Proceedings

A Conference on Post-Trial Responsibilities: Ethics and Implementation

18th September 2014 ● 7:30 AM to 5:30 PM

Harvard Law School, Wasserstein Hall, Millstein East ● Cambridge, MA

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Executive Summary

The Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT) collaboratively with the Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School hosted a one-day open conference on post-trial responsibilities on September 18, 2014.[1]

The objectives of the conference were to discuss implications of international guidance on post-trial responsibilities for clinical research, to articulate and understand the range of perspectives on post-trial responsibilities, to draw lessons from successful and unsuccessful attempts to implement post-trial policies, and to discuss potential scenarios and practical solutions for post-trial responsibilities that may inform policy in this important area moving forward.

A welcome given by Mark Barnes from Ropes & Gray and Harvard MRCT introduced the potential scope of the post-trial access (PTA) issue and specified some of the open questions regarding PTA that will be addressed during the conference.

The first session introduced current ethical and regulatory approaches as well as key controversies. Christine Grady from the National Institutes of Health (NIH) spoke about the ethics of PTA, its history, models, agreements and controversies. Jeff Blackmer from the Canadian Medical Association and the World Medical Association spoke about the Declaration of Helsinki and how it applies to PTA. This presentation was followed by

[1] Video footage of all presentations is available on the Harvard MRCT and Petri-Flom Center websites, and live blogging from the first four conference sessions is posted on the Bill of Health blog on the Petri-Flom Center website: http://blogs.law.harvard.edu/billofhealth/2014/09/18/live-blogging-post-trial-responsibilities-conference-session-i/, http://blogs.law.harvard.edu/billofhealth/2014/09/18/live-blogging-post-trial-responsibilities-conference-session-2/, http://blogs.law.harvard.edu/billofhealth/2014/09/18/live-blogging-post-trial-responsibilities-conference-session-3/, http://blogs.law.harvard.edu/billofhealth/2014/09/18/live-blogging-post-trial-responsibilities-conference-session-4/

Alex John London from Carnegie Mellon University who discussed the Council for International Organizations of Medical Sciences' (CIOMS) approach to PTA, and Seema Shah from NIH who focused on policy approaches to post-trial obligations of different countries around the world.

The second session conveyed important perspectives from a range of stakeholders. Richard Klein from the Food and Drug Administration (FDA) talked about PTA from the perspective of the FDA, some of the current avenues available for PTA, and why some of the myths concerning PTA are overstated. Daniel Wang from the Queen Mary, University of London talked about governmental requirements related to PTA, and how PTA has evolved and changed specifically in Brazil, and what this case study can teach us about future PTA. This was followed by Jocelyn Ulrich from the Pharmaceutical Research and Manufacturers of America (PhRMA) who shared the industry perspective on PTA issues, stressing that PTA must be clarified in pre-trial agreements while access to market-approved drugs should be the responsibility of the state or healthcare system. Ramadhani Noor from the Harvard School of Public Health offered his experiences related to PTA from the perspective of an investigator working primarily in Africa, stressing the need for frameworks and guidance for developing countries. This was followed by Mitchell Warren from AVAC who shared the participant/community perspective with the example of HIV prevention trials in the early 2000 when participants demanded life-long provision of anti-retroviral therapy.

The third session included case studies that shared lessons learned on implementing post-trial responsibilities in order to better understand real world experiences. Joseph Millum from NIH spoke about NIH policies regarding PTA for

antiretroviral treatment. He focused on a case study in which various stakeholders developed a creative solution to ensure that participants received PTA. This was followed by Nancy Padian from the University of California at Berkeley whose case study was a Phase III effectiveness trial of the use of diaphragms for HIV prevention, which were found not to be effective. Walter Straus from Merck told the story of Indinavir, focusing on the practical considerations of providing PTA to an HIV/AIDS drug during the 1990s. Laurie Letvak from Novartis outlined general factors and options regarding PTA and described two cases: the Gleevec® trial for Chronic Myeloid Leukemia, in which some patients were placed in a roll-over study after Phase II, and a case of a drug that was studied for a different indication than it was approved.

The fourth session featured a panel discussion of a complex hypothetical scenario involving different aspects of PTA.

The fifth session provided a wrap up and potential next steps that may be the focus of a Harvard MRCT working group on Post Trial Access:

- Create an agreed upon ethical framework for PTA, including:
    - Who is responsible? For how long?
    - What are the various roles of different stakeholders?
    - What are obligations to participants and community?
    - Should placebo group be differentiated?
    - Does commercial availability satisfy obligations?
    - How to deal with regulatory delays?
    - How can sponsors enter the conversation?

    - How to ensure clarity and greater transparency among stakeholders about issues and complexities?

- Create processes/options (implementation tools) for:
    - Delivering efficacious agents in a cost-effective manner to developing countries
    - Planning stage (e.g. extension studies, negotiations with regulators etc.)
    - "Practical" interpretation for Declaration of Helsinki
    - Positive and negative consequences of new regulations/mandates
    - Successful models of partnerships between various stakeholders that can be replicated
    - Training and education materials for investigators, IRBs, sponsors, government, and participants
    - Pragmatic approaches to execute responsibilities and learn how to include communities as true partners

Meeting Summary

All speakers[2] declared that they were presenting their personal views, not the position of their respective organizations.

Welcome Remarks and The Potential Scope of the Post-Trial Access Issue

Mark Barnes from Ropes & Gray and Harvard MRCT: "Scope of Post-Trial Access Issues"

Mark Barnes began discussions by introducing the Petrie-Flom Center and the Multi-Regional Clinical Trials Center at Harvard (Harvard MRCT). He started by stating that the "mysterious" Paragraph 34 of the latest iteration of the Declaration of Helsinki (DOH) "cannot mean literally what it says:"

> *"In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process".*

Barnes then specified some of the open questions regarding post-trial access (PTA) that would be discussed during the conference:

- What period of time is required for providing PTA?
- Is there a difference in post-trial access for chronic disease compared to transient disease?

[2] Speakers reviewed their respective proceedings in this report, or had an opportunity to do so.

- Do we provide PTA to stabilize the patient/participant, or must we provide it through the entire episode of care?
- If there is a lifetime commitment to provide PTA, how do we account for the migration of persons, families, and populations?
- Is the obligation to the participant level, or is it to the population?
- If the obligation is only to the participant level, does it mean continued access to the experimental drug if it appears to show positive results for the individual?
- Must there be continued access if the experimental drug is successful on the population level?
- Does providing post-trial access only to the study participants exacerbate the health disparities present across the population?
- Can individuals who were on one arm of the study, demand PTA of the intervention provided to another arm?
- How is it possible for a sponsor to provide PTA if the drug is not developed further or is not approved for marketing?
- If the drug is approved for marketing, what right does the patient have to PTA? Is it the right to purchase at market price, a discounted price, cost of production, or at no-cost? Barnes provided the example of Gilead Sciences announcing that it will make its Hepatitis C medication available at cost of production in many developing countries such as India.
- Does PTA also include obligations to improve the infrastructure of the host country?

After stating the open questions, Barnes established the goals and expectations of the PTA Conference. He stressed that the goal of the conference was not to reach conclusions. Instead, the goal would be to clarify the problems with the current approaches to PTA, and clarify the arguments supporting, and those opposing, PTA mandates.

Session I: Setting the Stage

Christine Grady from the National Institutes of Health (NIH): "The Ethics of Post-Trial Responsibilities: History, Models, Agreements, and Controversies"

Grady spoke about the ethics of PTA, its history, models, agreements and controversies.

In terms of the history of PTA, Grady explained that most guidance until the 1990s was silent on what should happen at the end of the trial. In the 1990s, there was a large increase in international collaborative research by countries with many resources in countries with much fewer resources which created concerns about the exploitation of people in these communities. Further, commentary to guideline 15 in the 1993 Council for International Organizations of Medical Sciences (CIOMS) guidance states that sponsoring agencies should "ensure that, at the completion of successful testing, any product developed will be reasonably available to inhabitants of the underdeveloped community in which the research was carried out."

Grady then presented data from one NIH study on the opinion of participants, Institutional Review Board (IRB) members, and investigators regarding who should have access to the drug after the trial is completed. She said that the overwhelming majority of participants, IRB members, and investigators believed that every person in the world who needs the drug should have access to it, rather than participants in the study or the inhabitants of their community.

Next, Grady placed possible post-trial responsibilities into three categories: First, responsibilities to participants, such as compensation for injury, transition-care, and PTA. Second, responsibilities to the community, such as continued partnerships, infrastructure development, and access to products developed within that community. Third, responsibilities to society, such as access to and integration of the resulting knowledge of the trials. Grady also described the evolution of the language regarding PTA in various guidance documents, including the Declaration of Helsinki and CIOMS, and reports of the UK Nuffield Council and the US National Bioethics Advisory Committee. Language in these documents describing who has access to what and who is responsible for assuring it has changed since 2000. Early documents suggested that sponsors or others non specified were responsible for "assuring", "securing", or "providing" the "best proven identified by the study" or "shown to be beneficial". More recent guidance says that access to "interventions identified as beneficial" or "other appropriate care and benefits" should be "addressed", "described", or "provisions made" by the investigator, sponsor, and host government and reviewed by the IRB/REC.

Grady summarized areas of agreement and disagreement regarding PTA. One area of agreement is that investigators have some post-trial responsibilities to participants, which include planning in advance what will happen at the end of the trial, describing this plan to review committees and participants, informing participants about study outcomes, and honoring any commitments that were made. Most people also agree that people should continue to receive the treatment or care that they need. Finally, people agree that most investigators are trying their best to meet their responsibilities. Justifications offered by commentators in favor of post-trial access include: Minimize exploitation, meet the needs of participants and avoid harm, reciprocity, duty of rescue, global justice, researcher-participant relationship.

According to Grady, people disagree on who should be responsible for post-trial access. They also disagree on the scope and limits of investigator and sponsor post-trial responsibilities. Importantly, many disagree on the underlying justifications for the responsibility. Arguments offered by commentators against post-trial access include: Research is not healthcare, researchers and sponsors are not in a position to provide such care, costs and logistical complexity, undue influence and therapeutic misconception, and giving priority to research participants may disadvantage others.

