded, to sites and participants in the developing world.

It is recognized that many attempts at creating template clinical trial agreements have been undertaken in the United States and Europe. Most notably, the National Cancer Institute and Institute of Medicine both have put forth model clinical trial agreement templates. The Model Agreement Group Initiative (MAGI), a private organization dedicated to standardizing best practices for clinical research operations, business and regulatory compliance, has done so too. Furthermore, the United Kingdom has developed a standard tripartite agreement for industry-sponsored research, which is fairly broadly utilized. While the resulting work product of these efforts is commendable and has arguably advanced the debate around certain provisions that were significantly more contentious five to ten years ago, the adoption of one agreed-upon standardized template has yet to, and may never, occur.

Sponsors still each tend to have their own template agreements that they require as a starting point, which many United States sites accept in large part. In the global context, there is an

increasing trend for international sites to insist on using their own internal templates that address local law, which can result in a “battle of the forms.”

Rather than attempting to create one idealized template provision for each target area (and expect parties to reach consensus on utilizing such language), Work Group Five proposes developing several options along a continuum for each topic, thus providing sites and sponsors a range of provisions from which to choose and increasing the possibility that common ground may be realized. Accompanying such template provisions could be the identification of certain countries or regions with specific laws or practices that are known to impact the negotiation around those terms. Furthermore, a checklist of critical terms that should be covered in any global clinical trial agreement could also be developed, to ensure that both parties have a comprehensive understanding of the key areas on which there should be agreement prior to conducting research.

It is not the intention of Work Group Five to dictate ethical standards by which clinical trials must be conducted through model language; but to help increase the transparency of various contract options available to sites and sponsors.

The following examples highlight some of the tensions in certain areas of contract negotiation that Work Group Five believes would most benefit from, and be amenable to, the bridging of expectations.

**Publication Rights.** The right to publish the results of research, including any negative results, is recognized as being integral to the scientific integrity and validity of any clinical trial. According to the International Committee of Medical Journal Editors, clinical trial agreements should not in any way impede the ability of investigators to have access to and analyze data or prepare and publish manuscripts. *See* ICMJE, *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*; *see also* ICMJE, *Sponsorship, Authorship, and Accountability* (August 2007), which outlines appropriate clinical trial agreement terms to ensure sponsors are not given veto-power over the content or existence of resulting publications. Furthermore, the movement towards required registration of trials has been driven by the recognition that transparency around the trials that are conducted and the results they yield is critical to accountable and ethical research. Notably, concerns about the publication of negative results does not exist only with regard to industry as some sites in certain regions have been known to request or demand that the local or national government be given veto power over any publication resulting from the trial where there is concern over the publication of any negative information regarding the patient population or local health care system, or other unrelated political information that may inadvertently be disclosed.

Agreements through which either side is given the ability to control, unilaterally, the dissemination or content of the results of the research contradict existing accepted standards for academic freedom. The insistence, through model contract options, on recognized standards for

publication rights and transparency of results in clinical trial agreements would help to equalize the investigators and sites vis-à-vis their own governments, as well as with respect to the research sponsors, and help to ensure the ethical dissemination of the results of the research for the benefit of patients and participants alike. In addition to the ability to publish, the question of whether authorship credit will be bestowed on local investigators, or to what degree they will have input into authorship decisions, also deserves attention in the clinical trial agreement, in accordance with existing standards for authorship. At the conclusion of a trial, local investigators may be neglected in publications if they are not involved in the design of the trial and the analysis of data, leading to resentment. Publication provisions should address if, when, and how local collaborators might be included on the publication committee, and the approach should be inclusive and consistent with any publication policy outlined in the protocol.

**Confidentiality and Non-Disclosure.** As with publication rights, overly restrictive confidentiality and non-disclosure contract provisions can undermine the academic freedom of investigators. Standardized options for such provisions should seek to enhance transparency while still protecting the intellectual property concerns of research sponsors.

**Fair Benefits.** It is important to the ethical conduct of research to provide individuals who participate in research, and in some cases their communities, with fair benefits in return for their participation, time, and assumption of risk. Fair benefits often take the form of access to treatment options that would not otherwise be available, absent the trial.

In response to requirements imposed by the Research Ethics Committee (REC) overseeing the study, some investigators, particularly those who are conducting research within resource-poor regions, ask research sponsors to guarantee upfront, through the clinical trial contract, access to any resulting drug therapy for which the data demonstrate effectiveness. This request is particularly common in trials for serious and life-threatening conditions, and some sponsors respond by providing expanded access to investigational medicines to participants in the interim between a trial's conclusion and when the product goes to market.

However, guaranteeing access to the drug indefinitely, after the drug has been approved for the market, is less common. Many see that responsibility as one of governments and healthcare systems. It should also be noted that there are significant difficulties to importing an unapproved drug for use outside the confines of a clinical trial, i.e., after the study has closed, much less indefinitely (among other issues that would arise from post-trial off-label use of an experimental medicine, and product liability concerns associated with that proposition).

It also is difficult to monitor recipients of such unapproved drugs for adverse events, indefinitely and after the trial has concluded. Manufacturing supplies of the drug may also be challenging, particularly when development programs are discontinued, as may occur when an investigational new medicine, while effective for some patients, nevertheless has an overall poor benefit-risk ratio.

There are, however, ways to respond to RECs' and investigators' interests in securing fair benefits for study subjects, perhaps in additional agreements or in side letters to a clinical trial agreement]. For example, sponsors can agree to use “best efforts” (although this may be a legal term which means different things under different laws) to provide special access programs for communities in very poor countries and to make available, at low or reasonable costs, appropriate care or medicines that would otherwise be prohibitively expensive. Often this is done in partnership with international organizations or local governments or NGOs. Again, a company providing access to medicines on such a basis needs to be mindful of the product liability position in a specific situation.

Some RECs may ask or insist that the clinical trial agreement secure ancillary care without limits for enrolled subjects (i.e. general health care which is unrelated to what is needed for participation in the trial). These requests usually become a matter for negotiation between the site, investigator and the sponsor. Contract provisions regarding ancillary care may be appropriate for many studies, especially where the participants are otherwise unlikely to have access to such care, although a sponsor pharmaceutical company will have to consider all logistical issues before committing to such a contractual obligation. Another alternative is to set aside a pre-determined pool of funds for ancillary care, leaving it to the discretion of the site to make it available to research participants on a priority basis. Note, however, that there can be limitations imposed by law or regulation, such as the U.S. Foreign Corrupt Practices Act, on if and how monies can be allocated to government officials, government clinics, etc. Achieving fair agreement through the clinical trial contract around cost-permissive access to care, both during and following the trial, helps to ensure appropriate benefits and fair treatment in exchange for a community's participation. The clinical trial agreement can be a useful place to manage both parties' expectations around these issues.

**Compensation for Injury; Insurance/Indemnification.** The degree to which research sponsors should be responsible for any harm incurred by participants in their trials is another area that deserves attention.

