

**Open Forum II: Key Issues in TB Drug Development – Day 2:
Challenges of Conducting Trials in High Burden Country
Settings
TB Alliance
December 13, 2006**

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[START RECORDING - TB Alliance Session 2]

DR. RICHARD CHAISSON, MD: In this next portion of the program we're going to be discussing the challenges of clinical trials, and to begin we're going to have a presentation on issues for trials of drugs in HIV infected populations, and I'm very please to welcome Javid Saed.

Javid is a TB HIV activist with the Treatment Action Group in New York. He's responsible for much of the advocacy that that group has been doing over the last couple of years; helped write their report on funding for TB research, and has graciously agreed to stand in today for Mark Harrington who was unable to be here. Javid, welcome.

JAVID SAED: Thanks, Dr. Chaisson. So, merely as all good activists do whenever they take the podium, they kind of push forward with an agenda that might not be reflective of the title, so I wanted to start with a little bit of something that might not be completely related to, but I think it does create the context in which the challenges for TB R&D overall exist, and that's the resources for TB R&D.

The second one again sort of following the lead of one of the previous speakers, Dr. Gellerman, nothing that I'll say will actually be new, but hopefully will just contribute to the conversation that's already

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happening right now, and as the trial design issues around TB HIV coinfection, as well as from XDR or MDR TB concerns.

The last thing I want to say before I go into the resources discussion is that if I don't sound clear, please just stop me and ask me, because I am having a reverberation in my own head and so I might not be able to communicate so clearly today.

So we did a report, which probably everyone has seen by now, it was out there on TB R&D for 2005, which was last year in which the most complete data was available, and we tracked about 40 largest investors for TB R&D and presented it at the last Union conference in November, and the Treatment Action Group's web site is also where you can download that report from, and what we found was something that might not be standing to any of you, but continues to be really shockingly pathetic, which is that we spend \$400 thousand, \$400 million, on a disease that kills one person every 15 seconds, and that's just shocking, and that the most of that money of course goes to drugs, which is; our message is never that this is enough or that this is a competition that the drugs and diagnostics and vaccines need to duke out amongst themselves, but that we need to actually increase the pie for everyone.

But this is what we found, was that drugs were the largest, followed by basic science and then vaccines. Last

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was this kind of catchall category, which also was because of some of the issues that I'll talk about a little bit in the presentation which was that a lot of the people who were even donors for this field were not able to track whether they'd given their money for drugs, diagnostics, vaccines or in each of those sections whether it was being given for preclinical or clinical data, clinical research and so we have this catchall category which came up to being about 11-percent.

The other thing that I wanted to point out which is again surprisingly just disheartening is that diagnostics, which is such an Achilles heel for TB treatment right now, and especially for people living with HIV, got the lowest amount of funding in all of the research and development categories, and was only four-percent.

Then who gives this funding? It was not surprising that most of the money did come from the public sector, which is great, partly because it is the kind of money that we have greatest influence on, and as a civil society can hopefully increase this amount further. And then the other amounts came from philanthropic pharmaceutical and the amount that's the pharmaceutical amount was about \$43 million, and it was really hard to get that information and only six companies disclosed that information. So one of our recommendations is obviously improved transparency for TB R&D amongst the private sector. This is a slight that kind of shows what we

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can get when we have public world and political world behind a disease area, and this is also a slight that was shown by Barbara Laughon yesterday, and it shows the discrepancies, or the inequities between TB versus HIV R&D investment.

And again, our message here is not that HIV gets too much, but that HIV has a particular way of bringing together researchers, political activists, as well as policy makers, and unfortunately that's not the case in TB all the while until quite recently. And so I think it's a lesson that we can learn from our HIV experience and trying to apply it to the TB communities.

This is, again, the same information in a different way, and this is, for each of the areas of drugs, diagnostics, vaccines and basic science we did this kind of breakdown of operation research. We did this kind of breakdown and this is the breakdown for drug development. So, as you can see again NAID [misspelled?] is one the largest contributors, and then some of the companies that prefer to remain anonymous are anonymous, and then there are some others that were willing to show, willing to demonstrate their leadership by also sharing their, not only their portfolios, but also allowing us to give their names, which is really commendable. Astra-Zeneca, Otsuka and Sequella, and Novartis; we should really commend people for that kind of transparency. The other good thing that we found was that

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high-burden countries like India for example, were substantially contributing to their TB R&D which is another element of the funding that we need to push forward.

So I'll just skip that last slide and move to the recommendation for it. The resources portion of my talk, which is that one of the things we discovered, is that there wasn't truly a comprehensive TB R&D agenda that was developed. The global plan has a good, some good elements to it, but it doesn't actually include things like operational and basic science research in a significant way, and so that needs to be added into the global plan.

And that industry needs to get more transparent about its TB R&D and reporting consistency is really needed, because what we saw was that it's really hard to find information and across different funders, and then also specific subcategories like TB HIV funding for example, was really hard to get from even an organization like NIH, who is actually very good at its resource tracking.

Further recommendations around it is that only \$400 million are available right now in 2005, and this actually falls pretty short to the global plan's vision of what is needed. What we found was that we needed nearly \$200 billion per year in order for the global plan's vision to be met, as well as the other unmet TB R&D needs to be met, so things like basic science and operational research which aren't part

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of the global plan to also be met. So, it's also a nice round number that activists can get our heads around pretty easily. So, \$200 billion per year; that's our call.

The other recommendations are that the public sector should continue to keep on funding, and it's in the portion that it does. Emerging countries like the high-burden countries continue to play a bigger role in their funding. Foundations and industry should also step up their donation to this area of research.

So this was kind of a broader context of R&D for TB and something that actually is a challenge for all TB R&D, and then this is the context for the TB HIV specific context, and it just shows that TB is increasing in these five African countries, and overall it's a lot of that increase is linked with TB HIV.

This is some of the issues that we've thought of in terms of how TB HIV will impact R&D for TB, and some of the background information obviously is that it's the highest, one of the largest leading killers of people living with AIDS, that people living with AIDS come into TB settings with pretty low CD4 and have often smear-negative and extrapulmonary TB which is not appropriately diagnosed, and that the people living with HIV die much sooner in TB programs, even up to 30 percent in the first two months.

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And of course this high level of mortality is even higher when they're infected with XDR or MDR TB, and that the ARTs have drug – drug interactions with Rifampicin, which is the leading TB drug, and one of the recommendations, especially in the context of yesterday's conversation; I'd like to thank the comrade from South Africa who brought up the issue, is that we really need people with AIDS with lower CD4s to also be involved in the TB R&D inclusion criteria, that it's not sufficient for TB drugs to be developed in a way that excludes people living with HIV and people with lower CD4s from inclusion into the clinical trials.