Grady summarized unsettled areas, including what counts as reasonable plan or effort, how circumstances should be considered in assessing the reasonableness of the plan, the scope and limits of responsibilities investigators/sponsors have and how these compare to the responsibilities of others, and how the researcher/sponsor should understand and divide post-trial responsibilities. Grady concluded that an earnest effort

should be made to find ways for participants who need care and treatment at the end of the clinical trial to receive it.

Jeff Blackmer from the Canadian Medical Association and the World Medical Association (WMA): "WMA Declaration of Helsinki, Process and Perspectives"

Blackmer spoke about the Declaration of Helsinki and how it applies to PTA. He was intimately involved in the recent revisions if the Declaration of Helsinki.

Blackmer began by describing the history and background of the WMA and the Declaration of Helsinki. The WMA was founded in 1947 and is an international organization that represents the physicians of the world. Physicians created the WMA "to ensure the independence of physicians, and to work for the highest possible standards of ethical behavior and care by physicians." After three years of debate, the first Declaration of Helsinki (DoH) was adopted by the 18th WMA in 1964. The DoH has been amended seven times since 1964, most recently in 2013. There have also been two notes of clarification. Since 2000, revisions have included a public discussion and consultation process.

The first reference to PTA was in the 2000 revision. This was primarily a result of the HIV trials in Africa. It was also a result of general agreement that the principles of justice were applicable to research ethics and bioethics more broadly. The language of paragraph 30 in 2000: "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study."

Paragraph 30 led to significant negative feedback from industry, the FDA and CIOMS, leading to the 2004 note of clarification. The WMA added a note of clarification in 2004. According to Blackmer, the DoH moved from a "should be" mandate to a "describe" mandate.

In the 2008 revision of the DoH, Paragraph 14 stated that the research protocol "should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits." In addition, Paragraph 33 stated that "patients 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 to the study or to other appropriate care or benefits.

In 2013, the WMA revised the DOH again. The final version of such revisions included reference to PTA in both Paragraph 22 and Paragraph 34. Paragraph 22 stated that the research protocol "must also describe appropriate arrangements for post-trial provisions." Paragraph 34, which is under the heading "Post-Trial Provisions," states that:

> *"In advance of the clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed during the informed consent process."*

Blackmer remarked that this language is in some ways a full-circle return to the 2000 mandate. He also stated that it is important to remember that the DoH may never be in a position to address and clarify all of the complex details around PTA because the DoH is intended as a declaration of ethical principles.

Alex John London from Carnegie Mellon University: "The Council for International Organizations of Medical Sciences (CIOMS) Approach"

London discussed the Council for International Organizations of Medical Sciences (CIOMS) approach to post-trial access. He focused on the 2002 CIOMS guidelines.

London began by describing the origins of the CIOMS guidelines. The goal of the guidelines, which were first released in 1982 in cooperation with the World Health Organization, was to indicate how the ethical principles set forth in the DoH, "could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements."

London then proceeded to analyze Guideline 10, the section of the CIOMS guidelines that pertains to PTA. He prefaced this analysis by stating that it is important to keep in mind throughout his presentation that the preamble of the guidelines states that the document must be read a whole. Guideline 10 of the CIOMS guidelines states:

> *"the investigator must make every effort to ensure that the research is responsive to the health needs and the priorities of the population or the community in which it is to be carried out; and any intervention or product*

developed or knowledge generated, will be made reasonable available for the benefit of that population or community."

London stated that CIOMS' rationale for this language was concern about the ability of low-income countries to "close the arc of translation" by transforming knowledge into clinical outcomes.

Next, London focused upon which "objects of post-trial concern" the CIOMS guidance focused. He stated that the first object of concern is whether the new knowledge is relevant to the health needs of the study population. When the only goal of the study is to gather new knowledge and not the direct development of a commercial product, it must be assured that the study population gains the benefits of such knowledge. According to London, other objects of concern include development of health care infrastructure, vindicated interventions to study subjects who benefit from the investigational drug, compensation for harm, supporting health services, and research-related capacity building.

London then talked about possible recipients of the objects of post-trial concern. First, he considered host countries and host communities. According to London, both may be able to receive new knowledge and improved infrastructure (including improved capacity for research-related activities). Second, he focused on study participants, who may receive vindicated modalities (from study conclusion to approval). Participants may also benefit from the new knowledge found by the trial.

London noted that the CIOMS guidance requires that sponsors and researchers have the duty to make sure that the above obligations are taken care of. They do not have to necessarily be the only entities to have the responsibility to provide it. Therefore, sponsors and researchers may negotiate with health ministries, local authorities, and other entities to ensure that post-trial obligations are met.

London concluded that, under the CIOMS guidance, limits should be made clear in pre-trial planning. This planning may alter the countries in which the sponsor may choose to conduct the trial, because certain countries may have better infrastructure to provide the post-trial intervention. London also stated that CIOMS views most post-trial responsibilities as "transitional." In other words, the sponsor's post-trial responsibilities end when the product is reasonable available.

Seema Shah from NIH: "Post-trial Obligations: Policy Approaches Around the Globe"

Seema Shah focused on policy approaches to post-trial obligations of different countries around the world.

Shah placed the individual regulations of various countries into five categories from most stringent to least stringent: "provide," ensure," "refer," "describe," and being "silent" on post-trial access. Shah was unable to find any countries that required that the researcher to "provide" post-trial access even if the subjects had alternative avenues to receiving the care. Shah placed Brazil, Canada, Nepal, Japan, and Cameroon within the "ensure" category. She found that the Philippines' guidelines stated that the researcher

should "refer" the participants to entities that could provide post-trial care. Shah learned that India, the Council of Europe, New Zealand, Nigeria, South Africa, and Australia all require that sponsors "describe" post-trial access plans in the protocol. The United States is silent on the issue.

Shah also found caveats within individual country's regulations. In Canada, obligations depended on the phase of the research and whether the treatment is beneficial and safe. In Japan, the regulations required that the sponsor or investigator "make an effort to ensure" post-trial access. In Nepal, post-trial obligations depended on the nature of the disease, trial and intervention. In Brazil, in order to vindicate their right to post-trial access, the subject must demonstrate superiority over the standard treatment. In India, "indirect community benefit may suffice" for post-trial obligations. Shah found that Canada, Nigeria, New Zealand, South Africa, and the Council of Europe all require that post-trial access plans distribute information and research results to participants and communities. Rwanda requires that study results be published in a Rwandan journal.

Next, Shah presented the policies regarding post-trial access of various funders of researchers. The U.K. Wellcome Trust has stated that funding post-trial provisions is outside their remit to support research. However, it says that it will consider post-trial provisions when deciding whether to award grants. The French Agence Nationale de Recherche sur le Side et le Hepatites Virales (ANRS) restricts HIV prevention research to areas where public ART programs exist. Shah believed that this was presumably to ensure post-trial access. The NIH encourages sponsors and investigators to work with host countries and stakeholders to identify available sources of ART. Shah voiced

concern about whether policies limiting funding to countries with sufficient infrastructure to provide PTA might divert important resources from countries that are already the worst-off.

Shah found some similarities between the individual countries' regulations and ethical guidance such as CIOMS and DoH: There was no clear consensus; there was some agreement that it was important to plan in advance and inform trial participants of the post-trial plan, and that PTA should only be provided if the intervention is beneficial.

Shah also found some differences between the regulations and ethical guidance: No regulations seem to require provision, while some of the guidelines do; and the ethics guidance documents seem to be more stringent, but they also seem to recognize a greater number of stakeholders.

Shah ended by citing two empirical studies. The first study looked at how the NIH Guidance document was implemented in the two years after it was passed. The second study examined trials on clinicaltrials.gov. The studies showed that although almost all protocols and sponsors addressed post-trial obligations, most plans focused on referral. A few provided free therapy for the short term, including up to commercial availability. Shah concluded by stating that more empirical data need to be collected.

Panel Discussion with Grady, Blackmer, London, and Shah. Moderated by I. Glenn Cohen.

Cohen began by asking the panel what they felt was the biggest mistake made in developing policies related to post-trial access. One member of the panel stated that one

of the biggest mistakes was the DoH making a really strong statement about post-trial access that did not reflect the nuances of implementing such a mandate. Another felt that the biggest mistake was that the 2004 clarification did not actually clarify anything, while also significantly weakening what should have been attempted initially. A third member believed that there should have been greater distinctions between what is owed to populations and what is owed to participants. The final member stated that the failure to provide early on a mandate requiring at least "best effort" led to greater institutional inertia. This had made it even harder to implement post-trial access policies today.

A member of the audience asked about the silence of the United States. The individual also stated that she was baffled by the lack of guidance for IRBs on post-trial access. The panel responded that the NVAC had said something about post-trial obligations. Also, it stated that the failure of the United States to fully comment on PTA might reflect the domestic population feeling satisfied with its own post-trial access. The panel agreed that greater training should be provided to IRBs on post-trial access. One panelist stated that there were three models between sponsors and participants: First, a commercial relationship in which each party gets what it wants. Second, a market model, in which there is a division of labor to create a global market for drugs and the market determines who gets the drugs. Third, a partners-in-inquiry relationship in which both parties buy into post-trial access because it improves public health generally. Another panelist added a fourth "human relationship" model, in which the research participant is joining the research to get treatment.

Another member of the audience commented about the possibility of a third-party such as the G7 providing post-trial access. This individual also asked whether the ethics of post-trial access might be rooted in some special relationship formed between the researcher and subject that created obligations beyond the initial interaction (for example, research subjects may be transformed into "co-owners" of the product).

A third member of the audience asked how PTA applied to healthcare delivery research. The panel answered that the CIOMS guidance referenced this type of research and explained how the PTA obligation in such a study might be to ensure that the knowledge gained would be accessible to the study population. The panel agreed that the United States should have better PTA programs.

A fourth member of the audience asked whether there were disparities in access created by the fact that only certain portions of the population would be eligible to enroll in a trial in the first place. This member also asked why ethical guidance documents did not mandate that trials only be conducted in countries that have the infrastructure necessary to support PTA. The panel responded that for some countries, the only opportunity to improve the infrastructure was through the clinical trial process.