In global research, issues of compensation for subject injury and the scope of any sponsor-indemnification and insurance coverage are frequently dictated by local law. For example, research sponsors conducting clinical trials in Poland are required to take out an insurance policy specific to the trial to cover subject injury. This is far from the current industry standard in agreements in the United States, whereby sponsors usually agree to cover the cost of treating any subject injuries beyond what is covered by the injured subject's third party insurer, and that obligation is often defined to include only those injuries that are believed to be directly related to the study product and not to the subject's underlying disease, the negligence of the individuals conducting the study, or failure on the part of the subject to adhere to the study protocol and relevant instructions for participation. In the UK the model clinical trial agreement for industry-

sponsored trials includes an indemnity given by the sponsor in favor of the hospital and its employees against claims brought by a study subject or their family arising out of or relating to the administration of the Investigational Medicinal Product under investigation or any clinical intervention or procedure provided for or required by the protocol to which the study subjects would not have been exposed but for their participation in that study.

The development of model contract provisions will assist research sponsors in having realistic expectations in the context of global research and in being receptive to analyzing and negotiating these issues from a non-US/European framework, while ensuring that sites are aware of the range of possible obligations that sponsors may undertake in compensating harmed subjects or protecting study sites. Furthermore, relating back to the issue of fair benefits, it is important to address what standard of care is required in the treatment of research-related injuries in the global context. If the local site's standard of care is well below what the subject would receive in other accessible countries or regions, what obligation does the sponsor have to facilitate the transfer of subjects to hospitals where better care is available or to make such care available locally in the event of an injury? Negotiating these issues up front through the clinical trial agreement ensures that the sponsor's agreed-upon obligation to provide and/or reimburse the costs of treatment for research-related injuries is meaningful and fair from the site's perspective.

**Privacy and Data Use/Sharing.** Ensuring the protection of privacy for all research participants is recognized as being critical to affording them respect. The laws around privacy protection and the ability to use or share data from the research, including future use of data and specimens for unspecified research and the exporting of data and specimens outside of the country in which the research is conducted, vary considerably across countries and regions. Identifying common standards and best practices that transcend or encompass these variances is essential to ensuring that participants receive the respect they deserve and that agreements can reach resolution on these challenging issues. Sponsors also have to be careful to avoid inadvertently attaching data protection obligations to personal data that did not exist before (e.g. by exporting personal data to the EEA from Africa or Asia, at which point EEA data protection obligations can attach to the data).

Part of this challenge involves clarifying the definitions of what the parties mean by critical terms such as “anonymous data,” “anonymized data,” “identifiable data,” “de-identified data” and “limited data sets.” Furthermore, both parties need to understand, as a factual matter, exactly what data, and in what form, the data must be shared to meet the objectives of a given research study. Finally, these provisions should not overlook the possible impact and harm to participants' communities that may result from data sharing.

## **Conclusion**

Research sponsors, CROs, sites, and investigators can work together to build a better framework for agreements that support multi-regional clinical trials, taking into account legal variations as well as cultural differences. Many sites and investigators, in particular, would benefit from better awareness of the range of possible contract terms which would ultimately increase the efficiency in the contracting process and improved ethical standards for the conduct of the research.

## **MRCT Project Report: Conclusions & Next Steps**

As of February 2009, approximately 2,900 new compounds were in clinical trials or undergoing FDA review, a full 52.6% increase over 1999 (PhRMA, 2009 as reported in Clark, 2009). The potential these compounds hold for reducing human suffering is great, and therefore the need for high quality clinical research is imperative. Yet few endeavors are as complex as international clinical trials, given the multitude of ethical, legal, regulatory, scientific, cultural, economic, and operational challenges that must be thoughtfully resolved.

Fortunately, there is universal agreement on foundational ethical principles (CIOMS, 2002; WMA, 2008) and successful international harmonization of regulations and standards for clinical trials (ICH-GCP/E6, 1996; Council of Europe, 1997). Regulatory reform is also being examined to ensure that regulatory approaches will be effective in requiring adherence to agreed-upon principles while remaining feasible and efficient methods of oversight (Glickman et al., 2009). As noted throughout this Report, there have already been many high quality educational initiatives, which have enhanced the expertise of thousands of professionals involved with clinical trial conduct around the world. Nevertheless, much more remains to be done.

This Report has focused on outcomes that sponsors and CROs have the ability to impact and, thereby, improve research ethics and data integrity in their own operations or through collaboration. Since there is already broad acceptance of foundational ethical principles, the next important step is to ensure operational alignment with those principles.

Predominantly, the MRCT Work Group proposals focus on achieving that alignment through greater professional competence of the many players who must contribute to the global research enterprise. Professionalism is essential to the ethical conduct of clinical research. Just as scientifically unsound research is unethical, so too is research conducted in a manner that cannot ensure the integrity of the science, the quality of the data, and respect for and safety of research participants. Assuring all individuals engaged in research are properly qualified through education and experience is a theme throughout this Report.

Many of these proposals will require resources, and empirical research will be necessary -- at least for some of them -- to ensure that they are appropriate responses to the challenges they are meant to address. Most proposals also will need greater definition of what success would look like and how it would be measured.

It is important to note that there are many reasons for industry and clinical research organizations to work together to address the challenges of globalization and ensure the integrity of clinical research. Many of these proposals have the potential to advance ethical imperatives and to improve the quality of clinical research. Regarding their potential scientific and operational return, many of the proposals promise to help deliver higher-performing researchers, research

sites, RECs, trial monitors, and DMCs. Even if only some of the proposals emerging from the Work Groups were implemented, together they could help build a cadre of sites with faster start-up times, better data, and in a manner protective of, and fair to, the human research participants and their communities.

As expensive as clinical research has become, poorly executed research is orders of magnitude more costly in wasted resources, lost trust, and regulatory exposure. Indeed, poor quality in the informed consent process or a breach in research integrity at a single site can close down an entire study, wasting R&D funds and potentially thwarting the approval of an important new medicine. Confidence in the trustworthiness of research is in everyone's interests -- those of research participants, host communities, industry, clinical research organizations, and patients who need proven therapeutics. MRCT participants look forward to enhancing that confidence through the many ideas described in this Report.

Finally, with regard to the MRCT Project and *where this project should go from here*, there is general agreement among the MRCT Project participants that industry needs to continue to address the challenges associated with the globalization of clinical trials and the recommendations in this Report. For that to be successful, industry has to do this in conjunction external experts in research ethics, external experts in the conduct of clinical trials, partners from academia patient advocacy groups, and others. *At the writing of this report*, Pfizer is in discussions with other companies and non-industry organizations to support the continued work of the MRCT Project.

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## **Attachments**

1. Work Group One, Sample Ethics Section for All Protocols
2. Work Group Three, Sample Section of Proposed Tool for Study Site Assessment
3. Work Group Three, Alternative Models for Managing Study Site Assessment
4. Work Group Three, Suggested Core Competencies for Investigators
5. Work Group Four, Core Competencies for Monitors related to Informed Consent and Human Research Participants
6. Work Group Four, Sample Questions Monitors Should Ask
7. Minutes from MRCT Summit Meeting held in January 2010 in Cambridge, MA

## Attachment 1

### Ethics Document to Accompany (Some/Certain) MRCT Protocols (Draft)

#### Ethical Criteria to Consider When Designing Global Studies

Please answer the following questions. They are intended to help you communicate to the REC how the proposed study takes into account key ethical issues, important in the design and conduct of global clinical trials. Answering them may also shape your decisions about study populations and design.

#### Collaborative Partnership

- How have local researchers, health policymakers, and the community been involved in determining the importance of the research, how it will be integrated into community, and in ensuring that the research is planned and conducted with respect for local values, culture, and traditions?