And some of the challenges that we see that might bring up is that there might need to be larger sample sizes, and the possible need for even looking at the various subcategories of populations within a clinical trial to be able to say something appropriate and accurate about smear-negative HIV positive patients.

The other work that needs to be done is the need for early drug interaction studies, so that it's not just enough to be able to screen out for 50 and be able to utilize that as a way of ensuring that drugs are, that the TB drugs are going to be appropriately used in coinfecting communities, but that they also need to be tested against some more commonly used ARVs to make sure that these drugs can be appropriately used with coinfecting communities, so that people who are in

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need for co-treatment actually get access to co-treatment and don't need to make the harsh choices that they are in the positions to make right now, which is to actually only focus on the TB drugs while they're in need for both.

The other parts of the conversation are that the clinical trial sites and networks should also help that the HIV clinical trial sites should also help to develop new TB drugs, especially among coinfecting communities, and this is a significant role that the HIV community can play, that new TB drugs should also be studied in children as soon as possible, and that we should also study drugs, along with drug-sensitive TB, we should also study it in drug-resistant TB.

This is again the third context that we wanted to talk about, which is again the XDR context and you're familiar with this data already. It's the data that shows the real high morbidity of people who are HIV and XDR TB co-infected, and also some other surprising information that showed that a lot of the people were not previously treated and so a lot of TB program conventional wisdom which is that it's the patient's fault that they've not been compliant was not actually appropriate in this situation, and that in fact, health care setting became potential sites for transmission of XDR TB.

The research implications and the trial design implications of XDR and MDR TB have been mentioned by the

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previous speakers as well, is that it can really be seen as a potential for getting fast tracked approval, accelerated approval for new TB drugs, and of course does not preclude studying it for direct sensitive indication as well. The big issue is that we need to have at least two new effective drugs, possibly three, in order for XDR to really be treated effectively, and we're not even close to that right now, because the ones, as you see, that are furthest along in the pipeline are also the drugs that have been around for a while and aren't going to actually be effective for XDR [inaudible] probably aren't going to be the bases on which XDR, MDR TB will get treated.

That MDR and XDR TB are not currently in the critical development path for TB Alliance and to be honest, in the development conceptualization with a lot of TB drug developers either, and that MDR indication again could become a faster and method of getting approval for drugs, and the bar might be lower because there actually aren't any appropriate drugs available that, at least they're less, the drugs that are available right now have pretty high toxicity and really terrible side effects and have really long treatment periods, and so the bar is kind of lower in what we need to prove in that situation.

The other research and trial design implications of XDR and MDR TB is that we again try to learn from our HIV

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experience, and perhaps a little simplistically bring it to our TB comrades, not necessarily as easy solutions, but as possible way for us to think through how this can be done differently, and this is a regimen, clinical trial design that was approved, or at least was said that would be appropriate for HIV salvage therapy, which we wanted to again pause it here, as we did previously in a meeting with TB Alliance and a number of other TB activists and researchers, and this isn't necessarily the end all, be all.

Obviously trial design, but it's just something that we can look at that was seen as appropriate for salvage therapy and see how we can modify it for the TB world, and again the ridiculous thing about optimized background regimen in MDR TB it's hard-pressed to even imagine that something in considered an optimized background regimen, and there might be a way to even do it in a shorter way.

So this was the meeting that we talked about a second ago I mentioned it. It's the meeting in which CDC, MSF, Partners in Health met with TB Alliance, along with a number of other R&D folks and activists, and tried to bring together the kind of conversation that we are having here today, and I was actually really enthused about the kind of creative thinking that was being demonstrated from the podium, because often time, as AIDS activists when we, and TB HIV activists, when we come into the TB community there's a lot of

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resistance to new ideas, and it was actually really really refreshing to hear from the podium these ideas that we need to rethink how we're going to do TB trial design. How we can shorten it, how we can make it faster, how we can actually address the need of communities who are most likely to die of TB, because when us TB HIV activists we got involved in TB HIV in the TB advocacy world we were told that well, TB HIV people are smear-negative and usually won't transmit the disease, and therefore aren't such a high priority for the health system, so I think we've come really far from that place and I'm really grateful for that.

The other meeting that I wanted to invite you to, and there are some MSF [misspelled?] folks here as well, and I'm sure there's some material out there. Is there some material out there for the next meeting that's happening on the 11th and 12th in new York which is going to be convening a similar group of people, of research and development people, of people who are also involved in various regulatory agencies and activists to discuss how we can move these conversations forward in a much more efficient way.

Of course industry's involvement is always critical, and that collaborative action and activities across our various sectors are really vital in order for us to move this TB R&D movement forward. It's not really a burden that only one of our sectors can bear.

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In conclusion, some of the things that I've mentioned before, I just wanted to reiterate again that we need around \$600 million a year for new TB drugs and about \$2 billion a year for the overall TB R&D movement. That we really need to have people with HIV-related TB in clinical trials for new TB drugs as early and as safely as possible. That we need to have drug-drug interaction studies conducted really soon, so that people with ARVs can get involved in new TB trials, and also get access to TB drugs ASAP. Linked with that, of course, is the fact that people who are positive but smear-negative need to get integrated into the clinical trial processes and need to be eligible for clinical trials. That XDR and MDR should be considered as a way to get approval for new TB drugs in a faster way, and that community needs to get involved in a way that's not just around being subjects for research but also participate in the development of research priorities.

I think that's it for me.

DR. RICHARD CHAISSON, MD: Before we move on, if there are any, yes, we have them up, right up in the second row here.

FEMALE SPEAKER 1: Thank you for that [inaudible] thank you for that very interesting talk.

I'd like to just add another bullet point to your sort of comments of needs, and at the moment there are very

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few labs in the world that can diagnose TB very well. There are even fewer that can diagnose MDR, and there's virtually no one that can diagnose XDR TB, so while we're thinking about setting up trials, and trying for new drugs, it's got to go hand-in-hand with diagnostics.

We can't launch a new drug and then do trials in Africa if there's no labs can test to see if it's resistant or not, so it's just a plea for adding diagnostics a little bit higher up on the list.

JAVID SYED: Sure, OK.

DR. RICHARD CHAISSON, MD: The next part of the program is a panel discussion, and I've been asked to briefly introduce some of the issues that will be discussed in the panel, so the purpose of my comments for the next few moments is to raise issues, not to try to necessarily address them in any thorough manner, and the topic is the challenges of conducting trials in high-burden countries.