Finally, Cohen asked whether benefits provided to participants would have to be "in-kind" benefits such as provision of the intervention or whether sponsors could meet their obligations by providing other benefits. One member of the panel responded that research was a unique good, and that participants were owed an "in-kind" benefit such as health care infrastructure. Allowing sponsors to meet their obligation through the

provision of other benefits, such as money, could lead to unacceptable disparities in knowledge and access for certain populations compared to others.

Session II: Important Perspectives

Richard Klein from the Food and Drug Administration (FDA): "Post-Trial Responsibilities"

Klein talked about PTA from the perspective of the FDA, some of the current avenues available for PTA, and why some of the myths concerning PTA are overstated.

Klein shared the FDA perspective about post-trial responsibilities. He started with highlighting the call for PTA in the Declaration of Helsinki. Klein argued that there was a justice issue with ensuring access to health care and modern interventions. He pointed out that while the FDA can encourage PTA, and allow an investigational new drug or device exception if there is significant data indicating effectiveness, the FDA has no authority to require or ensure it, as there are currently no FDA requirements related to PTA. For foreign trials, however, the FDA has limited jurisdiction over protocol applications that are submitted in the US, but PTA must be addressed by foreign regulatory agencies. Klein highlighted some specific considerations for protocol drafters and IRBs: particularly focusing on determining monitoring plans, figuring out financial responsibilities for the provision of PTA, and involving IRBs and the FDA if there are any changes or new data that emerge.

Klein noted that there was more of a moral obligation than a legal obligation, and PTA should be clarified in the informed consent document. The FDA was supportive of the provision of PTA, but has no guidance document related to PTA, and he argued that enthusiasm must be tempered as there are situations when PTA was not appropriate. He cautioned against putting too much weight on one specific trial, as data must be significant to indicate real benefit. Klein highlighted that studies that have significant safety concerns, studies of bio-markers, and potentially validation studies that do not specifically examine safety and effectiveness, might not be appropriate studies for PTA provision. There were also situations where PTA was simply not feasible, particularly if additional drugs did not exist, if additional supply was not available, if there was insufficient safety data, or if there was no practical capacity or resources to provide safety monitoring. We must be aware of financial limitations as well, especially for start-up biotech firms that might not have the resources to provide PTA.

He then discussed expanded access, also known as compassionate use, which allowed sponsors to make promising medical products available for use outside of the clinical trial once it has ended. There were requirements for when expanded use was appropriate, such as when the condition was serious or life threatening, when there was no satisfactory alternative therapy, when potential risks did not outweigh potential benefits, and when providing access was financially feasible. He briefly commented on how the FDA made this risk/benefit decision, highlighting that the risk must not be unreasonably high.

Klein ended by dispelling a few common myths that were seen as delaying PTA. Klein argued that the application process was not burdensome or too time consuming, nor was it too complicated. He argued that there were few data supporting the idea that PTA seriously interferes with marketing the drug after the trial is over. He also pointed out that the FDA approved the vast majority of requests for expanded access to study drugs, meaning the agency was not the barrier to providing PTA as it was sometimes portrayed.

Daniel Wang, from the Queen Mary, University of London: "Pharmaceutical Companies v. the State: who is responsible for post-trial provision of drugs in Brazil?"

Wang discussed the legal requirements related to PTA, and how PTA had evolved and changed specifically in Brazil, and what this case study could teach us about future PTA.

He presented in-depth information about the unique case of Brazil, highlighting that PTA had been greatly influenced by the legally enforceable right to PTA in Brazil, regulated by a Resolution of the National Health Council. The National Health Council established that sponsors were considered to be legally required to provide unlimited PTA. Wang pointed out that this resolution was not directly in line with the Declaration of Helsinki (DOH) particularly Principle 30 of the DOH, meaning that Brazil was truly a unique case in discussing PTA.

On the other hand Brazilian courts had also been recognizing a duty for the State to provide PTA, in reliance on the constitutional right to health enshrined in the Federal

Constitution. Therefore, in Brazil both the sponsor and the State could be legally required to provide PTA.

Wang methodically analyzed several important court cases that had set the scene for PTA in Brazil. In one case, a patient responding well to treatment had the treatment removed after the trial, and subsequently sued the sponsor. The patient won the case, with the court deciding that the sponsor was liable to continue providing treatment, as long as it was beneficial for the patient. Another case saw the government impleading the pharmaceutical company, after a trial subject sued the state to force the Ministry of Health to provide PTA. Finally, there was a case where the state of Sao Paulo sued three pharmaceutical companies for encouraging participants to sue the Ministry of Health to provide PTA. The state argued that the companies were trying to encourage participants to demand PTA from the state, when they should have been demanding PTA from the sponsors instead. Wang pointed out that these cases were still ongoing, and it was still unclear who would win. There was, however, a feeling that participants would often win in any legal claim for PTA, especially if they sued the sponsor.

Wang pointed out that these decisions had begun a legal battle in Brazil, with the government and sponsors fighting over which group should be responsible for the provision of PTA. This had led to "passing the parcel," with participants suffering the consequences of others trying to pass blame, rather than work towards real solutions. This also meant that participants were incentivized to litigate, because absent a clear decision from a court, the government and the sponsors each tried to shift the burden to the other party.

Wang ended by highlighting that too many legal protections could actually harm patients in Brazil. There was currently uncertainty about who should provide PTA, which could cause companies to pull out of testing in Brazil. He warned that PTA provision by the state could pit legitimate public health concerns against questions of cost-effectiveness and the desire to spur pharmaceutical innovation. He warned that the situation as it stands could cause a research drain out of Brazil, with sponsors preferring to go to countries where PTA is less likely to be enforced. While he had not seen data to this effect yet, it was something to be aware of, and there was anecdotal evidence that supported this concern.

Jocelyn Ulrich, from Pharmaceutical Research and Manufacturers of America (PhRMA): "Post-Trial Responsibilities Conference: Ethics and Implementation"

Ulrich shared the industry perspective on PTA issues, stressing that PTA must be clarified in a pre-trial agreement, while access to market approved drugs should be the responsibility of the state or healthcare system.

Ulrich started with a reminder that not all drugs tested ended with approval, and that the process was complex and time consuming. Developing a new medicine takes an average of 10 to 15 years. Furthermore, the cost of approval could be very expensive, meaning sponsors had to make difficult decisions about which drugs to develop and which ones to shelve. Ulrich stressed that PTA was a pressing, timely issue, especially with the expansion of multi-regional clinical trials.

Ulrich highlighted that biopharmaceutical companies were committed to providing ethical research, and acknowledged the value and importance of principles set forth in the Declaration of Helsinki. She pointed out that PhRMA recognized the value of clearly defining what constitutes PTA, especially because there was limited clarity in current guidelines. This extended to questions of who should provide PTA, who should receive PTA, and when obligations expire.

Ulrich went on to discuss sponsor's current role in providing PTA. Sponsors could offer PTA in life threatening conditions, when there were no alternative therapies available. She stated that the best available evidence must guide this, and PTA must be clarified and provided for in the clinical trial protocol, so that it could be discussed and modified pre-trial. By establishing expectations upfront, provisions could be made for circumstances where the sponsor may find that the risk was too great, decided to halt production of the drug, or if other factors arose that complicated the provision of PTA. If any changes had to be made to any commitment to provide PTA, it was essential that the sponsor was open and communicative about these changes, so that participant expectations could be clarified.

Ulrich was clear that access to pharmaceuticals that have received market approval must be provided by the state, or through another healthcare provider, but was not the responsibility of the sponsor unless previously agreed upon.

Ulrich concluded that biopharmaceutical companies conduct clinical research globally and PhRMA members place a great importance on respecting and protecting the safety of research participants. Furthermore, plans for post-trial access, including

discontinuation, should be guided by a documented pre-trial agreement on a case-by-case basis, in consultation with all relevant stakeholders. Finally, access to approved medications should be the responsibility of the government agency or other applicable payers through their health systems.

Ramadhani Noor from Harvard School of Public Health: "Post-Trial Responsibilities Conference: Ethics and Implementation"

Noor offered his experiences related to Post-Trial Access from the perspective of an investigator working primarily in Africa.

He argued that everyone understood that letting helpful products sit on shelves would not help people. He said the major questions from an investigator's perspective were to determine when PTA begins, what the role is of the investigator in providing PTA, and how long the obligation extends.

Noor argued that investigators needed guidance about PTA, as they could not make provisions on their own for such a complex and extensive undertaking. With examples from Africa, experience showed that PTA could not be provided in a vacuum, and some believed that it must coincide with changes to local healthcare systems, as well as improvements in the standard of care. Noor agreed that provisions should be made early, and should be detailed in the clinical trial protocol.

Noor posited that clinical trial guidelines had not taken an active enough role in addressing PTA. He argued that the Declaration of Helsinki was supportive but not specific enough in addressing PTA. The lack of US guidelines was particularly

problematic, especially for HIV/AIDS research. This had resulted in investigators having to take action themselves to support PTA. Furthermore, the problem was particularly striking in countries with less developed infrastructure. Noor pointed out that there was a lack of legal frameworks in place that could help provide guidance on the issue of access to research or new products, including PTA, as developing countries do not have regulations related to extended or compassionate use. He used the example of Ebola, and the problems related to access to research drugs for Africans, to illustrate this point. The lack of frameworks made it difficult to adopt and scale PTA programs, meaning that even if PTA was planned, it could be hard to follow through.

He used the example of vaccines for Hepatitis B, which took many years to reach developing countries, even though these countries arguably needed the treatment the most. Noor reminded the audience that this was not simply an issue concerning PTA. He pointed out that evidence to support plans for PTA must be generated in parallel with product development, so that PTA could be provided timely in a responsible and effective way. Noor told the audience that investigators were thrust into a difficult position if they had to fight for the provision of PTA, as provision was really a policy decision, with national governments being central, especially when it was related to introducing new "products" into markets.

Noor ended with the case study of developing a vaccine for malaria. He pointed out that this was a unique case, where philanthropy, international pharmaceutical industry, the World Health Organization, national governments, global financing alliances and NGOs had worked together, to make sure that the leading malaria vaccine

once approved was distributed to those who need it the most. He showed a flowchart of decision making processes for Malaria vaccine, which highlighted the importance of creating new partnerships so that the issues of PTA can be inclusively addressed.