#### Social Value

- Who is likely to benefit from the *results* of this study? What benefits will the community receive from the conduct of the research?
- Is the disease being investigated one that is endemic in or important to this population? If not, why has this study population been chosen?

#### Scientific Validity

- Will the proposed design realize the scientific objectives while protecting the rights of participants?
- Please explain the choice of comparator against which the investigational drug or device will be compared?
- Is this comparator an existing proven therapy that represents the worldwide best standard?  
\_\_\_ yes \_\_\_ no      If not, why not?
- If a placebo comparison is being used, please explain why.
- Is the study feasible given the social, political, and cultural environment?

#### Fair Selection of Study Population

- Explain how the targeted study population is appropriate to the scientific objectives?
- Are there additional protections for potentially vulnerable populations or groups?

#### Favorable risk/benefit

- What are the risks to human research participants participating in this study?
- What steps have been taken to minimize the risks?
- What benefits, if any, will accrue to the individual research participants who volunteer for this study?

- During the trial, will research participants be receiving medications not usually available to them? \_\_\_\_ yes \_\_\_\_ no
- Are there other benefits to individuals for participating? Please describe.

### **Informed Consent**

- Are recruitment procedures and incentives appropriate for this community?
- Will individuals be able to say no without penalty or community censure?
- Is the proposed consent process culturally, linguistically, educationally appropriate?

### **Respect for recruited participants and study communities**

- Describe procedures for protecting confidentiality, plans for monitoring of data and safety, care for research related injuries, plans for providing information back to participants and the community
- Plans for post- trial
  - o Once the study is stopped, will medications, known or learned to be effective, continue to be provided to the former research participants in both intervention and control arms? \_\_\_\_ yes \_\_\_\_no      If so, for how long? \_\_
  - o Have you developed, or do you intend to develop, a contract with the authorities in the local site(s) about providing post-trial access to the drug, if it proves effective? What steps are contemplated to make the drug accessible to this population?

**Attachment 2**  
**Draft Study Site Assessment Tool**

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For most sponsors, Study Site Assessment is the first step in country and site selection. By providing a framework to sponsors for completing study assessments and site selection, sponsors can improve the consistency and quality of the assessment process. Below is the preliminary framework for guiding sponsors through the assessment process. The framework provides suggested components as well as sources of information and sampling methodologies.

This framework was developed by:

1. Reviewing literature on the challenges of conducting of clinical trials in emerging markets,
2. Primary research: responses to a survey about the current methods companies use to complete study assessments. The survey was completed by 5 sponsors (2 CROs and 3 Industry Sponsors) in Q3, 2009, and
3. RapidTrials analysis of the participants processes.
4. Review of the ethics literature to ensure inclusion of questions related to ethical criteria for site selection

It is intended to be used as a springboard for further refinement and discussion, including sources from which the information may be derived.

**Source: RapidTrials, 2009**

	<b>Characteristic</b>	<b>Site Assessment Score</b>				<b>Potential metrics and source of data</b>
		<b>Low</b>	<b>Moderate</b>	<b>High</b>	<b>MRCT Guide-line</b>	
	The population suffers from the disease that will be studied					WHO indicators; in-country health statistics
	Standards of care are well established					WHO indicators: adult mortality rate (male and female -15-60)
	Country's costs of healthcare delivery are (high/low/average) compared to other countries being considered					World bank indices: healthcare spending per capital
	Country's costs of clinical development are (high/low/average) compared to other countries being considered					Company cost comparisons (*)

Country has well developed regulatory infrastructure					Evidence regulatory authority with internationally recognized standing?
Country has an Independent entity to do ethical review of studies and ensure human research participant protection					Primary and secondary research
Country has adequate financial support for regulatory infrastructure?					Perhaps an Infrastructure investment measured by WHO (schools, water, roads, etc.) can be and used as a proxy for Regulatory infrastructure?
Country has well developed communication channels to deliver study results to healthcare providers, research participants and the public after study conclusion?					Primary and secondary research
Country has an established process for investigational product shipment, storage, distribution?					Retrospective company data analysis
Country has a track record for productive, high quality studies/data?					Retrospective company data analysis
Country provides transparency/access to clinical trial information					Primary and secondary research
Health policy: favorable reimbursement environment/for investigational product					Intent to market
Potential public relations issues (strains, hormone replacement therapy) in this Country					Research/due diligence
Country's availability of					Country database of qualified

research sites					clinicians
Competition for target study subjects by other sponsors in this Country					
Country has available and suitable experienced sites					
Country has a favorable reimbursement environment for investigational product Protocol design (inc./excl.) is viable for enrollment in this Country					
Principal investigator experience/qualifications/training					Define how to measure experience knowledge and training (what is the gold standard-western medical training? hazardous material training? board certification?) Trained in ICH-GCP guidelines; trained in western medicine
Site has a community advisory board or the means to establish a credible one					
Infrastructure: facilities, equipment and technology					Protocol and non-protocol specific equipment and technology required (crash cart, sterile, etc.)
Access to patients					Data on target patient population served by site (preferably non self prepared)
Capacity: supply > demand for research resources					Total PI FTEs/research FTEs
Competition for provider resources, other studies					Mean studies per PI (clinicaltrials.gov); mean subjects per PI

	Performance metrics based on evidence					Company database
	Competition for study subjects by other sponsors					Number of sponsors conducting research
	Few sponsors conduct research in country					
	Availability of suitable experienced sites					
	Motivation for participating (experience with new molecules, meetings in foreign locations, publication financial gains, academic interest, funds for the department, other)					
	Protocol: achievable timelines/milestones					Comparison to historical timelines
	Protocol: achievable enrollment					Comparison to historical enrollment
	Budget factors					Comparison of total costs of conducting trial
	A site's principal investigator experience/qualifications/training					Define how to measure experience knowledge and training (what is the gold standard-western medical training? hazardous material  Trained in ICH-GCP guidelines; trained in western medicine. Training? Board certification?)
	The site's infrastructure: facilities, equipment, technology					Protocol and non-protocol specific equipment and technology required (crash cart, sterile etc.)

Access to patients/recruitment forecast					Data on target patient population served by site (preferably non-self-prepared)
Site's capacity: supply > demand for research resources					Total PI FTEs/research FTEs
Competition for provider resources, other studies					Mean studies per PI (clinicaltrials.gov); mean subjects per PI
Performance metrics based on evidence					Company database
Competition for study subjects by other sponsors					Number of sponsors conducting research
Few sponsors conduct research in country					
Experience of PI with specific of procedures					
Protocol: achievable timelines/milestones					Comparison to historical timelines
Site's planned enrollment rate					Comparison to historical enrollment
Site's estimated costs					Comparison to total costs conducting trial
Site's planned patient recruitment tactics					

Attachment 3  
Alternative Models for Managing the Study Site Assessment Process

Assessment is meant to be broader than standard feasibility assessment and should include ethical, operational, regulatory, financial and clinical capacities of a prospective research site. The table below provides alternative models (dedicated central group, outsource, audit) for completing the study site assessment process and pros and cons of each.

