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?