Noor summarized that legal frameworks and mechanisms for expanded drug access needed to be developed for developing countries' regulatory authorities; evidence to support decision making plans for PTA should be generated in parallel with product development, and partnerships are needed between investigators, sponsors, funders, philanthropy, governments, and global development agencies. Leaving this responsibility to industry and investigators alone potentially caused delays in PTA.

Mitchell Warren, from AVAC: "Post-Trial Access: An Advocate's Perspective"

Warren shared the participant/community perspective. He started by discussing AVAC, an HIV prevention research advocacy organization.

Warren stated that PTA had been crucial in combating HIV/AIDS, because management of HIV required a life-long effort. Not only did it require innovation in therapies, but it required a commitment to develop a mechanism to allow any therapy to be effectively disturbed. Warren pointed out that an important facet of PTA involved the translation of a successful clinical trial into a long-term public health improvement.

Warren told the story of an HIV prevention trial in 2004 in which participants demanded life-long provision of ART therapy if they became infected during the trial. In 2004, nobody was providing lifelong PTA, which led to a debate over who should be provided with PTA, as researchers wondered whether obligations extended to family

members or significant others. There was also a question about how long PTA obligations extended, and whether they might last for a patient's entire life.

Warren switched to focus on the Good Participatory Practice (GPP) Guidelines developed by AVAC and UNAIDS, and what these guidelines said about PTA. While there were guidelines for a number of diseases and conditions, Warren focused on HIV research guidelines. These guidelines were created in response to the 2004 controversies, and were intended to help prevent misunderstanding and miscommunication among research stakeholders. The guidelines helped define exactly who stakeholders were in any research undertaking. The final part of the guidelines related to PTA. The guidelines helped define what PTA is, how long obligations extend, and who the relevant stakeholders are. Warren argued that PTA was really about defining expectations; and that it was important to negotiate PTA upfront, so that expectations could be set and met appropriately. This involved not only planning for PTA, but also developing a clear strategy and funding mechanism to ensure access. Warren pointed out that obligations could not be nebulous, and could not extend indefinitely. Furthermore, the burden of PTA could not be placed solely on researchers. Indeed, all parties must play a role in defining PTA.

Warren concluded by discussing "research to roll-out" and how PTA could be incorporated into the process of clinical trials. He placed PTA at the end of the trial, but also, crucially, at the beginning, as this was the time that PTA must be planned for, and expectations must be set. He argued that an essential part of planning for PTA was planning for the rollout and delivery of PTA, which could often be the most complicated

part, especially in a resource poor setting with a low standard of care or poor medical infrastructure. Pointing to the experience of Oral PrEP in Peru, Warren highlighted a case where there was clinical trial success, but the therapy was not approved for marketing after the trial concluded. This was not because of a lack of application by the sponsor, but due to a delay by the regulatory agency. In a situation like this, the sponsor could do little to speed the regulatory process, and, on the flip side, regulatory agencies may have had little incentive to rush approval of a pharmaceutical to market, especially if there was only a small community that may benefit. Such situations complicated the provision of PTA, highlighting how difficult this issue could be.

Warren ended with a reminder that this issue was essential in building trust and support of the clinical trial process, and if sponsors did not figure out answers related to the complex problems of PTA, confidence and support of the research process may begin to erode.

Panel Discussion with Klein, Wang, Ulrich, Noor, and Warren. Moderated by Barbara Bierer.

The first question was related to whether PTA should be provided for life long conditions, or just for acute conditions. Panelists responded that PTA really had to be provided in a case-by-case basis, and that no broad generalizations were appropriate. This led to questions about how to properly value the benefits of research. A panelist stressed the need for more data regarding any potential research drain as a result of demands for PTA.

Next, the panel was asked whether individuals could realize the benefits of therapies even if they were not available immediately to the population. This led to a discussion of therapies that may have not been instantly available in countries where they were tested, but panelists agreed that helpful drugs did find ways to become available, even if it took a few years. This meant the question was more complex than simply whether a specific therapy was tested within a country.

Panelists expressed broad agreement that companies should seek market approval for therapy in any country that hosted those clinical trials, with some panelists even arguing that this should be a prerequisite for conducting a clinical trial. A panelist was asked whether to visibly incorporate the Declaration of Helsinki into all clinical trial protocols. The panel felt that the most important aspect was transparency and communication, especially in the initial phase of clinical trial protocols, so as to set and manage expectations. They pointed out that the provision of PTA in a country changes depending on what kind of sponsor is running the clinical trial, especially for investigator run trials. The panel was asked how typical the case of Brazil is in respect to PTA, and a panelist responded that the Brazilian case was actually atypical. The panelist also informed the audience that the ruling specifies PTA must be provided for sponsor-funded studies, implying that an investigator-initiated study would not require PTA.

The moderator asked whether investigators should not participate in a trial unless there was PTA. In response, panelists pointed out that this might be too dramatic a step. They focused on the fact that PTA must be combined with improving health services research to ensure proper delivery. This led to debate around the question of how strongly investigators should push for the provision of PTA. Some felt that investigators should

work to ensure that PTA is provided in the protocol, while others felt an investigator should go farther.

The panel ended with questions about what happens in the period before market approval, and how we could prepare steps to allow quicker marketing approval, as well as mechanisms to allow for faster manufacturing in the event that a biologic showed important and dramatic efficacy. Panelists all agreed that clearer plans, specifically clearer product delivery plans would be preferable, and would help with the rollout of PTA. When asked about off label use of drugs provided in PTA, there was agreement that doctors and prescribers should be allowed to use their best clinical judgment.

Session III: Lessons Learned - Case Studies on Implementing Post-Trial Responsibilities

Joseph Millum from NIH: "Case Study: NIH Guidance on Post-trial Access to Antiretroviral Treatment"

Millum spoke about NIH policies regarding PTA to Antiretroviral Treatment. He focused on a case study in which various stakeholders developed a creative solution to ensure that participants received PTA.

Millum began by stating the scope of the NIH guidance on post-trial access: it only applies to the provision of antiretroviral treatment following HIV antiretroviral treatment trials funded by the NIH and conducted in developing countries. The NIH states that funding "priority may be given to sites where sources are identified for the provision of antiretroviral treatment following the completion of the trial." The main justification for this policy is that without such a guarantee there would be a greater

likelihood that participants would not receive antiretroviral treatment after the trial at all, ending the benefits of the treatment received during the trial and affecting their ability to use certain antiretroviral drugs in the future. Millum believed that this justification might reflect a duty of "nonmaleficence." Millum clarified that the NIH is not statutorily authorized to provide funding for treatment. This explains why sponsors must look elsewhere for funding. Millum noted that the limited jurisdiction of the NIH does not prevent the United States generally from providing PTA.

His case study highlighted a trial conducted in low- and middle-income countries in which subjects who were no longer responding to first and second line antiretroviral drugs, were assigned to a third-line regimen on the basis of an algorithm based on HIV genotyping (instead of individualized third-line therapy). However, some of the therapeutic agents being evaluated were not available outside the trial in host countries, and many of the trial participants were expected to complete the trial still in need of these life-saving drugs. Millum described the two-part solution that addressed the issue of post-trial access. The first step was negotiating with the manufacturers to provide the antiretroviral drugs free of charge for two years after study participation, which was considered enough time for the licensing authorities of the study countries to approve the drugs. The second step was recognizing that the only way that subjects could receive the drugs at the study sites was if they were enrolled in research. Therefore, researchers added a third step to the study, which gave participants the option of staying in the study for an additional 96 weeks.

Millum concluded with five points that made this trial ethically interesting in the light of the broader discussion about post-trial access. First, there is an on-going debate

about who is responsible for PTA. Here, it required collaboration between multiple parties. Second, there is the question of how long PTA must be provided. In this example, it was for two years, but is that sufficient? Third, post-trial access is often conceptualized as access to drugs. Here, optimal post-trial care required more than just the antiretrovirals. Fourth, in this case PTA was not provided *post-trial*, but instead through incorporation into a new trial. Is this preferable? And does such a method of providing PTA lead to further obligations? Fifth, it was unclear how far the NIH guidance guided the investigators to reach their solution. The risk is that more directive guidance might rule out solutions such as the one applied in this case.

Nancy Padian from the University of California (UC) Berkeley: "Post-trial responsibilities conference"

Padian's case study was a Phase III effectiveness trial of the use of diaphragms for HIV prevention. In the trial, all women were fitted with and practiced using the diaphragm before being randomized. Women in the control group were promised a diaphragm if it was found to be effective. The study found the diaphragm intervention not to be effective.

One issue that the investigators failed to consider was the impact of the study's rolling recruitment on post-trial access. Rolling recruitment meant that some women exited the trial before results were final. These women wanted to keep their diaphragms, even though the intervention had not been shown to be effective. Padian and her team's solution was to provide additional counseling to the women, explaining that they did not know the efficacy. The women had to complete a post-test after receiving the counseling

to ensure that they understood that the diaphragms were not effective. Only after passing such a test were the women allowed to decide whether they wanted to keep their diaphragm.

Next, Padian described how the diaphragm trial raised interesting questions about how the availability of PTA might impact the design of the study. In the diaphragm trial, both arms of the trial received risk reduction services that exceeded the local standard of care, such as counseling and condom provision. According to Padian, the problem with providing the control group with care above and beyond the status quo in their country was that such provision would reduce the ability of the trial to measure the effectiveness of the intervention within the country's population as a whole. Instead of asking "whether diaphragms are effective given local standard of practice" the study was in reality asking "are diaphragms effective over and above a comprehensive prevention practice that probably cannot be sustained after the study is over."

Padian explained why she had nonetheless decided to provide the control group with the additional resources. First, it was because she "felt responsible for the care of every person in the study." Second, she believed that such provision motivated control participants to enroll and be retained in the trial. Third, IRBs were happier with this approach. Finally, it allowed attribution to a very specific intervention.