Model	Study Sponsor	Outsource to full service CRO	Outsource (niche service provider feasibility only)	Rating or QA agency
<b>Definition</b>	Perform site assessment on own projects	Perform assessment and manage	Commission independent expert consultants to provide project due diligence services; not involved in execution	Assess and evaluate quality and accuracy of site assessment study completed by another group ( e.g., accounting firms audit the financial reports)
<b>Example</b>	Worldwide central/ dedicated site assessment resources			Example financial industry rating firms accounting firm auditing a company's books and records healthcare accreditation bodies/nursing homes licenses and permits for building
<b>Strengths</b>	+ Methodological	+ Consistency across programs	+ Consistency across	+ Public perception

Model	Study Sponsor	Outsource to full service CRO	Outsource (niche service provider feasibility only)	Rating or QA agency
	<p>expertise</p> <p>+ Standardization (process)</p> <p>+ Consistency across programs</p> <p>+ Quality metrics</p> <p>+ Assurance of adequate resources</p> <p>+ Limits investigator bias (separation of site selection from feasibility)</p> <p>+ Efficiency in database purchases to support decisions (similar to market research groups within commercial organizations)</p>	<p>(provided sponsor process deployed across all CROs and to conduct studies</p> <p>+ Quality metrics</p> <p>+ Public perception (if arms length from any operational aspects of study or companies implementation</p> <p>+ Efficiency in database purchases to support decisions (similar to market research groups within commercial organizations)</p>	<p>programs (provided sponsor process deployed across all CROs used to conduct studies)</p> <p>+ Quality metrics</p> <p>+ Public perception</p> <p>+ Efficiency in database purchases to support decisions (similar to market research groups within commercial organizations)</p> <p>+ Accountability for site assessment</p> <p>+ Adequate resources</p> <p>+ Can ensure that expertise includes a balance between technical and operational issues</p> <p>+ Attention to ethical considerations limits investigator bias limits internal bias (if guidance followed)</p>	<p>+ Accuracy</p>

Model	Study Sponsor	Outsource to full service CRO	Outsource (niche service provider feasibility only)	Rating or QA agency
<p><b>Weaknesses</b></p> <ul style="list-style-type: none"> <li>- Potential for finger pointing if unable to distinguish between poor feasibility and poor implementation</li> <li>- Attention to ethical considerations</li> <li>- Difficult to scale</li> <li>- May lack therapeutic area expertise</li> <li>- Small pharma may lack ability to tailor its operational approach to the feasibility data</li> </ul>	<ul style="list-style-type: none"> <li>- Potential for finger pointing if unable to distinguish between poor feasibility and poor implementation</li> <li>- May not limit investigator bias (CROs have many sponsors and studies)</li> <li>- CRO vested interest in the adoption from an operations perspective if bundled</li> </ul>	<ul style="list-style-type: none"> <li>+ Public perception</li> <li>- May be more costly</li> <li>- Companies may be concerned about conflicts of supporting multiple sponsors with same indication</li> </ul>	<ul style="list-style-type: none"> <li>- End of process approach which may require rework</li> <li>- How to enforce if rating is poor?</li> </ul>	

## Attachment 4

### Suggested Core Competencies for Investigators

Clinical Research Investigators (staff) should have basic core competencies to successfully implement and manage clinical research that satisfies performance, quality and compliance expectations. These competencies may be obtained through experience, training or a combination. Global training programs to support core competencies should be available for investigative sites as needed. The training programs could be modified or tailored to suit specific regional (geographic) or cultural requirements.

#### Basic core competencies for clinical trial investigators

- Fundamentals of Clinical Research (General)
  - Purpose and Objectives
  - Study designs
  - Randomization
  - Analytical approaches
  - Elements of a protocol (study design)
  - Differences in the objectives of clinical research and medical practice
- Responsibilities of an investigator
  - What is a 1572
  - What it means to be solely responsible for all aspects of a clinical trial
  - Delegation of Authority
- Ethical principles in Clinical Research
  - Applicability of the research to the potential study population.
  - Differences between clinical research and medical practice; conflicts of interest within physician-researchers
  - Difference between a patient and a clinical research volunteer
  - Need for ensuring fair benefits to subjects
  - Nature of the comparison group (worldwide best standards or local ones? Placebo?)
- IRBs/ Ethics Committee:
  - Role
  - Identifying an appropriate IRB/EC
  - Potential responses and site level actions
  - Ongoing review
  - Reporting requirements
- Informed Consent
  - Process to educate patients and to obtain informed consent
  - Assuring informed and voluntary consent
- Global Regulatory Framework and Strategy
  - Protocol approval process
  - General overview of requirements to obtain marketing license in developed and emerging countries
  - Local requirement for product approval

- Good Clinical Practice Regulations (ICH)
  - minimum requirements for source documentation
    - what constitutes source documentation
    - archiving
  - control of investigational product
    - documentation of dispensation
    - storage
  - informed consent
  - safety reporting
  - ethics committees
  - monitoring
- Principles of Safety Reporting (FDA, EMEA and local authorities)
- Patient Recruitment and Retention methods and plans
- Audit preparedness
  - Sponsor audits
  - Regulatory authority audits
  - Types of audits
- Understanding of clinical trial infrastructure
  - finance and economics related to clinical trials - study costs, resources, time, equipment, and contracting
  - staffing
  - space
  - equipment
- Elements of project management related to organization of the study site to manage patient recruitment, complete procedures and track progress
- Communication requirements in Clinical Research: between site staff, with patients, with the study sponsor, with ethics committees and others as necessary.
- Data Safety and Monitoring Committees (International Data Monitoring Committees) – roles, responsibilities and how to interact with them
- Monitoring
  - Purpose
  - Role of the monitor
  - Difference between monitoring and auditing
  - Data retention

**Attachment 5**  
**Core Competencies for Monitors related to**  
**Informed Consent and Human Subjects' Protection**

- Human Subjects Protection
  - Nuremberg Code, Declaration of Helsinki, Belmont Report
  - Investigator compliance with ethical standards of behavior
- Informed Consent
  - Principles and Process
  - Essential elements
  - Data protection
  - Documentation
  - Ongoing informed consent required for study changes/subject safety
  - Special populations, cultural considerations, ethics review, healthcare access, economic
  - Potential Obstacles
  - Site compliance with ICH/GCP
  - Ethics Committee / IRB Requirements and Role
- Protocol Compliance
- Naïve investigators
  - Investigational Drug Development and Regulations
  - General Considerations
  - Standards for Good Clinical Practice
- Investigator responsibilities, delegation and oversight
- Subject safety
- Investigational product
- Record keeping

## Attachment 6

### Sample Questions Monitors Should Ask

#### Top Level Questions:

- Describe your informed consent process for new potential subjects?
- Describe your informed consent process for ongoing subjects?

#### Questions to prompt the site for more information:

- Who first approaches the potential subject?
- Which staff members are involved in the consenting process?
- What explanation of the consent process is given to the potential subject?
- How do you ensure you are using the most current version of the ICF?
- If the subject comes from your private practice, what procedures are in place to ensure that subjects do not feel obligated to participate because the investigator is their treating physician?
  - Where do they read the ICF?
- Do you send them home with a copy prior to signing?
- Where is the discussion with your staff held?
- How do you ensure they have adequate time?
- What steps do you take to verify that potential subjects understand the contents of the ICF?
  - What questions do you ask of the subjects during the consenting process?
- How do you document the consenting process?
  - That consent was obtained prior to any study procedures?
  - That a signed copy, if applicable, was given to the subject?
- How often do you review the ICF with the subject during the course of the study?
- Does your IRB/EC have written guidance for obtaining informed consent?