So, to begin with, I think it's important to emphasize where the TB is the world, and the WHO map of cases here shows the high-burden countries colored in dark brown, India and China with more than a million, and in red all the countries with between a hundred thousand and a million tuberculosis cases. Clearly these are countries that are largely in the developing world.

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If we look at where the resources are and where the products are, the new drugs for TB, and where the money to study new drugs for TB are, they're in the developed world, and this map is a conceptual map, so please don't take it literally. I apologize if you're currency or your country is not properly represented, but the point is that the products are where the cases aren't, and the money is where the cases aren't, and bringing the products and the money to where the cases are is essential if we're going to study new drugs for TB because that's where they're needed and that's where they'll ultimately be used.

So in bringing trials and bringing resources to developing countries to study tuberculosis there are a number of really important and somewhat different issues that are confronting researchers, as opposed to studying them in developed countries.

The first is that we are largely working with vulnerable populations. They're made vulnerable because of their poverty, because of the stigma associated with tuberculosis, because of high prevalence of HIV in many areas which also adds to stigma, and because of, in many cases, a low educational status which can affect access to medical care, utilization of care and understanding of clinical research.

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There's limited access to medical care in general, and bringing in first world medicine for a GCP clinical trial in a setting where routine care may be very limited is frequently a challenge. There are language, cultural and social barriers that need to be overcome. There's a very limited infrastructure in many places. The laboratories just mentioned; that's part of the infrastructure which is often dramatically limited. There are constraints on human resources. Nurses are in short supply. There's a brain drain, and research in fact ends up competing for human resources that go into the public health sector, and this can be a source of conflict, and then there are the ethical and regulatory challenges of doing this work in this setting.

So the challenges that we've been asked to address in the panel today are these: community engagement, informed consent and research ethics, regulatory processes, training and laboratory. Now obviously we could go on for about a day and a half on these topics and not even begin to thoroughly address them, but we'll at least try to scratch the surface on each of them.

So, starting with community and community engagement, the first question that needs to be addressed is who's the community? What community? That's a term that is thrown around, but in fact in bringing clinical research to

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developing countries there are a number of very important communities who need to be engaged.

So the first, obviously, is the patients and advocates for the patients who need to be engaged, but then there's the larger population from which the patients are drawn, who may be different from the patients, but nonetheless are important to engage.

Health care workers are an important community for engaging because they are the ones who are ultimately going to use the results of the research. They will be participating in the research often, and if not engaged can become an important obstacle to doing research. And then finally, government, NGOs and other important stakeholders in the country need engagement.

So what are the concerns of some of these different communities? For patients and for patient advocates the concern is about being a guinea pig. "Why are you experimenting on me?" They're concerned about whether the research will affect their care. Oftentimes they're concerned that it will affect it in a positive way and that's a good thing, but there's certainly a concern about whether research is going to alter their care, and will it cost them money, money spent either in time participating in the study, or money spent on diagnostic tests and so forth.

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I think the larger population from which patients are drawn worries about whether this is going to really help them. Whether this is something that's being done for the benefit of the population, or is being done do the population.

Health care workers, I think, have different concerns. They're concerned about any change in the routine. There's a way that things are done. This is how we do it. Why do you want to do it differently, and will it work anyway? And often, why do I have to do extra work because you want to do research?

I think governments and NGOs involved in providing services are concerned about what the impact of the research will be on their systems that are in place in the short term when the research is ongoing, and in the long term with the results of the research perhaps leading to changes in policy and care. They're concerned about whether they're carrying the burden of the researchers' whims. We're here to do our study, and we're here to exploit your infrastructure to do it. Is that appropriate, and is the research proper, is it good research that meets the needs of the country?

I think there are many approaches to community engagement. I just wanted to show you a few examples from some of the trials that we've been conducting with colleagues

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in Rio de Janeiro. We've done social mobilization for research, so shown here is a magazine that is published regularly for HIV patients in Brazil, and we've used pieces in this magazine to promote particular clinical trials that are important for HIV-infected patients and it's a very effective communication device for a mass audience; likewise, putting into clinics these brochures which promote TB and HIV co-infection interventions, again reaching large numbers of people through a social mobilization campaign. And then there's direct contact. Here we see, this is the inside and outside of the same building in a favela in Rio de Janeiro where community engagement is being undertaken by talking to the population here a group of adults, and here a group of children, explaining tuberculosis and the interventions that are being developed. Nonetheless there are many ways to engage the community, and I think it's important to try to obtain support from the community, so your studies will be well received and effectively conducted.

Moving on to the issue of ethics and consent; it's clear that ethical review and informed consent are essential, and they are intended to protect patient rights and to prevent exploitation of individuals; however, for many of us, the review process and the consent process has become incredibly bureaucratic and legalistic, probably because many of us come from countries with too many lawyers. And it's the

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experience of many that, in fact, the review process can actually interfere with the spirit of medical ethics, but we can't let the fact that the process has become cumbersome and difficult overshadow the fact that there are enormous challenges faced in the ethical conduct of research and in obtaining consent, and some of them are listed here: language barriers, an understanding of research in general, our descriptions of risk and whether they're meaningful, and the use of placebos and comparator regimens, and whether that's something that can be justified to an ethics review committee, and whether that can be explained adequately to a patient entering a trial.

I just thought I'd show you some language, some boilerplate language from a JHU, Johns Hopkins, consent form, and this is the simplified version, and this relates to privacy. The US law HIPAA, which we all dread, requires that we inform patients enrolled in clinical trials about how their personal health information will be utilized, and this is the simplified form that our legal office has provided for us in international studies.

Now we've argued to our IRBs, without much success, that if the professors with whom we collaborate in developing countries can't understand the consent forms, how can we expect the patients to understand them?

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Nonetheless, this is the type of language that enters into the consent process, and I think interferes with consent because it's so distracting, so confusing, and so utterly irrelevant. And so I think a lot of attention should be paid to how consent is obtained, and to how effective consent is.

Just to give you an example of an alternative approach to getting consent, rather than using multi-page forms that are highly legalistic, this is a cartoon used to provide consent, obtain consent in a treatment of latent TB infection study that we're doing it with Sueto [misspelled?] colleagues at the perinatal HIV research unit, and it just clearly shows that the doctor is explaining that there are four treatment regimens in the study, that there's a process for randomization, but there are four treatments and the nurse is going to open an envelope and pull out a card that tells you which treatment that you're on.