Citing a paper written by Alex John London, Padian then explained reasons why one may not want to provide the control group with the Global Best Standard. First, if it could not be attained and sustained by the host community, the research may not be relevant to the institutions or practices of the host community and may create problems of continuity of care and prevention post-trial. Second, as stated above, provision of the

"Global Best Standard" would alter the primary study objective. Therefore, according to Padian, it might be best to provide the control group with the highest attainable and sustainable standard.

Padian ended her presentation by talking about the infrastructure improvements created by her team. The team built new clinics and provided many vehicles. They also trained a large staff, many of who worked for other trials within the country. However, such improvements were not absorbed by the host governments, creating pressure for the investigators to conduct another trial using the same infrastructure.

Walter Straus from Merck: "Post trial access: A case study"

Straus told the story of Indinavir (known as Crixivan™), focusing on the practical considerations of providing post-trial access during the 1990s.

Straus explained that by the early 1990s, HIV/AIDS had been recognized as perhaps the major global public health issue of our time, but that there were no drugs that provided robust and durable responses to HIV infection. Early HIV/AIDS treatment strategies focused on the control and prevention and opportunistic infections due to HIV; HIV-specific therapies were hampered by the rapid emergence of resistance.

Indinavir was developed in less than six years – an exceptionally rapid time-frame. Straus stated that one goal of sharing this history is to illustrate some uncertainties associated with drug development, only some of which can be anticipated. For example, one of the company's senior biochemists, and the driving force for the protease inhibitor program (leading to development of Indinavir), was tragically killed in the bombing of Pan Am flight 103 over Lockerbie, Scotland. Straus also described the unprecedented

complexity of first synthesizing and then scaling up manufacturing of Indinavir in the setting of a clinical research program that was so rapidly progressing. The molecule was the most complex that the company had ever developed, and very large therapeutic dosages were required. This led to challenges both at the level of pilot plant production as well as the subsequent manufacturing plant. The pilot plants, which provide generally small quantities of investigational drugs for clinical research (and which plants are shared across the company), were all diverted to production of Indinavir, while the dedicated manufacturing facility was being constructed as rapidly as possible. These decisions were largely made based on the recognition of the extraordinary importance of developing a breakthrough treatment for HIV/AIDS, and would not have been realistic without the active encouragement of AIDS activist organizations as well as by the commitment of the FDA to spur development of safe and effective novel drugs for HIV/AIDS.

Straus stated that Merck conducted late-stage clinical trials on Indinavir in the US, Europe, Australia, and Brazil. PTA was provided to all participants in each of these trials. The company did not have prior experience conducting clinical research in Brazil. Since several Brazilian study sites did not have the necessary laboratory equipment to run specific assays required by the protocol, the company provided equipment and training. At the time, the company did not have a formal PTA policy and developed the approach for Indinavir based upon local considerations. Furthermore, Merck decided to provide the study drugs to participants for up to five years. This interval was selected based upon the company's expectation that the drug would have been both licensed and generally accessible in this period. The company decided to conduct the PTA program as an extension of the clinical trial. Although doing so was more resource intensive than other

possible mechanisms, it also provided the highest level of assurance of complete safety and efficacy data collection.

Straus concluded by providing his observations on PTA gained from the Indinavir experience. This case showed that PTA program considerations varied by country, and that conducting a PTA program within a study setting provided assurance that safety data would be reliably captured. Furthermore, multi-stakeholder involvement was critical to successful PTA design and implementation. Prioritization of this program within the company led to the effective allocation of research and manufacturing resources, which were also necessary for the program's success.

At the time of introduction of Indinavir, the World Health Organization had not issued guidelines for the primary treatment of HIV/AIDS. When the International AIDS Society issued its own recommendations for the design and conduct of PTA programs (2003), it incorporated many of the features that had been used in the Indinavir program. It recommended preferentially conducting clinical trials in countries with established national treatment programs (so that licensed drugs could effectively be considered for introduction and practical use in country), and that PTA programs be continued for two or more years (to assure equity and continuity of care).

The Indinavir experience illustrated practical challenges in developing a novel therapeutic drug to address a major public health problem: that multi-stakeholder involvement was essential for drug development, and how a PTA program was successfully designed and implemented in a developing country setting.

Laurie Letvak from Novartis: "Lessons Learned, Industry Case #2"

Letvak began by providing general factors important to consider regarding PTA. Factors included whether the drug was currently being marketed for any indication and whether the drug had been marketed for the same indication that was being studied or for another indication. Letvak noted that PTA was much easier if the drug had been marketed for the same indication that was being studied. PTA was more difficult if the study was for an off-label indication as there may be challenges for reimbursement if the drug was prescribed or drug supply may be limited. If the drug had not yet been approved/ marketed for any indication the challenge was greatest and generally had more limited options. Letvak stressed that study team and investigators during the PTA planning process should consider contingencies that may be implemented if the trial was stopped early for efficacy, futility, or safety issues.

Then, Letvak provided potential options for PTA: a built-in study extension which allows patients to continue on the study until they meet discontinuation criteria; an extension study which allows patients to receive treatment after completion of primary analysis; a protocol amendment where an extension was not anticipated or other changes in protocol required to implement; and a roll-over study/basket protocol which allows patients to be treated after completion of parent studies, if the investigator believes patients will benefit from ongoing treatment. Such studies would still collect safety data.

Next, Letvak described two cases: The first was about an imatinib mesylate (Gleevec®) trial in Chronic Myeloid Leukemia. Originally, PTA was not included in the informed consent forms of the Phase I trial and Phase II trials. However, the overwhelming efficacy seen during the Phase I trial led to the company chairman committing that the subjects would receive the drug for life. After the commercial drug

became available, many patients chose to receive drug commercially with local physicians so they did not have to return to the study site. Following the Phase II extensions, many of the patients were placed in a roll-over study in which the patients could receive the drug as long as the investigator felt they were receiving a continuing benefit. In May of 2002, Novartis started an access program in over 30 countries that would provide the drug until it was approved within the country. Efficacy and safety data was collected for these patients as well.

Letvak briefly mentioned her second case study of a drug that was studied for a different indication than it was approved. According to Letvak, the bottom line was that based on promising preclinical and pilot data there was a Phase III trial of six months of treatment. Then patients were rolled over to an extension study if they were felt to be benefitting. After submission of data to health authorities the company was asked to provide more data to support approval; a decision was made not to initiate new trials. Investigators and patients who were doing well wanted to continue drug and several options were discussed. It was decided to implement a roll-over study with collection of safety data and this was able to meet most of the needs of remaining patients.

Letvak closed by summarizing that proactive planning and anticipation of various scenarios was the best approach. Furthermore, the extent of data collection and study procedures needed to be considered and adapted over time. There was also a need to communicate and align expectations of all stakeholders, to consider local regulations and limitations, and to provide for drug supply following core studies, particularly when additional data were no longer required, which needed partnership and commitment of multiple stakeholders.

Panel Discussion featuring Millum, Padian, Straus, and Letvak, moderated by Holly Lynch

Lynch first asked whether post-trial access might be considered by those overseeing and regulating research as coercive or unduly influential of people to participate. The panel agreed that in many countries even small benefits may be some type of inducement. However, the panel's experience with IRBs was that they mostly worried about money and care unrelated to the science of the trial.

A member of the audience asked whether the research in Brazil would have continued if a lawyer told the pharmaceutical company it would be obliged to provide PTA for an indeterminate period. A panelist responded that if the verbiage had changed from five years to an indefinite period of time, the pharmaceutical company may have changed its decision.

Another member of the audience asked the panel what the opportunity costs of PTA were to trial sponsors and what the value was of the additional data gained through PTA. One member of the panel stated that the more efficacious the drug, the less this concern arises. The panel also stated that industry and other sponsors had limited resources, and the additional resources required by PTA definitely had a real impact. A panel member explained that it was also difficult to manufacture a new drug, for which there was high demand, at larger scale which diverted the pilot plant's capacity to create other therapies they might have tested.

Another member of the audience asked about countries in which national health programs had very strict formularies. If companies that tested drugs that were outside the national formulary provided PTA, would this create disparities that were unacceptable?

One panelist responded that many of these countries already had significant disparities, where higher income individuals on private insurance had greater access to care. The panelist also stated that there were less ethical qualms with moving some up as long as others did not move down. Another panelist responded that formularies may change after the study was conducted. The panelist added the fact that the individuals who were in the trial were bearing the risk, and therefore PTA might be a form of additional compensation for such risk.

Next, a member of the audience asked why/how all the parties involved in one of the case studies decided to cooperate. A panelist responded it would be very difficult to create such coordination do novo, but such partnerships were already present when the trial was being conducted.

Another member of the audience asked how pharmaceutical companies and sponsors decided the criteria as to when to provide PTA. A panelist responded that one of the areas with greatest need for PTA had been HIV and other chronic infectious diseases and oncology. In other cases, e.g., comparison of drugs, the case for PTA would be less compelling. Another panelist talked about anticipating the sustainability of what one is evaluating. A third panelist added that the crucial areas were "the size of the loss" for those whom their condition would be fatal otherwise. The cost had to be relative to what they can access and to how large the benefit was to what the sponsor was providing, e.g., whether it saves participants' lives. Issues about cost and opportunity cost were debatable.

Finally, a member of the audience remarked that if we were asking Ministries of Health to commit to expensive medications, they may not provide other kinds of care.

The challenge was what happens after a 2-year or 5-year commitment ends and the sponsor had to walk away. A panelist responded that the picture was complex and depended on who provided access. The opportunity costs would be pressing. An outside sponsor may not be committed to spending for health care in this country. This was a complex issue.

Session IV: Working Toward Solutions: Discussion of Hypothetical Post-Trial Scenarios

Christine Grady, Mitchell Warren, and Richard Saver (UNC Law), and Luann Van Campen on panel, moderated by Mark Barnes.

Session four of the Post-Trial Responsibilities conference featured a panel discussion of a complicated hypothetical scenario involving different aspects of PTA. The scenario was designed to be complex, so that audience members could think about the difficult choices facing all parties in this issue.