#### Questions related to special populations:

##### Pediatric/Adolescent populations

- What is the legal age of consent in your state/country?
- How does your normal process differ if the potential subject is below the legal age of consent?
- How do you verify legal guardianship?
- If your state/country requires consent from both parents, how do you handle situations where one parent cannot be contacted?
- If the child denies assent but the parent wants to consent, how do you handle that?

##### Cognitively impaired populations

- How does your normal process differ if the potential subject is considered to be cognitively impaired?
- How do you verify legal or medical power of attorney if required?

**Subject's first language is not the predominant local language:**

- Do you routinely have ICFs translated into another language?
- How do you ensure that subjects whose first language is not the one the ICF is written in understand?
- How do you document this process differently than the normal process?

**Non-literate subjects:**

- What safeguards do you put in place to protect illiterate subjects?
- What is your understanding of "impartial witness"?

**Visually, verbally or physically impaired subjects:**

- What accommodations can you make for visually or verbally impaired subjects?
- How do you obtain the equivalent of a signature for subjects who are unable to write?

## Attachment 7

### **MRCT SUMMIT MEETING MINUTES**

January 19-20, 2010

Harvard Faculty Club

Cambridge, MA

Below are minutes from the MULTI-REGIONAL CLINICAL TRIAL (MRCT) Summit Meeting held January 19-20, 2010 at Harvard to discuss how sponsors and clinical trial stakeholders can improve multi-regional clinical trials, especially those that involve resource constrained/economically deprived regions of the world and initial recommendations of five (5) working groups established by Pfizer with participants from leading pharmaceutical companies, contract research organizations, research institutions, institutional review boards, academic institutions, non-government organizations and other stakeholders.

The five Work Groups and the co-chairs of those working groups were as follows:

- Work Group 1: Enhancing the Quality and Efficiency of Ethics Review (led by David Forster (Western IRB) & Susan D'Amico (Novartis));
- Work Group 2: Enhancing Data and Safety Monitoring; (led by Chuck Knirsch (Pfizer) & Janet Wittes (Statistics Collaborative));
- Work Group 3: Enhancing Site Selection and Investigator Team Expertise (led by Linda Meyerson (GSK), Amir Kalali & Adam Chasse (Quintiles); and Tracey Blumenfeld (Rapid Trials));
- Work Group 4: Enhancing the Professionalism of Monitors (led by Deborah Copeland (i3 Research) & Craig Wozniak (GSK)); and
- Work Group 5: Transparency of Contract Terms (led by Kate Heffernan (KGH Advisors) & Mark Barnes (Office of the Provost, Harvard)).

The Summit Meeting was co-sponsored by Pfizer and Harvard, with Dr. Rob Califf (Vice-Chancellor for Clinical Research, Duke University) and Dr. Millie Solomon (Associate Clinical Professor, Harvard and Vice-President, EDC) serving as co-chairs.

### **DAY 1 – JANUARY 19<sup>TH</sup>**

#### **Welcome to Harvard**

Justin McCarthy (Pfizer) & Marc Wilenzick (Pfizer) opened the MRCT Summit Meeting. Mark Barnes (Harvard Office of the Provost), Professor Dan Brock (Harvard Medical School), and Professor Glenn Cohen (Harvard Law School) welcomed participants on behalf of Harvard. Mark Barnes explained that Harvard was co-hosting the 2-day MRCT Summit with Pfizer because Harvard also conducts clinical research crosses national and international borders and given that Harvard has an earnest interest in the issues surrounding the conduct of multi-regional clinical trials.

Justin McCarthy and Marc Wilenzick emphasized that although participants and their respective organizations/companies may be undertaking good faith initiatives on their own accord, it is important that participants of the MRCT Summit collaborate and develop overarching principles, concrete ideas, and *actionable* items to improve the conduct of multi-regional clinical trials. They also urged participants to consider how they might complement ideas and solutions that are already underway but lack momentum or sufficient sponsor support.

Marc Wilenzick then introduced the MRCT Summit Meeting's panel of distinguished guests, which included: *Dr. Edson Moreira of the Oswaldo Cruz Foundation, Brazilian Ministry of Health; Dr. Renee Ridzon of the Gates Foundation; Dr. Robert Califf of Duke University; Dr. Joseph-Matthews Mfusto-Bengo of the University of Malawi College of Medicine; Dr. Jim Lavery of the University of Toronto; Dr. Deborah Barker of Novartis; and Dr. Vasantha Muthuswamy of the Indian Council of Medical Research. Panelist, Dr. Jan Pachl of the University Hospital Kralovske Vinohrady* joined the panel later that day.

## I. Global Trials – A Systems Approach

Professor Greg Koski presented **“A Global Approach to Clinical Research Excellence: To Slip the Surly Bonds of Conventional Practice.”**

Dr. Koski noted that clinical research is a global endeavor being conducted in a still futile world. He challenged participants to stop thinking about multi-regional trials in terms of the “rest of the world,” rather to think about the mission in terms of engaging the entire world to work together in a collaborative fashion. Dr. Koski urged the audience to think broadly about how we might go about solving the problems facing multi-regional clinical trials by looking outward to see how other industries have handled similar challenges.

Dr. Koski directed the audience's attention to the International Air Transportation Association (IATA) as a positive and pertinent example from which lessons can be taken. For the IATA is charged with defining a global set of standards for airline safety, security, and facilitation. It is an integrated set of standards, not necessarily unified because many different areas of expertise need to work in concert in many varying locations (i.e., airlines, airports/air traffic controllers, freight forwarders, etc.).

Dr. Koski challenged participants to think about what the situation might look like if the IATA model was translated over into the area of clinical research. In this regard, we could have a global network of accredited research sites and research ethics committees, a shared information infrastructure (including real-time access to pharmacovigilance data) and a standardized set of policies and operational procedures.

Dr. Koski believes that we are on the cusp of being able to build such a system today since essential pieces of the system have already been built. Likewise, critical partners, such as the World Health Organization (WHO), have also already expressed an interest in being involved in the development of such a system.

## II. Research in India followed with Q&A

Dr. Muthuswamy discussed "Clinical Trials in India – Current Scenario."

Dr. Muthuswamy provided an overview of the strength of the current health-related infrastructure in India (i.e., approximately 350-400 medical colleges, 400 universities, 300 research institutes, 11,000 hospitals, etc.). She highlighted some of the advantages associated with clinical trials in India, such as scientific manpower, low labor costs, world-class IT professionals, world-class biotechnology industries, and a large English speaking population. Overall, Dr. Muthuswamy believes that India is catching up quite quickly with established regions, such as the U.S. and the EU.

In India, the majority of medical costs are borne by households directly as opposed to being borne by the central, state and/or local governments. This dynamic creates a pool of potential volunteer candidates for purposes of clinical trials. There exists a current need in India for the following: medical diagnostics, medicines (synthetic, recombinant and herbal), vaccines, biomedical devices as well as new therapeutics (stem cell therapy and gene therapy).

Dr. Muthuswamy also provided an overview of the current status of clinical trial regulations in India, including the Indian Council of Medical Research (ICMR) Guidelines for Clinical Research. Dr. Muthuswamy pointed out that although the ICMR Guidelines are meant to be followed, there is currently no enforcement mechanism in place to "police" compliance. Participants also learned about the Indian Clinical Trial Registry (ICTR) that was launched on July 20, 2007 and the registration data set associated with the ICTR. Dr. Muthuswamy also presented on a "speaking book" entitled "What it Means to be Part of a Clinical Trial" – such book acts as an audio/visual aid for potential subjects considering whether to enroll in a clinical trial, helping to supplement the informed consent process. The book was launched at the World Medical Association Assembly in Delhi in October 2009 in the English, Hindi and Telugu languages.