I think the Cochran Collaborative would accept this as proving that allocation has been concealed, but it explains to the patient very clearly, and then they're treatment is explained. If you're on the INH 6-month treatment, this is how you take your medication. Very simply, doesn't require a lot of words, and then the treatment risks are also shown graphically.

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Informed consent is a really important issue. I think the legalistic approach taken in developed countries undermines informed consent in some cases, and there are alternative approaches that are very simple and I think more appropriate that ought to be utilized more.

Regulatory challenges; the regulatory challenge of local IRB's. Are there local IRB's? Do they exist? Are they registered? If the NIH is funding a study, you need to have a registered IRB. Does the IRB know how to go through the registration process?

National IRBs that oversee local IRBs; what role do they play and how do they contribute to the process. The drug approval agencies obviously play an important role. We heard some about that this morning. Drug importation issues, specimen exportation issues and data exportation issues all become important.

This is just an illustration of some regulatory issues faced with TBTC Study 28 being done in Rio de Janeiro, and I show you this as an illustration of the long process, and I don't particularly blame anybody, but it's just an example of how this process can be very cumbersome. So, the Hopkins IRB approved the protocol a month after it was submitted in 2005. It took another month to translate the

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consent forms and the protocol and the approval letter into Portuguese. It was submitted to the local IRB in Brazil a month later, and it took two and a half months for approval there. Once it was approved at the local IRB it was sent to Brasilia to the national IRB CONEP, and it took six months for CONEP to approve a protocol that had already been approved by two other IRBs, and then an application to ANVISA, and a representative from ANVISA is on our panel. The drug approval agency in Brazil was made, and then a reasonably short amount of time the application was reviewed and approved. A second application was required for importation, and that was reviewed and approved in a few months, and then the drug finally arrived on the site 16 months after the process was started.

So there are multiple steps involved and each step is associated with a delay, and in the long run it take a year and a half to get your drug into the hands of the patients who are going to be enrolled in the trial. And I can tell you that I've had very similar experiences in South Africa, so this is not at all unique to Brazil.

So, streamlining the regulatory process is obviously something that we're all interested in doing. From the investigators' side, having funding for regulatory staff is important and often overlooked. To reiterate something that

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was said by Jordi this morning, you should start early, or if possible, start earlier. You really have to start the process as early as possible.

I think it's important for us to simplify our protocols and consents to the greatest extent possible, and avoid writing and rewriting and changing them, and particularly avoid making trivial changes to protocols which require eight levels of re-review. There's a lot of details that gets put into protocols that's totally unnecessary, but can add months to the review process because somebody decides that a word should be changed and has to go back down the line of review.

Pre-review with the regulatory agents and pre-filing consultation was recommended this morning, and then finally simultaneous review by multiple agencies and boards at the same time. It's risky, because they all may come back with different recommendations, but if you can reconcile them all you might save a half a year.

Training for health care workers; clearly important, and lots of issues they need to be trained on. A few examples from studies in Brazil of the training that is provided: basic training in clinical issues related to the study, basic training in clinical research, and then a training pyramid that we have been using so level one is something that

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everybody gets. GCP training, protocol training, basics in epidemiology, ethics, privacy and confidentiality, and then higher level training for people who have higher level needs or desires leading up to degree programs funded by agencies like Fogarty, the Fogarty International Center for a select few.

Finally, laboratory issues were brought up earlier and I hope will be discussed. Clearly there are huge gaps in the laboratory network, or there's maybe not even a network. Most TB patients are diagnosed by sputum smear.

The way this is going to work is we're going to allow each of our panelists to make three or four minutes worth of comments, and then we'll open it up for discussion, and Roxanne, you are first.

ROXANNE RUSTOMJEE: Good afternoon, everyone. Thank you for this opportunity to address this audience. I have three slides, and they are really to bring out some points that we could discuss in the panel, and these points have arisen from working on actually most, if not all of the new drugs that are currently being investigated for new drug development in TB. So we've acquired this experience by doing the trials, and one of the first points I'd like to mention is bringing a balanced partnership, and what is essential is that control in management is often skewed when developing developed country partnerships, and skewed in favor of the

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developed countries, especially when it comes to training of PhD students, infrastructure and resource allocation and budget formulations. So I think right from the onset it's a good idea to balance this.

And then to in developing countries, to avoid depletion of limited resources. Often investigator-driven trials are heavily dependent on national programs or national organizations to run the trial, and with increasing GDP and GOP requirements, we find that we burden the systems with investigations and follow-up that goes beyond the normal functioning of that system.

And then sharing of information and exchange of expertise is another critical component and to set up a communication network between partners that offers an equal exchange from protocol development to day-to-day running of the trail. To share knowledge on formulating study budgets and to be extremely transparent about allocation of funds, and to ensure that capacity building costs are also incorporated in these grants because we really do not want to deplete developing countries' resources.

To ensure that monitoring capacity is enhancing rather than debilitating. We have extensive, I mean there are some clinical trials that are monitored to GCP standard three times a week. So, you spend as much time entertaining

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monitors as you do running the trial and it can be an exhausting process.

Eventually we hope that the collaboration reveals the excellence in the type of trial conducted, but we must realize it is a journey rather than an endpoint, and what is also interesting is to try and maintain the link after completion of the projects to understand that some partnerships have evolved over five years and indeed there is now a clinical trial infrastructure that can sustain another trial or many other trials.

And then another point is to encourage, within country, cooperation instead of competition; a point especially relevant I think to South Africa where there are a number of very competent clinical trial sites and not to play them against each other. Those are the main points that I would like to bring to you. Thank you.

[Applause]

DR. RICHARD CHAISSON, MD: Christian.

DR. CHRISTIAN LIENHARDT, MD: OK, I've just been told I have to be very quick. In fact, when I started, first good afternoon everybody. When I started preparing that I know that they could do this extensive presentation, which I think was very good in addressing all of the main problems, and I think that main challenges in clinical trials in high-burden countries, so I'm sorry if I might repeat some of the points

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which have been addressed already by some others [inaudible] this morning, and [inaudible] colleagues, but maybe be repeating them it's important also to stress the importance of addressing them.

So first of all the [inaudible] trials are more likely to be removed for development of new drugs and a regimen for treatment of TB. I think this is quite well understood, but what we should be aware of is the problem of the drastic difference that can be seen and observed between industrialized and low income countries, and again I will repeat maybe some of what the former presenters say, but I think it's important to understand, when we are looking for clinical trials in low-income countries and low-income settings there is a viability of situation, and the first one which we are facing is the viability of the International Ethics Committee and the ethics committee or International Review Board and their composition and their terms of reference in their meetings, and here we have to adapt to really [inaudible] a situation. There's a problem of lack of training on GCPs and GLPs which are really very, very dogmatic and written in [inaudible] with which we are very familiar here, but maybe our collaborators are not so much familiar with.