> In this hypothetical, the Ministry of Health in Angola collaborates with a Belgian biotech company, BelgiqueTec. BelgiqueTec is a start-up, funded by investment capital but lacking the deep pockets of an established pharmaceutical company. BelgiqueTec is interested in conducting a clinical trial to test its new diabetes drug. The Angolan government agrees to contribute $25 million to finance the trials in Angola, in part due to the population's growing diabetes problem and long delays for treatment in the government's diabetes clinics. In return, the Angolan government will take a small ownership stake in the company. Angola

has committed resources to bolster study sites, which will be hospitals or clinics owned by the Angolan government or ministry of health (MOH). The agreement ensures that Phase I and II trials will be conducted in Angola, while Phase III trials would feature at least a single site in Angola.

The Phase I trial was completed with no incidents, and the drug showed no adverse effects. Subsequently, a Phase II study enrolled 200 treatment-naïve Angolan citizens with diabetes. Half the group showed marked improvement in managing their diabetes. However, three participants demonstrated decreased cardiac function that seemed to be associated with drug administration.

First set of questions: If the adverse events cause drug development to be halted at Phase II, what are the obligations of BelgiqueTec and the MOH to the 200 Phase II subjects? Because a number of participants demonstrated improvement while taking the experimental drug, must BelgiqueTec provide the experimental drug or the standard of care? How long do the obligations continue? Also, if the patients demand specific access to the experimental therapy, should BelgiqueTec be required to provide it?

The panelists agreed that if the company decided not to continue developing the drug, then it would be under no obligation to provide the drug to participants. However, panelists argued that there might be a minimum obligation to refer the participants to other diabetes treatments. Some felt that the government's involvement in BelgiqueTec could increase the obligations. In response to the prospect of allowing the participants to jump the waitlist for the government clinic, panelists pointed out that if the individuals on

the waiting list did not have the opportunity to join the trial, then this outcome would be problematic. All agreed that such a question would depend on the situation in the particular country, and factors such as how many health care clinics there were available for diabetes care.

There could be a heightened obligation to the three participants who suffered decreased cardiac function. This obligation could be as little as continued monitoring for worsening adverse events, to a heightened responsibility if the condition causes pain, suffering, or monetary loss for the three individuals. There was disagreement over this question, particularly related to the question of how long post-trial obligations should last, and whether ancillary costs, like laboratory testing or future hospitalizations, would fall under the scheme of post-trial obligations.

The panel pointed out that the situation probably changed depending on what commitments had been made by BelgiqueTec and the MOH regarding what would occur at the end of the trial. Hopefully in the informed consent form there would be provisions for post-trial access, as well as agreements concerning what would happen in the event of early termination so that expectations could be clear at the outset. If a commitment was made, the panel agreed that the responsible thing to do would be to honor the commitment, or at least be transparent and communicative about any reasons that the plan has to be changed. However, panelists later raised the concern that including too much information could complicate the already arcane informed consent process.

Panelists noted that there were important differences between the doctor-patient context and the research context. In the United States, there are almost no obligations

when a provider ends a treatment relationship. This made panelists wonder what made the situation different in a research context. Panelists highlighted that the uncertainty of benefit in clinical trial research lead to a heightened responsibility from providers. This heightened responsibility could extend to post-trial obligations. The panel further discussed the informed consent process, suggesting that there had been a tremendous amount of work devoted to assessing how people understand the informed consent process – but almost no data were available concerning participant expectations about PTA.

The panel turned next to whether it would be acceptable for clinical trial participants to substitute a sicker family member to receive post-trial care, rather than themselves. This was not simply hypothetical, as panelists had directly observed this phenomenon during early antiretroviral studies in impoverished areas. It was difficult to interdict this process, as some people went to the lengths of impersonating others to be able to get treatment from a study. Panelists told stories of participants even selling their treatments for money for other life essentials. While panelists were sympathetic to how difficult it could be to monitor safety and efficacy if patients could "trade" slots, they also recognized the reality that this practice would continue in some fashion, as long as health care is not accessible to all.

The panelists next considered issues related to BelgiqueTec's status as an early-stage company. Panelists were sympathetic to the fact that being forced to provide post trial access could mean hindering future research efforts by BelgiqueTec, which did not have the financial resources of a larger pharmaceutical company. However, panelists

warned that separating obligations by categories of sponsors of trials could be very problematic, and lead to differential treatments for sponsors conducting similar research. This could also influence participant expectations, rather than institute uniform requirements, as PTA could vary widely depending on the sponsor. The general consensus was that PTA was important enough to have everyone do their best to provide it, with one panelist proposing a fund that could be set up to help provide resources for startups, through a tax that would finance PTA. PTA should also correspond in some way to the standard of care available in the country, especially if the experimental therapy would not be provided.

The panel turned to the issue of research literacy and the need for greater understanding of patients' expectations throughout the process. A panelist pointed out that there could be an inaccurate perception among participants in clinical trials that if they were in a successful trial, they would immediately be rewarded with a product they could purchase. However, the reality was that manufacturing issues, regulatory problems, and other unforeseen events could result in years of delay.

Q and A throughout the Panel:

- Is there a difference in PTA between placebo and treatment group? The panelists argued that it should not matter, and all groups should be provided PTA if any group is.
- Can we separate out different obligations to different groups, and perhaps break up PTA like this? It was pointed out that, in real life, the study would probably be done with a control group receiving the standard of care, so the provision of the

standard of care as PTA could be an option if the experimental therapy is not practical.

Session V: Wrap Up

Barbara Bierer and Rebecca Li of Harvard MRCT:

Bierer and Li provided the following next steps that may be the focus of a Harvard MRCT working group on Post Trial Access:

- Create an agreed upon ethical framework for PTA delineating how sponsors may enter the conversation and consider how to manage this obligation. Clarify differences among sponsors, if any; create processes by which to navigate the choices.
- Focus our scope on developing solutions on how to deliver efficacious agents in a cost-effective manner to developing countries.
- Develop a framework to answer ethical questions such as:
    - Who is responsible?
    - For how long?
    - What are the various roles of different stakeholders?
    - What obligations are owed to the participants and the community?
    - Does commercial availability satisfy obligations?
    - Should the placebo group be differentiated?
    - How to deal with regulatory delays?
- Create a framework/process/options in the planning stage to enable the plan to be developed (e.g. extension studies, negotiations with regulators etc.).

- In reference to the Declaration of Helsinki, create a “practical” interpretation that ensures that caveats are spelled out. Also explore whether clinical protocols should state that they follow CIOMS instead of the Declaration of Helsinki on all post-trial issues.
- Currently there is a lack of data that shows the impact of new regulatory mandates (i.e. Brazil). Need to explore what the positive and negative consequences are of the new regulations/mandates.
- Explore whether there are successful models of partnerships between various stakeholders that can be replicated across various scenarios.
- Develop training and education for investigators, IRBs, sponsors, government, and participants (e.g., what can WMA do to educate patient communities).
- Address clarity and a greater level of transparency among stakeholders about the issues and complexities, and seek to understand whether and how participants understand the plan.
- Develop pragmatic approaches to execute responsibilities and learn how to include communities as true partners.

Appendix 1: Meeting Participants

First Name:	Last Name:	Affiliation:	Company:
Ramadhani	Abdallah Noor	Conference Speaker	Harvard School of Public Health
Jacob	Abrams	Participant	Alexion Pharmaceuticals, Inc.
Carmen	Aldinger	Harvard MRCT	Harvard University, Multi-Regional Clinical Trials
Hend	Alfintoukh	Participant	
Wanda	Allen	Participant	Harvard University Center for AIDS Research
Janis	Anderson	Participant	Brigham & Women's Hospital
Avery	Avrakotos	MRCT Sponsor	PRIM&R
Babak	Babakinejad	Participant	Imperial College London
Andreea	Balan-Cohen	Participant	CRA International
Mark	Barnes	Harvard MRCT; Conference Speaker; MRCT Sponsor	Ropes and Gray LLP
Kelsey	Berry	Participant	Harvard University
Barbara	Bierer	Harvard MRCT; Conference Speaker; MRCT Sponsor	Brigham and Women's Hospital
Jeff	Blackmer	Conference Speaker	Canadian Medical Association
Meghana	Bohra	Participant	Brigham and Women's Hospital
Adrienne	Bonilla	Participant	University at Albany, State University of NY
Danielle	Boram	MRCT Sponsor	Biogen Idec
Elizabeth	Bowie	Participant	Mount Auburn Hosptial
Carolyn	Brokowski	Participant	Columbia University
Stacey	Brown	Participant	Brigham and Women's Hospital
Martha	Brumfield	Participant	Critical Path Institute
Kathy	Carbone	MRCT Sponsor	Biogen Idec
Dorota	Chapko	Participant	University of Aberdeen
Maureen	Chase	Participant	BIDMC
Robert	Chew	Participant	HILR Harvard Institute for Learning in Retirement
Susan	Chin	Harvard Law School	Harvard Law School
I. Glenn	Cohen	Conference Speaker; Petrie-Flom Center, Harvard Law School	Harvard Law School/Petrie-Flom Center for Health L
Deborah	Collyar	MRCT Work Group Member	Patient Advocates In Research
Liza	Dawson	Participant	
Bet	Day	Participant	FDA
Assunta	De Rienzo	Participant	Brigham and Women Hospital/ Harvard Medical School
Anurit	Dhillon	Participant	Northeastern University
Mariellen	Diemand	MRCT Sponsor	PRIM&R
Lucas	DiLeo	Participant	Broadland Advisors
Dimitrios	Dogas	Harvard MRCT	MRCT Center, Harvard University