Q&A session was held with Vasantha Muthuswamy and members of the panel. There was discussion about the mismatch between diseases and clinical trial activities in India and what steps, if any, might be taken to incentivize industry to meet the disease needs of India – potential tax incentives were discussed as a possible incentive. Dr. Muthuswamy also discussed differing regional perspectives when it comes to the assessment of risk/benefit ratios in connection with adverse events.

## III. Comments on MRCT's and Industry's Roles

Vice-Chancellor Rob Califf presented "The Evolution of Clinical Research: from an effort to simulate a laboratory to a part of routine clinical practice."

Dr. Califf began his presentation by asking participants to hold 2 conflicting principles in mind:

- (i) *that globalization is good; and*
- (ii) *that globalization exposes flaws.*

Dr. Califf also reviewed the following general points: *globalization is a “done deal”; harmonization will be a work in progress for our lifetimes; clinical research is a common pathway for multiple societal goals; clinical research is complicated and difficult for people to understand (even for professionals); and if the goal is better health for the global population, unintended consequences of well intended policies must be carefully considered.* Dr. Califf guided the audience through the taxonomy of clinical trial errors (i.e., design errors, procedural errors, recording errors, fraud and analytical errors). Dr. Califf urged the audience to shift focus from just the investigator to the entire investigative site.

Dr. Califf concluded with the following thoughts:

- *globalization is here to stay (it is a good thing and it exposes flaws by giving us comparative data);*
- *drug development is only one part of a much bigger clinical and translational research system;*
- *policies and standards should consider intended and unintended consequences;*
- *the goal should be to pursue higher quality, but the definition of quality depends on the purposes of the research being questioned; and*
- *a key question at every stage of the research project mentality should be: What have we left behind that will elevate the standard next time?”*

#### **IV. The MRCT Work Group Recommendations**

Professor Millie Solomon presented **“Ethical Premises of MRCT Recommendations.”**

Professor Solomon reminded the audience of the goal of the MRCT Recommendations – which is to enhance respect for research participants via patient safety and fairness, all while improving the quality and efficiency of global clinical trials. Professor Solomon reviewed the 8 ethical criteria established for global clinical research: (i) partnership; (ii) social value; (iii) scientific value; (iv) fair participant selection; (v) favorable benefit-risk ratio; (vi) independent review; (vii) informed consent; and (viii) respect for participants. Professor Solomon then associated each of the recommendations suggested by Work Groups 1-5 with one or more of the 8 ethical criteria.

##### **A. Work Group 1 Report – Enhancing Quality & Efficiency of Ethics Review**

Professor Solomon introduced the co-chairs of Work Group 1: Susan D’Amico (Novartis) and David Forster (Western IRB).

Work Group 1 had the following goal: arrive at consensus on the most efficient and actionable means to improve REC capacity and quality in all parts of the world.

To this end, Work Group 1 made the following 6 recommendations:

- In every protocol (or some protocols), there should be an ethics section which sponsors could answer before submitting their study for REC review. That information could also be provided as separate document to accompany the Protocol.

Summary of Panel/Audience Feedback: It would be beneficial to many RECs to have an ethics section included in the protocol or a document accompanying the Protocol. Ethics issues are often addressed in the protocol and it would be helpful for REC members to have something that calls out those issues; for Sponsors, this document would draw additional attention to the ethical issues. It would also enable ethical issues to be presented in a very transparent manner.

- Encourage accreditation of human research protection programs globally.

Summary of Panel/Audience Feedback: International accreditation will be very difficult and may need to be considered a “nice to have” item – potentially national systems of accreditation (as opposed to a singular global system) needs to be considered. It should be noted that the AAHRPP accreditation is based on the site/entity meeting both the relevant national standards and ICH standards, however.

- Create a pool of funding and develop a grant application process to enable RECs to apply for financial support to facilitate progress toward accreditation.

Summary of Panel/Audience Feedback: A straw vote showed that most participants believe that this recommendation is actionable.

- Enhance continuing education for already-trained fellows and create mentoring opportunities for new REC members.

Summary of Panel/Audience Feedback: A straw vote showed that most participants believe that this recommendation is actionable.

- Through a series of best practice case examples, promote a worldwide trend toward more efficient models of ethical review.

Summary of Panel/Audience Feedback: A straw vote showed that most participants believe that this recommendation is actionable.

- Promote the establishment of Community Advisory Boards (CABs) to ensure authentic community involvement and the cultural acceptability of a prospective clinical trial for a given venue.

Summary of Panel/Audience Feedback: A straw vote showed that most participants believe that this recommendation is actionable. Comment from the audience noted that many CABs exist already.

## **B. Work Group 2 Report - Enhancing Data and Safety Monitoring**

Professor Solomon introduced the co-chairs of Work Group 2: Dr. Chuck Knirsch (Pfizer) and Dr. Janet Wittes (Statistics Collaborative).

Work Group 2 had the following goal: build capacity of Data Monitoring Committees (DMCs) serving, in whole or in part, in resource constrained/economically deprived regions of the world so that these DMCs can effectively monitor the safety of research participants and the efficacy of treatments in trials.

To this end, Work Group 2 made the following 2 recommendations:

- Develop an apprenticeship program to train potential DMC members.

Summary of Panel/Audience Feedback: Dr. Edson Moreira shared that the DMC role in Brazil is often misunderstood and/or confused with that of the IRB. Another point raised was that of the larger ethical issues surrounding drug development more broadly rather than the ethical review of individual trials. Dr. Renee Ridzon described as an example the series of HIV prevention trials that tested the first generation of microbicide candidates. These trials were funded by The Bill and Melinda Gates Foundation, NIH, USAID and DfID and tested several candidates of the same class that were nonspecific topical agents, however, alignment among funders and the field as a whole was not optimal. Retrospectively, this may not have been best practice as it is not clear that as the field moves into the next generation of trials of antiretroviral containing agents that there will now be sufficient funding for these expensive trials and that multiple negative trials may have impacted public trust and buy-in to next trials.

Audience members also raised the following observations: (i) RECs do not have ready access to DMC work. Work Group 2 might consider a proposal that would help to facilitate a better cultural awareness of what DMC work really entails and how such work might be made more accessible to RECs; (ii) DMCs require more expertise than any other part of the clinical trial process, and as such the notion of an “apprentice” program may not go far enough. Perhaps Work Group 2 should consider whether a full-fledged certification program should be required instead; (iii) there exists general unevenness in the sophistication of DMCs and, therefore, sponsors need to do a better job of concretely defining the remit of the DMCs they engage; and (iv) the word “apprentice” may turn persons away from participating in such a program.

- Develop a sample DMC Charter directed to studies that include countries in the developing world.

### **C. Work Group 4 Report - Enhancing the Professionalism of Monitors**

Professor Solomon introduced the co-chairs of Work Group 4: Deborah Copeland (i3 Research) and Craig Wozniak (GSK).

Work Group 4 had the following goal: have sponsors assume a leadership role by enacting measures that support and enhance 2 primary focuses: (i) the monitors’ understanding of, and influence on, the consent process and (ii) overall professionalism of monitors.