There is a problem also of monitoring, which is a problem [inaudible] the best foundation. The problem which

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has been raised by Ruth before about laboratory standardization and really to guide the problem of transfer specimens from sites to reference laboratories. There is a problem of the lack of reliable equipment, power cuts, [inaudible] asking for TB trial we have been exposed to that very frequently about the fact that our power is not permanent. There is the problem of internet access. So we have to deal with all these issues, and which are, in fact, extremely practical, and are these issues are bringing gaps between what is the concept of GCP and what is the reality in the field.

Most of them are related to cultural issues, social economy, and Dick [misspelled?] raised the problem of informed consent, making sure that we have informed consent, which I understand very well. Most of the time they are really tried, too complicated, very much difficult to understand. We have to make it extremely simple, and making sure that we do it in a language and in a way that patients do understand so they don't say yes to something which looks completely vague to them.

We have to deal, again speaking very practically, about the problems of patient's address, which are not the same in all countries and might have difficulties of getting the right address which makes problem then in the patient's follow-up, and again if we have to follow-up patients for a

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long time, what does it mean? Every time we want to see the patient that means that's the cost of the transport for the patient to come to the clinic has be addressed, because we cannot ask patient to come every time just because we want to see them. It's an expense. They have to leave work. They have to stop activities, so we have to consider that.

The problem of [inaudible] treatment, that by [inaudible] that for instance recently we've been raised an issue about local treatment which had an impact on the [inaudible] level, so for the problem which I raised yesterday were of concern to that and this is, this was [inaudible] treatment so we have to know about that to be a [inaudible] of treatment being taken.

So all these are always available problems, but they need to be properly addressed, and one of the questions which I think is [inaudible] regulatory agencies is what will you be prepared to accept, and what could you propose in order to cope with this difference, essentially in GCP and GOP requirements that may arise?

One of the main solutions we could propose is training. I think training is the paramount solution to most of the problems which I just raised, because that could help with consultations with health workers and patients trying to find exactly what the problems are. Training of health workers, and again Dick spoke a lot about that. Training in

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GCP, training in GCP, training in all of the aspects which are related to trials. Also, consultation with health workers and patients for informed consent; again that's been addressed but that's extremely important with upgrading sites and laboratories to stable standards.

Another point which I think is important to address is the fact that the [inaudible] point used presently in Phase Three trials of treatment of TB is the relapse rate, and as we have seen in the last two days, alternatives or short-term points should be considered, because there is the problem of follow-up. There is the problem of relapse. What does this mean? Relapse that is occurring, especially in areas where there is a high level of HIV infection. What would be a relapse? What would be a reinfection? Here we have to consider bringing the new technologies of DNA fingerprinting, and then consider a recurrence, rather than a relapse as an end point, so this a problem which has been addressed quite extensively today and I think that's a very important one.

Then, just to finish the challenges which I think are important, is how much information would be needed for new compounds before they are tested within [inaudible] drug combinations, and that has been addressed again this morning. What are the necessary steps [inaudible] regulatory [inaudible] on these issues? What do the problem with

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combination with [inaudible] drugs? And yet, last but not least, would the trials of the effectiveness of [inaudible] compound combination under frail conditions be recommended. More down the line, trying to test what we are doing under field conditions, and see whether in the conditions of nationality program what we are proposing does effectively work. Thank you very much.

[Applause]

DR. RICHARD CHIASSON, MD: Andreas.

ANDREAS DIACON: I would like to thank the TB Alliance who have invited me here. I have been the PI in the last three years of EBA studies in part and collaboration with Roxanna, and I would just like to give you some personal points that I have come across while trying to bridge that gap between first world requirements and third world context.

The studies that are partly conceived here, and the protocols that are reviewed by many people present here, they are extremely complex. The Phase Two studies, they have safety elements, they have pharmacokinetic elements in them. Things happen really quickly, and we have to do them according to FDA or other agency registration standard, which is something that is not a tradition in TB.

TB drugs before have not been being investigated to that type of standard, so we cannot look back to experience

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from previous trials. We have to create this infrastructure fresh every time.

The demands that the sponsors have are extraordinary, and Roxanna has mentioned this. A couple of years ago, we use to stick in our dial-up connection for the Internet once a week, to download e-mails, and now we are expecting to run the trials in Blackberry management style, responding within an hour to every question that comes in from sponsors from around the globe at any time of the day. The words "timelines" and "deadlines" are still probably on the waiting list of the Oxford dictionary of South African English [laughter], and there are certainly no such words in Afrikaans or any other African language, and it's important that you know that.

I have, I'm lucky enough to have a rather high-tech laboratory in a university that's right in the backyard of my trial site, and we have high biosafety standards, but we don't have accreditation with an overseas agency, because that is much too expensive for us to maintain and to achieve. [inaudible] with? And if we say none they look at us with eyes like this. We are expected to have a very fit clinical trial site. They want us to have perfect infection control in place, a GCP-experienced team, and 24-hour care for our TB patients that are expected to be in the hospital waiting for trials to be conducted on them. But the reality is that in

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our country, TB is an outpatient disease that is treated by nurses with specialist training. Most TB patients never have a doctor contact in their entire treatment. So, doing a trial like this means that we have to set up the whole infrastructure. We have to hospitalize them. We have to pay for that. We have to pay to find a place to do this, and that's a huge burden of work.

In a third world context, we do have high patient numbers and this is essential for these trials to actually happen, and this is why the agencies come to us in the first place. There is a certain discrepancy in certainly our country between policy and reality. If US sponsored companies download the policy documents [inaudible] and TB treatment that the South African government and our health authorities have on the Internet, you will have an excellent appreciation of how the health care is run in this country, and it's true that the policy documents are very good, and they're regularly updated, and they're written by really knowledgeable people, but what happens down there on ground level is often quite discrepant from what should happen, because there's a lack of resources and it's work in progress, so one can't really expect things to be like they are on the Internet, and our regulatory bodies; they do not receive a TB trial with open arms, because we are just waiting for TB trials to happen. TB trials have to queue up

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with all the other [inaudible] studies that are being run in South Africa, and there is no special provision made for our trials. Sometimes sponsors are disappointed about that, and my personal, most important point is the last one.