Kristen	Elwell	Participant	Harvard University
Kathryn	Erat	Participant	Regis College
Marilyn	Eshikena	Participant	NYSPI
Nir	Eyal	Participant	Harvard Medical School and Harvard School of Public Health
Holly	Fernandez Lynch	Petrie-Flom Center, Harvard Law School	Petrie-Flom Center, Harvard Law School
Howard	Fingert	MRCT Sponsor	Takeda Pharmaceuticals
David	Forster	MRCT Sponsor	WIRB-Copernicus Group
Elizabeth	Frank	MRCT Work Group Member	Dana Farber Cancer Institute
Phillip	Gallacher	MRCT Sponsor	Biogen Idec
Chris	Galvin	Participant	DHHS/OIG
Nancy	Gerber	MRCT Sponsor	Biogen Idec
Gabrielle	Glick	MRCT Sponsor	Biogen Idec
Barbara	Godlew	MRCT Work Group Member	The FAIRE Company, LLC
Christine	Grady	Conference Speaker	NIH Clinical Center
Carol	Haley	MRCT Sponsor	Pfizer Inc
Sara	Harnish	Participant	Dana-Farber Cancer Institute
Nina	Hill	MRCT Sponsor	Pfizer
Hon	Ho	Participant	Partners Healthcare / Harvard
Jianyuan	Hua	Participant	NYSPI
Elisa	Hurley	MRCT Sponsor	PRIM&R
Aizhan	Imasheva	Participant	Kazakhstan Institute of Public Health
Keren Nicole	Insalaco	Participant	
Maureen	Jean	Participant	The Miriam Hospital
Suela	John	Participant	Boston University Law
Leigh	Keating	Participant	Brigham and Women's Hospital
Aaron	Kesselheim	Participant	Brigham and Women's Hospital
Richard	Klein	Conference Speaker	FDA
Lori	Knowles	Participant	University of Alberta
David	Korn	Participant	
Barbara	Kress	MRCT Sponsor	Merck
Bruce	Kupelnick	Participant	Tufts/NEMC
Mayumi	Kusunose	Participant	Institute of Medical Science, University of Tokyo
Sang Gyu	Kwak	MRCT Sponsor	DCUMC/CIMI
Kien	Lang	Participant	Independent
Sarah	Larson	MRCT Sponsor	Biogen Idec
Joaquina	Lazaro	MRCT Sponsor	Pfizer
Heidi	Ledford	Participant	Nature magazine
Laurie	Letvak	Conference Speaker; MRCT Sponsor	Novartis
Rebecca	Li	Harvard MRCT	MRCT Center, Harvard University

Cynthia	Liu	Participant	Mass General Hospital
Alex	London	Conference Speaker	Carnegie Mellon University
Melissa	Lopes	Participant	Harvard University
Pete	Lyons	MRCT Sponsor	Deloitte Consulting LLP
Simon	Lyu	Participant	HGSE
Izabela	Malinowska	Participant	Brigham & Women's Hospital
Brian	Malkin	Participant	McGuireWoods LLP
Priya	Mannan	MRCT Sponsor	Novartis
Mariam	Masandika	Participant	Muhimbili University of Health and Allied Sciences
Colleen	Mathis	Participant	Critical Path Institute
Justin	McCarthy	MRCT Sponsor	Pfizer
Joseph	Millum	Conference Speaker	Clinical Center and Fogarty International Center
Jules	Mitchel	MRCT Sponsor	Target Health Inc.
Dileep	Monie	Participant	Harvard University
Sandra	Morris	MRCT Sponsor	Johnson & Johnson
Richard	Murray	MRCT Sponsor	Merck & Co., Inc.
Laurie	Myers	MRCT Sponsor	Merck & Co., Inc.
Patrick	Nealon	MRCT Sponsor	Takeda Pharmaceuticals
Lachlan	Oakley	Participant	EX
Ellie	Okada	Participant	Boston Cancer Policy Institute, Inc
Onochie	Okoye	Participant	University of Nigeria Teaching Hospital
Nancy	Padian	Conference Speaker	University of California, Berkeley
Hyeongsu	Park	Harvard Law School	Harvard Law School
India	Perez-Urbano	Participant	Harvard University
Robin	Pierce	Harvard Law School	Harvard Law School
Alex	Pirie	Participant	Immigrant Service Providers Group/Health
Jeannette	Potts	MRCT Sponsor	Takeda Pharmaceuticals International Co.
Beth	Roxland	MRCT Sponsor	Johnson & Johnson
Michele	Russell-Einhorn	Participant	Office for Human Research Studies, DFCI
Rachel	Sachs	Petrie-Flom Center, Harvard Law School	Harvard Law School - Petrie-Flom Center
Ameet	Sarpatwari	Participant	Harvard Medical School
Jim	Saunders	MRCT Work Group Member	New England IRB
Richard	Saver	Conference Speaker	UNC School of Law
Jessica	Scott	Conference Speaker; MRCT Sponsor	GSK
Kwong Ee	See	Participant	DMS BBS
Amish	Shah	Harvard MRCT; Harvard Law School	MRCT Center, Harvard University, Harvard Law School
Nisha	Shah	Participant	Northeastern University
Seema	Shah	Conference Speaker	NIH Clinical Center
Zachary	Shapiro	Harvard MRCT; Harvard Law	MRCT Center, Harvard University, Harvard

		School	Law School
Kishore	Shetty	Participant	HEALTHCARE
Bran	Shim	Participant	Center on Medicine as a Profession
Im Hee	Shin	MRCT Sponsor	MRCT Center, Harvard University, DCUMC/CIMI
Jack	Smith	Participant	Tax Law Office
Aqilah	Solail	Participant	Student at MCPHS
Alexis	Soule	Participant	
Catherine	Stehman-Breen	MRCT Sponsor	Amgen, Inc.
Walter	Straus	Conference Speaker; MRCT Sponsor	Merck & Co., Inc.
Elyse	Summers	MRCT Sponsor	AAHRPP
Magdalena	Taber	Participant	Self employed
Jocelyn	Ulrich	Conference Speaker; MRCT Sponsor	PhRMA
Gerald	Unger	Participant	Broken Gavel, Inc.
Julian	Urrutia	Participant	Harvard
Luann	Van Campen	Conference Speaker; MRCT Sponsor	Eli Lilly and Company
Sueli	Vieira	Participant	L.O. Baptista - SVMFA
Manabu	Wagatsuma	Participant	Tokyo Metropolitan Law School
Daniel	Wang	Conference Speaker	Queen Mary / London School of Economics
Mitchell	Warren Weigel	Conference Speaker	AVAC
Carol	DiFranco	Participant	Mass Eye & Ear
Sabune	Winkler	MRCT Work Group Member	The Harvard Catalyst
Natalie	Zaidman	MRCT Sponsor	Pfizer
Audrey	Zhang	Participant	Harvard University
Minglian	Zhao	Participant	MGH

Appendix 2: Agenda

What: **Post-Trial Responsibilities Conference: Ethics and Implementation**

When: September 18, 2014: 7:30 AM – 5:30 PM

Where: Harvard Law School, Wasserstein Hall, Milstein East AB, 1585 Massachusetts Avenue, Cambridge, MA 02138

Who: Clinical research sponsors, investigators, funders, regulators, trial participants, and other stakeholders

Introduction / Background:

The term "post-trial access" is used broadly to connote a wide range of possibilities for providing continued access to study interventions (and potentially other care) once a trial is over, or a subject's participation has ended. For the purposes of this conference, we will focus discussions on the following:

1. Continued access to study intervention(s) and/or other care for **people who were enrolled in the clinical trial** and were benefitting (whether between the end of the trial and product approval or indefinitely)
2. Provision of the study intervention(s) and/or other care to **people who were enrolled in the clinical trial but did not get the intervention** and would like to try it (whether between the end of the trial and product approval or indefinitely)
3. Provision of the study intervention, other care, or other resources to the **community** in which the trial was conducted

Law, policy, and guidance are vague, sometimes conflicting, and generally lacking in concrete solutions for questions regarding post-trial responsibilities. The issues are complex and demand thoughtful discourse to move the clinical trial enterprise towards meaningful solutions. Areas that currently lack clarity include:

1. How are recommendations regarding post-trial responsibilities influenced by the trial phase and/or prior experience with the intervention?
2. What types of interventions or resources should be included within post-trial responsibilities? Do recommendations include ancillary care, treatment of side effects and adverse events, etc.?
3. What is a reasonable duration for post-trial responsibilities to extend?
4. What is the mission and purpose of various stakeholders (sponsors, governments, investigators, etc.) in the conduct of clinical research and how do these roles intersect with post-trial access responsibilities? In particular, how do government and sponsor responsibilities relate to each

other? Do recommendations change when research is sponsored by non-profit entities?

This conference will bring together diverse stakeholders to address some of these questions

Objectives:

- To discuss implications of international guidance on post-trial responsibilities for clinical research sponsors, governments, investigators, and other stakeholders
- To articulate and understand the range of perspectives on post-trial responsibilities
- To draw lessons from successful and unsuccessful attempts to implement post-trial access policies
- To discuss potential scenarios and practical solutions for post-trial responsibilities that may inform policy in this important area moving forward
- To identify key priorities for a Post-Trial Responsibilities Working Group to be launched by the Multi-Regional Clinical Trials Center at Harvard

Agenda:

7:30 8:00 am	Participants Arrive, Breakfast, and Registration	
8:00-8:05	Welcome Remarks	Mark Barnes (Ropes & Gray, MRCT), Barbara Bierer (MRCT), I. Glenn Cohen (Petrie-Flom, Harvard Law School)
8:05-8:15	The Potential Scope of the Post-Trial Access Issue	Mark Barnes

Session I: Setting the Stage (Moderator: I. Glenn Cohen)

Objective: To introduce current ethical and regulatory approaches, as well as key

8:15-8:35	The Ethics of Post-Trial Responsibilities: History, Models, Agreement, and Controversy	Christine Grady (NIH)
8:35-8:55	World Medical Association (WMA) Declaration of Helsinki – Process and Perspectives	Jeff Blackmer (University of Ottawa)
8:55-9:15	The Council for International Organizations of Medical Sciences (CIOMS) Approach	Alex John London (Carnegie Mellon University)
9:15-9:35	Policy Approaches Around the Globe	Seema Shah (NIH)
9:35-10:00	Panel Discussion and Q & A	Panel and Audience
10:00-10:15	Break	

controversies.

Session II: Important Perspectives (Moderator: Barbara Bierer)

Objective: To convey the range of stakeholder perspectives and current approaches from sponsors, regulators, patients, and investigators, and identify areas of convergence and divergence

10:15-10:35	FDA Perspective	Richard Klein (FDA)
10:35-10:55	Governmental requirements	Daniel Wang (London School of Economics)
10:55-11:15	Industry perspective	Jocelyn Ulrich (PhRMA)
11:15-11:35	Investigator perspective	Ramadhani Noor
11:35-11:55	Participant/community perspective	Mitchell Warren (AVAC)
11:55-12:15 pm	Panel Discussion and Q & A	Panel and Audience
12:15 - 12:45	Short break to pick up lunch, reseat for next session	

Session III: Lessons Learned: Case Studies on Implementing Post-Trial Responsibilities (Moderator: Holly Fernandez Lynch, Petrie-Flom Center)

Objective: To better understand real world experiences implementing post-trial responsibilities, including both successes and failures, and to more clearly articulate and assess the complexities involved.