To this end, Work Group 4 made the following 9 recommendations:

- Endorse a professional paradigm.
- Establish a comprehensive set of recognized and expanded core competencies for monitors.
- Inventory existing training programs and conduct gap analysis.
- Develop an educational framework stipulating the characteristics of high quality professional education programs.
- Encourage and reward professional certification.
- Develop greater clarity about the nature, scope and importance of an optimal informed consent process and the role monitors play in this regard.
- Ensure that all monitor training programs include a focus on the monitors’ role in assessing and maintaining a high quality informed consent process.

- Develop a kit of strategies and resources which monitors can use to enhance informed consent in the field and throughout the trial.
- Elaborate how this kit can be disseminated so that it is widely adopted by monitors serving various regions of the world.

Summary of Panel/Audience Feedback: Given timing constraints and the number of recommendations offered up by Work Group 4, it was decided that comments would be taken in 2 general categories: *(i) matters of professionalism and (ii) matters of informed consent processes*. Specifically, with regard to matters of professionalism, it was agreed by an audience member that it would be very helpful to have less experienced monitors paired with more experienced monitors (i.e., a mentoring roll of sorts). It was acknowledged that experiential training of monitors is critical, especially in the areas of compliance, systems and protocols. It was highlighted that monitors will require unique training, separate and apart from any general training they may otherwise receive, to be successful in different markets (i.e., a monitor in Brazil will need a different subset of skills than a monitor in Malawi - and vice-versa). Audience also discussed the need for training that would go beyond just basic regulatory matters, but perhaps local issues, interpersonal skills and therapeutic training. It was also noted that the role of the monitor intersected with a proposal already made by Work Group 1 – such that if the informed consent was drafted to include an ethics section, the monitors would need to be trained to “keep an eye on” this section to make sure that the protocol is being adhered to in a proper manner. A general comment was made about needing to enhance/improve the image/status of monitors as the monitor’s role is unfortunately sometimes viewed as administrative and menial.

#### **D. Work Group 3 Report - Enhancing Site Selection and Investigator Team Expertise**

Professor Solomon introduced the chairs of Work Group 3: Linda Meyerson (GSK), Amir Kalali (Quintiles), Adam Chasse (Quintiles) and Tracey Blumenfeld (Rapid Trials).

Work Group 3 had the following goal: to focus on practical measures that industry can adopt to better assure appropriate global site selection, including appropriateness of the population to be approached as well as training and education provided to investigators and site personnel.

To this end, Work Group 3 made the following 7 recommendations:

- Industry should formulate, adopt and commit to a common ethical and quality framework for selecting study population and sites.
- Develop and measure the impact of a common Study Site Assessment methodology to identify countries and sites that meet the ethical, scientific and business criteria.
- Evaluate and compare the benefits and shortcomings of a centralized study site assessment model versus individual project team site assessment.
- Share information on site quality to ensure industry-wide visibility on country-specific (and possibly site-specific) quality trends, as legally permissible, and collaborate to improve selection of high quality sites.
- Study with greater rigor the value of certification programs for enhancing the knowledge, skills and performance of investigators and research coordinators.

- If validation of the effectiveness of certification in improving investigator quality is demonstrated, industry should preferentially place trials with those sites that offer certified investigators and consider other ways to promote certification.
- To ensure a global standard of medical competence, CROs and sponsors should seek verification of the medical expertise of prospective physician-investigators.

Summary of Panel/Audience Feedback: Focused questions were asked of the panel/audience.

With respect to the first question posed by Work Group3 – *“What do you think of the merits of adding ethical, scientific or broader operational issues to the usual site assessment process?”*

- Panel member indicated that the addition of such issues to the usual site assessment process would prove to be an added value, without question. Another panel member asserted that although this would be a great start, we needed to consider the fact that excellence in enrollment in one disease at a site does not equate to excellence in enrollment in another disease at the same site. Another panelist asked Work Group 5 to consider what is meant by “ethical.” It was also noted that communities should be given an active voice – how do we reconcile (i.e., operationalize) such community input in an effective and meaningful manner? Member of the audience asked whether anyone had any experience with CABs.

With respect to the question posed by a member of the audience – *“Does any member of the audience have first-hand experience with CABs?”*

- Mark Barnes volunteered his input based on experiences he has had in Zimbabwe. It was cautioned that CAB membership needs to be handled very diligently as you do not want to have a well-intentioned CAB subsumed by a special interest agenda. One must put ample forethought into the formation of a CAB – when done well the benefits can be enormous and can really engage community involvement (i.e., political, civic clubs (e.g., rotary clubs, etc.), mosques, churches, etc.). Also noted that CABs must receive adequate training so that they can readily help to identify ethics issues as well as help with media relations and squelching of rumors.

## **DAY 2 – JANUARY 20<sup>TH</sup>**

### **Welcome Back: Day 2 of the MRCT Summit Meeting**

Dr. Califf and Professor Solomon provided a welcome back to the participants. Dr. Califf encouraged participants to continue on in their work on the MRCT initiative. Professor Solomon noted that it was wonderful to witness the willingness to share permissible information amongst various organizations.

Dr. Walter Straus (Merck and Public Responsibility in Medicine and Research (PRIM&R)); and (ii) Dr. Freda Lewis-Hall, Chief Medical Officer of Pfizer Inc. joined the meeting on Day 2.

## I. Working Group 5 Report – Transparency of Contract Provisions

Professor Solomon introduced the co-chairs of Work Group 5: Mark Barnes and Kate Gallin Heffernan (KGH Advisors).

Work Group 5 had the following goals: (i) identify key provisions of global agreements (i.e., those that are contentious (delay negotiation/resolution) and those that raise ethical concerns), (ii) develop contract term options along a continuum for such key provisions; (iii) include information regarding known country-specific requirements/practices; (iv) develop a checklist/guidelines of important elements for all contracts; and (v) phase II: tackle other important contract provisions in order of priority.

To this end, Work Group 5 identified the following 5 key contract provisions: (i) publication rights; (ii) confidentiality/non-disclosure; (iii) fair benefits; (iv) compensation for injury (including insurance and indemnity provisions); and (v) privacy and data use/sharing.

Work Group 5 sought feedback from the panel/audience regarding the key contract provisions which they had identified, as well as the next steps proposed.

### Summary of Panel/Audience Feedback:

- Audience member suggested that Work Group 5 consider adding “dispute resolution” as a 6<sup>th</sup> key contract provision. Work Group 5 acknowledged that the addition of such a provision would be helpful to both small and large institutions.
- It was suggested that perhaps a provision on the use of CABs may be warranted.
- Suggestion made that Work Group 5 should further parse the issues associated with provisions dealing with publication rights.
- Dr. Califf suggested that we should consider banning confidentiality agreements (or at least limit such confidentiality to a reasonable/short period of time) in entirety for post proof-of-concept trials.
- Discussion on secondary use of tissues and samples was undertaken. *How does one effectively negotiate up front for secondary specimen use?* It was proposed that if we can achieve better transparency -- by helping subjects understand the intended secondary uses -- then it should be more acceptable (and possibly benefit “everyone”). Mark Barnes suggested that we are generally overly restrictive on such secondary uses, given the enormous scientific potential that secondary research offers. It was noted that there was published literature on this subject indicating that the general public is generally willing to authorize secondary research, with few or no limitations, once they understand the potential societal benefits. Dr. Lavery challenged the fact that broad secondary use benefits “everyone” – noting an example in which a resource constrained/economically deprived country had been sending flu samples to the WHO year after year, but never received flu vaccine in return.