We need adequate staff to run these trials. We need to train them, and GCP training is a culture. It's not a matter of a one-day or two-day GCP course. And it needs a year or two of practicing this in trials and being monitored and being inspected and being audited until people really understand how this works. One needs to practice this, and then one needs to retain this stuff, which is not easy because as soon as you've trained them up, private industry wants to snatch them from you, and because you are a TB unit you can't pay them very well, so they're tempted to leave.

I have just one more slide, and this expresses it all. This gentleman in the middle, looking slightly uncomfortable, has given me permission to show this slide. He's about to become the first man in the world to be given TMC207, and people around him are my trial staff, and they make all this possible, and it's just a huge responsibility that we have by doing this, because if we make mistakes in doing these trials, a compound like this might just be abandoned. It might never be given to any other patient or just disappear from the surface. So, for us it's important that we need regular Phase Two and Three studies to maintain

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these trial sites and to retain these people so that they can get our structures ready for moving this forward together with all of you. Thanks.

[Applause]

DR. RICHARD CHAISSON, MD: Margareth.

MARGARETH NDOMONDO-SIGONDA: Good afternoon, everybody. First and foremost I need to take this opportunity to thank the organizers of this meeting for affording me the opportunity to come and share our little experience in the mission of clinical trials in Tanzania, and I think, most importantly, the opportunity to also be here learning from the vast experience of the experienced experts in the clinical trials, microbiologists and also [inaudible] from the rest of the world, so I thank you very much for that.

So what I'm going to do here is to first and foremost try and give you a background of Tanzania Food and Drug Agency, for you to be able to appreciate the kind of challenges we are facing, and to talk a bit about our experience with the concept of clinical trials in Tanzania, and of course then explain about the challenges we are facing, and of course later on, conclude.

In as far as TFDA is concerned, we are a government agency, under the assumption of the Tanzania Food, Drugs and Cosmetics Act, and that was only in 2003 that we were established, but before that there was a pharmacy board and

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also the food control commission which were responsible for regulating food and drugs in the country. We are an agency under Minister of Health and Social Welfare responsible for regulating the quality, safety and efficacy of food, drugs, cosmetics and medical devices in the country.

Now in as far as controlled clinical trials is concerned, you will notice that it's only in 2003 that we started regulating clinical trials in Tanzania as a regulatory agency. Before that there was a National Institute for Medical Research which was [inaudible] with the responsibility of regulating all medical researchers in the country. And so, what we've been doing since then is to use the [inaudible] Guide for Clinical Trials, and in this we do require all the applicants for clinical trials to submit all the relevant information, including the application forms, trials protocols, and investigators [inaudible] submitting all the preclinical and clinical data on the investigational product. Clinical and pharmaceutical data, and also they have to have an ethical clearance from the National Institute for Medical Research, and all the other relevant data that is required by GCP.

Now having done this work for a relatively short period of time, and having [inaudible] high burden of disease, and that is, we're talking about not only TB but also HIV, AIDS and malaria. But also you need to understand

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that we have a problem of marked drug-resistant TB and which to a point of six-percent resistance rate, and that is for re-treatment cases, and that is for all first line drugs, so you can imagine the kind problems we are in, and in view of all this, we see an increase in the number of clinical trials being conducted in the country, and over the past five or six years we have received a total of twenty applications since 2000, and most of these applications involve trials on TB, Malaria and HIV drugs, and currently there is a trial being conducted, and this is Phase Two and Phase Three randomized double-blind placebo-controlled efficacy trial of mycobacterium leprae vaccine in patients coinfecting with HIV AIDS.

I'm informed that this is the only trial that is being conducted in the world, but I may have to confirm that, but this is funded by, it is done under the Muhimbili College of Health Sciences in Tanzania, but is being funded by the Division of AIDS under the National Institute of Health in the United States of America.

So this is the only trial that is related to TB that is being carried out in the country. Now in as far as evolution of trials in concerned, we do have a limited capacity in terms of human resources, in terms of numbers but also competency, in order for us to be able to do the assessment properly, so we tend to use more of external

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experts from academic institutions and therefore you will notice that our evaluation depends solely on the availability of these experts who also have other equally important obligations. They have very tight schedules, and sometimes they are out of office for long periods of time, and you can imagine that could be one of the reasons why, as Richard was saying, it can take up to 16 months for an approval to be given for a particular trial.

In terms of qualification and experience of investigators, it's another challenge, because of the availability of clinical competent and medically qualified persons to carry out clinical trials is a bit of a problem. We have very few clinicians, pharmacists or other persons involved in trial who have attended GCP training, and I know, as my colleague said, attending GCP training is one thing, but having the hands-on experience is another thing altogether, so that is one of the challenges we are facing, and therefore this next compliance to ethical standards a bit uncertain.

In as far as construction of trial sites is concerned, we don't rely on the [inaudible] GCP standards for compliance checking. We are required to monitor the trial sites. The advocacy effects the protocol requirements and other documentation, but again we do have very limited capacity to do the inspection of the trial sites.

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In terms of insurance and indemnity issues, we have no guidelines for the same, but what we are trying to do now is to ensure that we incorporate these requirements into the guidelines that we are now in the process of developing.

In terms of capability of the trial sites to carry out clinical studies, the sites do lack the necessary resources to do the trials, in terms of equipment, materials and human resources, especially in the lab, and therefore, the issue of conformity to GCP is uncertain. So far we have only a few, about seven sites in the [inaudible] hospitals [inaudible] academic institutions.

We also have a challenge in terms of publication of trial findings and sharing of information because the tendency has been that there is a lack of sharing of information from the clinical trials between the relevant institutions, including ourselves, and therefore it become difficult sometimes to really provide rational advice, either to make any change in policy protocols or even treatment guidelines, and it is presumed that the sponsors are the ones who are benefiting more from the trial findings.

In terms of ethical considerations, we have no national ethical committee. We rely more on the National Institute for Medical Research, as I said initially, to issue the ethical clearance. But again, the same National Institute

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for Medial Research also does research and development activities, including the clinical trials, so you can imagine the kinds of decisions that are going to come up for this committee.

In terms of regulations and guidelines, we do not have any regulations as yet to regulate the kind of clinical trials in the country. Much as we're intending to do that starting from next year, but we do have some drafted guidelines on which I base on GCP, and also have incorporated a bit of ICHGCP, but largely we have relied more on the South African [inaudible] community guidelines, which form the basis for our own guidelines.