12:45-1:05	NIH Global HIV Research Case Study	Joseph Millum (NIH)
1:05-1:25	Investigator Case Study	Nancy Padian (UC Berkeley)
1:25-1:45	Industry Case Study #1	Walter L. Straus (Merck)
1:45-2:05	Industry Case Study #2	Laurie Letvak (Novartis)
2:05-2:35	Panel Discussion and Q & A	Panel and Audience
2:35-2:45	Break	

Session IV: Working Toward Solutions: Group Discussion of Hypothetical Post-Trial Scenarios (Moderator: Mark Barnes)

2:45-3:00	Objectives for panel discussion of scenarios Presentation of scenarios and key questions

3:00-4:00	Panel Discussion: Christine Grady, Mitchell Warren, Richard Saver (UNC Law), and Luann Van Campen
4:00-4:30	Audience discussion

Session V: Wrap Up (Moderator: Barbara Bierer, Rebecca Li)

4:30-5:30	Group discussion to identify key priorities for new Post-Trial Responsibilities MRCT Working Group

Appendix 3: Post-Trial Access Scenarios and Discussion Questions

Post-Trial Access Scenarios and Discussion Questions

[Background: During the conference, we will discuss this hypothetical and its different versions. The moderator will present the scenario, and will pose several of the questions below to a panel of experts for discussion over about 1 hour. Then we will open the floor to the audience for additional discussion over about ½ hour. If areas of consensus are identified, those will be noted; the goal of this session is not, however, to develop consensus, but rather to help highlight complexity and identify questions that will be developed into the charge of the new MRCT post-trial access working group. That charge will be discussed over the final 1 hour of the conference.]

Fundamental questions re: post-trial access:

- Under what circumstances is post-trial access ethically required? Post-trial access to what? And for how long?
- Who bears responsibility for post-trial access (and related costs)?
- How should evidence (or lack of evidence) regarding safety and effectiveness weigh in to access considerations? What about approval status of the drug/device?
- Should post-trial access include free care or just availability of the investigational product?
- If access is provided, is medical care for adverse events secondary to use provided, and if so, by whom and at what cost? Should they be compensated? Should adverse events be reported to the sponsor and/or the regulatory agency?
- How does one balance the expectation or obligation to provide access, if one exists, with other resource needs of the community or country?
- What role can and should the consent process play in managing and defining post-trial access expectations?

Scenarios/Questions:

The Ministry of Health of Angola, whose budget had experienced significant increases due to national oil revenue increases, entered into a collaboration agreement with a Belgian biotech start-up, BelgiqueTec, which had developed an experimental treatment for diabetes. The incidence of diabetes had increased and severely affected the Angolan population, as its diet has become richer over the past two decades. Under the agreement, Phase I and Phase II trials of the experimental treatment would be

conducted in Angola, at the major teaching hospital in Luanda, that had previously benefited from equipment provided by USAID and the EU, and whose internal medicine and endocrinology leadership had been provided additional training in diabetes management at leading hospitals in London and Boston. Because the Angolan investigators for the Phase I and Phase II studies have sought to be involved fully in the Phase III studies as well (if the treatment advances that far), the collaboration agreement contemplates Phase III trials primarily sited in Angola, Brazil and Portugal. The Angolan government, through its sovereign wealth fund, has made a capital contribution to BelgiqueTec amounting to approximately $25 million, which will finance, among other things, the Phase I, II and III studies, and also has made an in-kind commitment of resources from the MOH-owned Luanda hospitals that will be the study sites. The Angolan government also agreed to an additional $20 million investment, as needed by BelgiqueTec in its drug development program. In return, the Angolan government has received a 45 percent equity stake in BelgiqueTec.

There were no Phase I study adverse health effects, and thus Phase II trials were initiated. The protocol included 200 Angolan citizens, all previously diagnosed with moderate to severe diabetes but who were treatment-naive at time of study enrollment. In the Phase II trial, over half of the subjects showed significant improvements in diabetes control and abatement of symptoms, but there was worrisome decreased cardiac function in three subjects, all associated in time with the administration of the experimental drug.

Questions: If BelgiqueTec and MOH decide at this point, after analyzing the adverse events in the three subjects, to end the development of the drug, then what is the obligation of BelgiqueTec and MOH to continue to deliver diabetes treatment of any kind to the 200 Phase II subjects, none of whom, before the trial, had access to diabetes treatment? What if BelgiqueTec and MOH disagree about how to proceed?

If there is an obligation to treat, does it fall on BelgiqueTec or MOH or both? Does that obligation to treat only extend to the experimental drug or to standard therapy? How long does the obligation continue? Should adverse events and secondary complications of diabetes be treated, and if so, by whom and who should finance? Should routine monitoring (Hemoglobin A1C, glucose monitors) and screening tests (e.g. annual ophthalmologic and renal function tests) be provided, and if so, by whom and who should finance? Does it matter what the participants were told/promised during the consent process (especially if their expectations were explicitly limited)?

At the Luanda Hospital, there is a waiting list of over 1000 patients for treatment and medication in the diabetes clinic, and many of those on the waiting list have waited for

over one year and are in more serious condition than those who volunteered for the study. Should the 200 subjects jump the queue, and take priority over those on the waiting list? Does it matter whether those on the wait list were eligible to have been enrolled (i.e., were willing to accept the risks, burdens, and benefits of research)? Does it matter if those on the waiting list had been offered enrollment and declined?

About two dozen former subjects have spouses or parents on the waiting list of 1000, and some among those spouses and parents urgently need treatment – much more so in some cases then their family members who were also former research subjects. Should we let a subject in that situation "substitute" a sicker family member for himself/herself in any jumping of the clinic wait list?

Is it reasonable to expect BelgiqueTec to use its own resources to finance additional diabetes treatment for the 200 former subjects by adding capacity to the hospital clinic, so that the clinic could assume care for those specific 200 former subjects? Consider that BelgiqueTec is a start-up company, with very limited resources. It was because of those limited resources that BelgiqueTec had originally sought financial partnership with the Angola government. If BelgiqueTec is forced to pay for lifetime diabetes treatment of these 200 patients, then BelgiqueTec will not be able to test the other two promising diabetes treatment agents whose IP BelgiqueTec owns; instead, BelgiqueTec will plan to use its remaining capital to buy an annuity, issued to a Belgian trust made in favor of the 200 former subjects, and will close up shop.

How, if at all, should the analysis change if BelgiqueTec were not a start-up company but rather a major, established pharmaceutical company?

Given Angola's resources, should we expect Angola to give preference – either in the MOH budget or by way of special allocation from the Angola sovereign wealth fund – to the diabetes treatment needs of these 200 former subjects, over other health and public health needs in Angola?

Do the answers differ if we change the country that hosts the clinical trial? What if Angola had fewer resources? What if the reason the population lacked access to basic diabetes care was because its government prioritized military funding (or some other budgetary issue) over health care? What if the government was corrupt or politically unstable?

In a further hypothetical, consider if the clinical trial took place in the United States. How would the analysis be any different, if at all?

If lifetime care is to be paid for by someone – either by Angola or BelgiqueTec – then will hospitalization, amputation, prosthetics etc. be required to be part of this paid-for treatment? What is the scope of services that will be encompassed by the duty to treat for life? Should the 200 former subjects receive amputation, hospitalization, and prosthetics, even though the Luanda hospital provides none of these services for free for diabetes patients who are in current outpatient treatment? Should the continued, lifetime diabetes care for these 200 people be superior in quality of care and scope of services to that provided to all other Angolans who receive the standard of care at the same Luanda hospital?

If some of the subjects who receive continued post-trial access to diabetes care repeatedly fail to comply with treatment, and therefore have very high (but most likely avoidable) care needs, should these needs be met? Even if this means that limited Luanda hospital and clinic resources are diverted to the care of these subjects and away from diabetes care for patients with severe conditions, who were compliant with treatment?

Remember that over half the subjects in the Phase II study did very well on the experimental drug. What if the drug appears to be efficacious, but will be substantially more expensive than other treatments? Can BelgiqueTec or the MOH substitute less costly treatment? What if the drug were only moderately effective?

What if a large number of trial subjects demand continued access to the experimental drug (as opposed to other diabetes care), even though MOH and BelgiqueTec have decided to stop its testing and development? And if some of those subjects go on to develop cardiac problems later in their course and with longer exposure, as might be predicted, should BelgiqueTec or MOH be required to provide treatment for their cardiac symptoms and, potentially, alternative diabetes care? Consider what this would mean for diversion of the company and MOH's limited resources. And what if BelgiqueTec goes out of business? Assume that a continuing obligation to make the experimental drug and to provide it to these former subjects would divert limited resources that would otherwise be used to test other, more promising drugs, and/or used for MOH's general purposes. And if BelgiqueTec ultimately goes out of business, due to the failure of its other two pipeline drugs, then should MOH be expected to continue making the experimental drug for the lifetime of the former subjects who want it?

If, after analysis of the adverse events, the decision is made to continue to a randomized Phase III trial with 2000 subjects (1400 of whom are in Luanda), many of the same questions remain about whether and how to continue to provide access to the

experimental product or other diabetes care when the study (or study participation) ends, but become even more pronounced. For example:

- Continued treatment of 1400 diabetes patients would place even more strain on the Luanda hospital's diabetes clinic, to the detriment of other non-study patients. Is this ethically required?
- If after Phase III trials, safety information leads BelgiqueTec not to take the drug to approval and marketing, then what about continued access for those subjects who did well on the drug? Even if it does proceed to marketing, what about access during the intervening period? And if after marketing, what if the participants were unable to afford the drug?
- Would continued access either to the study drug or to regular diabetes care be diverting resources from other programs, such as diabetes care for non-study patients, development of other promising drugs, and/or other MOH priorities?