## II. Discussion of Next Steps

Marc Wilenzick led the discussion regarding next steps for the MRCT initiative. Participants discussed the following areas, generally:

- *Finalization of the draft MRCT report (i.e., timing, endorsement, etc.); and*
- *Continuation of the MRCT Work Groups (i.e., continue/sunset, partner, etc.).*

There was unanimous support for the MRCT initiative to continue in some form. To the extent that the MRCT Work Groups can focus on a few quick “wins” (i.e., easily actionable proposals) that would be attractive, since such “wins” would add credibility and momentum to the overall effort.

Developing a pathway for investigator and CRO certification is something that is unlikely to happen without sponsor support, and the MRCT forum may be a way to develop that support. The audience also discussed the fact that adding an ethics section to protocols, as well as undertaking accreditation and certification is important. Participants were encouraged to keep things simple as we begin to implement – it was further suggested that we keep our work outside of the protocols as we do not want to get into situations where we need to amend protocols. We may also want to consider improving qualifications and certifications as some easy “wins.” It was suggested that we consider the opportunity to advance the MRCT’s initiatives at PRIM&R’s next conference (i.e., over 2500 attendees, with international research ethics being a major priority over the last ½ dozen years). Finally, it was suggested that MRCT participants consider a publication in a peer reviewed journal.

### **III. Work Group Reports from Breakout Sessions**

By way of background, the results from the straw poll were as follows:

- Work Group Proposals to Pursue on a Leadership Basis: (i) develop/validate/use a common site assessment tool; (ii) develop a sample model DMC Charter focused on multi-regional trials that is directed to studies conducted in the developing world; (iii) encourage accreditation of RECs; (iv) encourage investigator accreditation; (v) preferential placement of studies with PIs who have certification; (vi) establish a mechanism for sharing information about site and PI quality/performance; (vii) establish core competencies for monitors; and (viii) establish preferential use of CROs that offer certified monitors.
- Additional Work Group Proposals to Pursue on a Secondary Basis (positive voter response, but received less votes): (i) include an ethics section in/accompanying protocols, for certain trials; (ii) promote establishment of CABS; (iii) fund a study of the value of site/investigator certification programs; and (iv) support enhanced continuing education for RECs/REC members.

The foregoing results were utilized as the basis for discussion in the various Work Group Breakout Sessions. High-level reports from the various Work Group Breakout Sessions is as follows:

#### Work Group 1 (Enhancing Quality and Efficiency of Ethics Review):

- Work Group 1 focused its discussion on the accreditation of RECs since such proposal received “leadership status” in the straw poll. Work Group 1 decided a *different term for accreditation should be used*.
- Work Group 1 also believes that the final accreditation system needs to be international rather than based in the regulations of a single country.
- Work Group 1 also decided that possible next steps should include *defining the characteristics of a “good” REC*. In terms of next steps, Work Group 1 also wants to review AAHRPP and WHO standards to determine if either of these standards might provide guidance/direction. Work Group 1 was especially keen on understanding WHO standards. Work Group 1 also wants to further consider the notion of providing RECs with business and administrative training, teaching RECs how to fund and run their respective RECs as opposed to giving them grants for operations, filing cabinets, etc. (note: perhaps fees could be the source of funding). *Revised proposal: Create a comprehensive process for the accreditation and capacity development of RECs.*
- There was discussion in Work Group 1’s Breakout Session as to whether an ethics section should be included directly in the protocol given that if there is a change to the section after the protocol has been approved, and then the protocol would need to be amended.

#### Work Group 2 (Enhancing Data and Safety Monitoring):

- Work Group 2 believes, the straw poll notwithstanding, that an apprentice program to develop new DMC members is important to pursue. Work Group 2 spent a considerable amount of time discussing reasons why their proposals did not receive more support in the straw poll. They found it surprising that people were opposed to training potential members of DMCs. Specifically, they questioned whether the word “apprentice” (as opposed to mentoring) was offensive in some way.

#### Work Group 3 (Enhancing Site Selection & Investigator Team Expertise):

- Work Group 3 recommended that industry set standards for improved site selection, with deliverables to improve that process across the industry. They also recommended that the MRCT project include further work on accreditation – who funds, how do you build capacity, etc.

#### Work Group 4 (Enhancing the Professionalism of Monitors):

- Work Group 4 spent time discussing and clarifying what the role of the monitor should be, especially in resource constrained/economically deprived regions of the world.
- Work Group 4 also spent time refreshing its thinking regarding keeping additions to the protocol document at a minimum and using addendums and other docs instead. Work Group 4 noted that assessing the core competencies needed to run and monitor trials today (i.e., electronic collection of data as opposed to paper based) is important. List competencies and look at training available from various sponsors and institutions. Face-to-face training is too costly and, therefore, must look at alternative ways in which to conduct training. Emphasized the need for operational plans to be developed before study start.

#### Work Group 5 (Transparency of Contract Provisions):

- With respect to publication rights, there was discussion of authorship, and the need for a prior determination of authorship and of trying to ensure that local collaborators are involved so that they can receive appropriate credit in publications as authors and contributors.
- With respect to confidentiality/nondisclosure, there was discussion of the need for sites to be able to speak about their work on specific trials as a way to build capacity (by letting others know the good work undertaken by these sites) and to reflect principles of professional/academic freedom. Also discussed need to have any penalties for disclosure of such information to be more limited, so as not to chill routine discussions by investigators as to the kind of work they and their sites are doing – this especially relates to having reasonable time limits on any non-disclosure/CDAs.
- With respect to subject injury, there is a need for more clarity as to when treatment will be covered – either treatment as per local standards or a global standard of care in some cases (that otherwise might be unavailable to a patients in that area). Also, restrictions requiring that subjects comply with the protocol may be unreasonable since often it is the result of AEs, that patients are unable to comply with the protocol.
- With respect to privacy and data use, better standards are needed to communicate what is actually to be shared (a lot of times the language is overly broad) and sponsors need to be more sensitive to the potential for sharing of specimens to be seen as exploitive and/or pose the risk of community harm (i.e., sharing of specimens). An option presented for further discussion was the possibility of establishing a single IRB which would have responsibility for decisions, across a multi-regional trial, for issues about secondary use of tissues and samples.

#### **IV. Closing Comments**

Drs. Solomon & Califf provided words of thanks to all participants. Dr. Califf spoke briefly about funding issues for the MRCT initiative moving forward – where will such funding come from? It was graciously acknowledged that Pfizer has provided funding to date, but participants need to seriously consider where future funding might come from and whether other sponsors might also contribute to funding the collaboration. Professor Solomon took the opportunity to reiterate that funding issues are being reviewed with Pfizer and others and that perhaps funding might be pooled from MRCT participant organizations/companies and managed by an independent third party.

#### **V. Adjournment**

Justin McCarthy thanked the MRCT Summit Meeting participants and encouraged the participants to consider whether participants' organizations/companies might want to undertake some of the opportunities on an individual basis, while others might be things that the MRCT Project would need to develop further or which would need to involve other groups/stakeholders.

## **MRCT SUMMIT MEETING (JANUARY 2010): PARTICIPANT LIST:**

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