But what we're planning to do is now come up to conduct a meeting that is a step for us. Meeting with all the key players in the clinical trials, including the National Institute of Medical Research, the investigational research boards, the public health programs like the National Community Advocacy Programs, the EPI, and the NACP programs, so that we come up with a common understanding and consensus building on roles and the responsibility of each player in the conducting of clinical trial, but also in the control of the same.

So in conclusion therefore, I think it's important not that it is a fact that we have an increase in the number

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of the burden of disease, and also we are facing an increase in the trend of MDR TB, but we have limited capacity in terms of human resources, competent human resources, and also the numbers of human resources to do the clinical trials, but also the researchers also have limited capacity to do so.

But still we have the mandates to protect the public against indiscriminate use of human subjects in the conduct of clinical trials on drugs and related products. And still we are supposed to ensure access to new drugs [inaudible] to the people, and therefore I feel that there is a need for us to be able to invest, and this one I don't know whether it should, I think it's for all of us to see how best we can facilitate the process of investing in drug research and development and medicine integration in order to make sure that the public do access the medicines which are of good quality, which are safe and efficacious.

So with that, I really want to thank you so much for listening.

[Applause]

DR. RICHARD CHAISSON: So Granville will speak from the podium.

GRANVILLE GARCIA de OLIVEIRA: Since I don't have any slides to present, I'll speak from here.

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First of all I'd like to say that it's my great pleasure to be here representing Brazilian regulatory agency, where I'm the head of the clinical trials and the new drug area. So we can control since the beginning of the project, up until the end. That's quite important.

First of all I'd like to say that I'm very happy to be here in this unique and I'd say pioneer initiative, and I would say that it's a result mostly from the ideas, and partly from Maria's phrase brilliant mind, if she is here, and I would like to applaud her and the Global Alliance for that. I think it is a major and important way to show that somebody is saying the things, how they are going in the world right now, because everybody here knows that TB is exploding again, and it means that the distribution of wealth in this our planet, our planet Earth is getting worse, and I think that we must keep in mind if somebody here didn't already get this idea in their minds, that the developed countries are being invaded by deglobalization, by AIDS and this problem will be very quickly here in the other side of your walls and your condos, so you've got to pay attention to that.

Well in Brazil we have a very nice situation, because we represent the Planet Earth. We have the most wealthy guy besides the worst condition ever, so I think we are a good representation of the Planet Earth, Brazil. We have the best

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situation ever that you can imagine, but by just beside of the worst situation ever, so we can speak with some authority about this, and so I think that the most important in this event here is to establish concepts. We don't need to be punctual in the details, but I think the concepts must be established here, and I think this idea that I think Bill Gates, I think just get his outer [inaudible] he's not from the scientific environment, but he is seeing clearly what's happening, and a lot of people from the scientific environment didn't reach this conclusion so far. That's very preoccupying.

Well let's go back to our subject again. Brazil, in Brazil we have a very nice condition for clinical trials. In the last year we have more than a thousand clinical trials that were analyzed and approved by our agency, and we have a very good and respective bioethical basis. We have about more than 500 geographically peripheral committees of bioethics. All of them, they are attached directly to a national committee of bioethics. You cannot do a clinical trial in Brazil without being submitted to one of these two levels of authority. If you want to do one of the clinical trials that comes from outside of the country, you've got to go to the national level, see? And we also, we participating in this condition.

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We have some problems right now. One of the problems is that we're trying right now in the moment to make this evaluation in a parallel way, simultaneously, because in the very, in the past, these were done in one after the other, and this would make some people to just give up their clinical trials in Brazil, but right now this problem is being solved so our environment is very favorable.

Another thing is it's quite interesting in Brazil. We do not have payments for the people. We just give just enough to them to participate in the trial, which is food or some transportation. We don't pay nothing for participation exactly to avoid the idea of guinea pigs. We are not guinea pigs, see? And the people speak just one language which is Portuguese. It is 180 million speaking Portuguese, so we don't have any problem in translation between the investigator and the subject. So the only thing you've got to have is just some time to explain what's happening, and eventually it's interesting for the subject to be on that clinical trial.

Well another very important thing that we must establish here, I think we should establish here, is that in terms of reducing the time and the process of reviewing these new drugs that should have a cooperation among all the regulatory agencies in the world, FDA [inaudible] and so on.

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I think that would reduce the timing of the disposition of this drug.

Well in Brazil we're doing another very important thing that is right now being done, which is trying to expedite the review of certain processes, specific processes. So right now it is a public consultation in Brazil. It is a process. First we draw a draft and we put it in the Internet and everybody in Brazil can give their contribution, and after we finish the general and make a rule, make a general rule, it's finishing right now consultation number 51, which established a fast track for very specific points which are first, Brazilian public health programs, like for example, the very good national tuberculosis program, which will be in the afternoon, Dr. Margareth Dalcolmo, she'll be here explaining how it works [inaudible] in terms.

For example, our level of resistance is just about one percent, because we go to pick up the people inside the house if they don't come to take medicines which are free. The Brazilian government gives freely all the diagnostic and goes to pick up the people that are suspect, and we give them the drugs, and eventually we see that they are swallowing the drugs also. So, we try to avoid the defaulters.

Another thing that I think is quite important here is, going back, the second point in which we do a fast-track

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will be drugs that are supposed to be used in life-threatening and disabling diseases like cancer or some like.

The third situation would be for emergent and reemergent diseases, and the fourth is something that I didn't see here why people say something about orphan diseases. If is orphan diseases today here in the union, the European Union, will not be tomorrow, so you have to pay attention to this possibility, which is a major possibility. So, what is orphan drug today will not be tomorrow, see? In our country is not orphan drug definitely, but we have orphan drugs rarely of course, just like here.

So, I would say that Brazil is a very good place to make clinical trials, except for the reason that we have a somewhat low level of resistance. If we are going to specifically utilize this type of patients, but in general you just are open to go there and contact our researchers, because we have a very large number of network of researchers that work in this area, and can work together with you, if you come from else around the world.

So, thank you very much.

MALE SPEAKER 1: [inaudible] unit in the [inaudible].
My question is really to, I've had to use your buzzwords about capacity viewed in developing countries among various categories of stuff needed and institutions needed for

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clinical trials. Just to wonder, what, if we shouldn't be talking about the possible methodologist. If you, for example need labs for TB diagnosis in developing countries. Labs are needed for clinical trials [inaudible] will have these labs for routine clinical care, so is an opportunity in the cost of setting up for a clinical trial to provide the lab that would go on to be useful for clinical use?

My question is do you set up labs in tertiary institutions, in secondary institutions, or district health centers? That's, and do you go into a developing country, set up for clinical trial piggybacking on an existing institution, or do you start out fresh?

ROXANNE RUSTOMJEE: OK, I will speak for the laboratory that we run for our tuberculosis clinical trials testing, and we have a collaborative venture between the University of [inaudible] and the medical research consulate. It is purely a TB research laboratory and we run the full spectrum of TB investigations from molecular to basic diagnostic at that lab. I think that answers your question.

CHRISTIAN LIENHARDT: Yes, if I may I would just like to give an additional comment. The [inaudible] for TB trial which had presented briefly yesterday. We are intervening sites in West Africa where we are working with the national

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TB control program, and in fact, our approach by contacting these groups, these persons will really in order to base and to root the trial in the existing infrastructure, and what was interesting is that what our collaborator's head of national programs told us was yes we'd be interested in conducting trials with you, but that should serve us.

So, we don't want something that we're going to be [inaudible] what we are doing, so therefore that means all the various levels have to be respected, i.e., smears diagnostic and health centers, so in the centers where we're intervening, then we're making sure that their smear diagnoses were done.

We're not going to set up a new culture system in the health centers because that's not the existing structure, but there is a culture, laboratory for culture at the head of national TB programs, so that is why we have put energy in terms of resources and training, so that at the end of the day when the trial is finished, the national TB control program is set, and is improved a facility for a laboratory, and I think that's a very important approach to have is really not to put, as you say, not to piggyback and put something on top, but really go through what infrastructure is existing in order to reinforce it.

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DR. RICHARD CHAISSON, MD: OK, back there. We're going to have to make these very pithy.

FEMALE SPEAKER 2: Thank you so much. I am [inaudible] from Pakistan. I have many points, but I will try to be quick. Thank you for bringing the patient's perspective in this discussion and this is very important.

I really like having patients in this process of new drug development, but there are certain question which is really important for me to ask, like we have the current approaches to enroll patients and community, like WHO endorsing, ACSM model and we're having different, other patients capacity building improvement, but the important thing is their lack of patients are enrolled at country level. They are not enrolled in anywhere like they need to be there in that national TB control program level. They should be involved at all levels, if you go up a level, and my question is if we go for the new drugs, like we were having the discussion the last day, like the amount of sputum and slide work. In my country especially, I am talking about from Pakistan side, the patient did not know what the sputum is and how they can give their sputum for testing. Then they give sputum we are not even know whether this is a real amount, whether this is the sputum or not. It may be affecting the findings of the research. It might be good to think about how we can improve their capacity in this regard.

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And the second question is the research language. This language of research is very technical and complex, and the patients are unable to understand what they are asking about. And the third is research ethics and protocol, mostly in the country where I am from. The recent ethics and protocol are not followed. If they are not followed, there are so many questions which have been raised. And the fourth and very important point is there is very less amount of investment in patient empowerment and capacity building, so how we can improve all these?

I have other many questions, but I will ask them individually. Thank you so much.

DR. RICHARD CHAISSON, MD: We'll take your points as commentary, that's very welcome so that you for making those points. I'll respond just to say that we've all been trying to learn from the experience with HIV where the community involvement has been so strong for so long, and TAG and other organizations like TAG have been leading the way in trying to bring that to TB, and we're all benefiting from that.

MALE SPEAKER 2: I am [inaudible] from India. My question is to Dr. Margareth that do you do Phase One for a new drug in your country, or you take Phase One from another country and go to Phase Two and Phase Three? Do you also study the animal toxicology clinical data before consenting for trial?

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MARGARETH NDOMONDO-SIGONDA: Thank you. As I said initially, what we have so far, and as far as the trials are concerned, the current vaccine trial is the Phase Two, Phase Three study. We have not had Phase One trials as of yet, and even there are other ones that I mentioned about. I said we have a total of about twenty trials that are being conducted in the country. Most of them are under Phase Three. So this is the status of the trials that are being conducted in the country.

DR. RICHARD CHAISSON, MD: And this will be the very last brief question.

PAUL SUMMERFELD: Paul Summerfeld, and my comment relates to my role as chair of the Advocacy Communication Social Mobilization working group of the Stop TB partnership. I'm really just wanting partly, Chair, to respond to your initial comments when you, and I was very happy to see in your outline that you spoke at some length about the importance of community engagement, and I think I would have been interested, and perhaps there isn't time now, but I would have been interested to have heard more from the rest of the panel about their concepts of what community engagement means when talking about clinical trials. It seems to me that it's something that one should be building in to the way in which you are thinking from the outset of a trial design, and a site design, rather than having as a sort of

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add-on thought later on, but in terms of synergy within Stop TB partnership, my specific question I think would be, is there something that we in the, particularly on the country level side of the Advocacy Communication Working Group could actually do in terms perhaps of developing advice to assist with the community engagement aspects of clinical trials? Thank you.

DR. RICHARD CHAISSON, MD: Anybody care to tackle that?

FEMALE SPEAKER 3: In all the trials we have conducted, no sponsor was prepared to put money down for community participation, so given that we have what's nice to have, and what we have to have, and GCP GCP take precedence. We build in community participation to the best of our ability in terms of being the medical research consult, having a certain amount of corporate outreach and presence, and then in the hospitals and clinics that we work from, as a direct patient to patient contact kind of thing, but that's it at the moment.

DR. RICHARD CHAISSON: And Javid is going to make a final comment.

JAVID SYED: It was actually, it's in relation to the last couple of comments. It's interesting because I think all of the inequities that were couched in the global north and global south context in these presentations are also quite

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easily transposed to the distinctions between researchers and communities in many contexts.

And so I think a lot of the issues that are proposed as solutions for researchers in the global south could also be posed as solutions for activists in communities in which research is happening, so training, capacity building, research literacy, awareness of resources in the community that can get supported and built up in a way that doesn't excessively tap the community's resources are all also potential strategies to strengthen a community's capacity to participate in a trial in a more equitable way.

So I think it's certainly things, that I know the [inaudible] consortium I know has done a lot of work on and I'm sure a lot of the other researchers have also done a lot of work on, but it's something that we do need to emphasize in settings like this, lest it's seen as a luxury that's not necessary. Especially from the HIV world, we've seen when that's not engaged in an appropriate way, like the Smart study for example, it can just blow up in our faces for really terrible reasons, and we don't want to have those experiences for the TB community as well.

DR. RICHARD CHAISSON, MD: OK we are going to take a one-hour lunch break, and I'd like to ask you all to join me in thanking the panel for a great presentation. [Applause]

[END RECORDING - TB Alliance Session 2]

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