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REVIEWING HIV-RELATED RESEARCH IN EMERGING ECONOMIES: THE ROLE OF GOVERNMENT REVIEWING AGENCIES

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Abstract

Little research has explored the possible effects of government institutions in emerging economies on ethical reviews of multinational research. We conducted semi-structured, in-depth telephone interviews with 15 researchers, Research Ethics Committees (RECs) personnel, and a government agency member involved in multinational HIV Prevention Trials Network (HPTN) research in emerging economies. Ministries of Health (MOH) or other government agencies often play pivotal roles as facilitators or barriers in the research ethics approval process. Government agency RECs reviewing protocols may face particular challenges, as they can lack resources, be poorly organized, have inconsistent review processes and, limited expertise, use differing definitions of national interests, including upholding national reputation and avoiding potential exploitation and stigma of the country's population. The MOH/governmental review body may be affected by power dynamics and politics in study reviews; may consider issues both related and unrelated to research ethics as understood elsewhere; and may prioritize particular diseases, treatments, or interventions over other topics/types of research. Poor communication and deeply-rooted tensions may exist between sponsor and host countries, impeding optimal interactions and reviews. Investigators must understand and plan for the potential effects of governmental agencies on multinational collaborative research, including preserving adequate time for agency review, and contacting these agencies beforehand to address issues that may arise. Better understanding of these issues can aid and advance appropriate global scientific collaboration.

Keywords

Ministries of Health; Ethics; Institutional Review Boards; Research Ethics Committees; Emerging Economies; HIV

INTRODUCTION

Researchers from industrialized countries seeking to conduct multinational collaborative studies in countries with emerging economies face various challenges, including obtaining appropriate approval from within the host country, such as from local, institution-based

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Institutional Review Boards (IRBs) or Research Ethics Committees (RECs) (both hereinafter used interchangeably), as well as RECs or research review committees operated by ministries of health or national research agencies. While there are sound reasons for these processes and approvals, they may also pose several obstacles, hampering important research efforts.[1] This problem is not unique to multinational collaborative research in emerging economies.[2] For instance, in developed countries, researchers have criticized IRBs/RECs for impeding and delaying research.[3]

Several studies have examined aspects of IRBs in the developed world, mostly in the US, focusing mainly on logistical details (e.g., sociodemographic characteristics of members, lengths of time for approval).[4,5,6] Several articles describe aspects of RECs in one or more emerging economies.[7,8,9,10,11] But most empirical studies have focused on logistical aspects of RECs[12,13] – e.g., whether national ethics committees and/or regulations exist, how often an REC meets, how many protocols RECs review yearly, what formal ethics or other training members have had, and whether and from what sources RECs receive financial support.[14] Several countries have one national REC, not individual institutional RECs.[15,16,17,18] These studies have found needs for training and expertise in ethics and science, and resources.[19,20,21,22,23] Many RECs lack standard operating procedures (SOPs),[24,25] and in some cases, lack diversity in gender and community representation.[26] A few studies have explored views and decision-making of RECs in emerging economies, and across different countries. For instance, IRB/REC members in the US are more likely than those in South Africa to think that subjects in emerging economies understand informed consent forms, risks and benefits, and the concept of placebos.[27]

US IRBs operate within complex institutional contexts, shaped by federal laws and agencies.[28] But many questions remain about the contexts involved abroad – how these committees in emerging economies operate, make decisions and interact with investigators, researchers, and others.

Among the most challenging issues IRBs face in many emerging economies concern studies on HIV. From the onset of the HIV epidemic, HIV prevention studies have generated controversies, including use of placebo controls to study mother-to-child transmission, male circumcision, female microbicides, and pre-exposure prophylaxis.[29,30,31,32,33]

Given concerns associated with REC review of HIV-related research, we decided to explore the related challenges faced by those who have been involved with multinational collaborative research associated with the HPTN (HIV Prevention Trial Network), a global network funded by the US National Institutes of Health (NIH)`. Specifically, we conducted in-depth semi-structured-interviews with HPTN researchers, REC chairs and others to understand their experiences and views concerning reviews of HPTN research in emerging economies. Interviewees described several challenges they faced concerning reviews of these protocols. One area that they repeatedly mentioned is the role of ministries of health (MOH) in study approval processes. In emerging economies, MOH committee or government REC approval of a protocol is often required in addition to local or institutional REC approval. Governmental agencies, particularly MOH in emerging economies, which often assume this authority or act as sponsor of a national REC, therefore are able to

determine whether and how research sponsored by US entities is conducted in those countries. But, how government agencies and government RECs in emerging economies actually impact US-sponsored studies has received little, if any, previous empirical study.

METHODS

We contacted by e-mail 66 researchers affiliated with one or more HPTN studies, of whom 25 agreed to participate (yielding a response rate among researchers of 38%). Of these, 13 were based outside the US, in emerging economies. We were able to schedule interviews with 12 of these 13 researchers, who were involved in a total of 7 HPTN studies. Thus, of the 12 HPTN studies being conducted at the time, at least in part in emerging economies, researchers involved in 7 were included in the study (yielding a response rate among studies of 58% – i.e., 7 of the 12 studies). Two of these 12 respondents were also members of their REC. We informed the others that we would like to interview a member of their REC as well; and asked them to put us in contact with their IRB chair or administrator. Several provided contact information or confirmed that they had attempted to contact this individual directly, asking if we could interview them. We were able to interview 3 additional REC chairs in this way – one of whom was a member of the government agency REC. One of the other REC chairs declined to be interviewed. We do not know whether all of the researchers in fact tried to contact their REC chairs on our behalf. In some cases, researchers provided e-mail addresses that were incorrect. The other REC chairs did not respond to e-mails from the researcher or from us, leaving us with an REC response rate of 30%. Principal Investigator (RK) conducted semi-structured, in-depth telephone interviews of about one hour each with these 15 respondents (researchers, REC and government agency personnel). As shown in Table 1, there were 8 male and 7 female interviewees. The interviewees represented several geographic regions: Sub-Saharan Africa (7); Asia (4); and Latin American/Caribbean (4). The Columbia University Department of Psychiatry Institutional Review Board approved the study; and all respondents gave oral informed consent, consistent with our approved protocol.

Field notes were recorded during and after each interview. Interviews were audiotaped, transcribed and verified for accuracy against audio recordings. A content-analysis was then conducted that was informed by Grounded Theory.[34] The iterative analysis process, which involves constant comparison, allowed for refinement of themes throughout the data collection stage of the study.

RK and three research assistants (RAs) systematically analyzed the interviews to assess interviewees' perceptions of research review processes. This involved identification of themes and/or categories of ideas (i.e., codes). Two coders (RAs) analyzed each transcript independently. A coding manual was developed and areas of disagreement in code development were discussed amongst the 3 RAs and the PI until consensus was reached. New themes that did not fit into this original coding framework were discussed, and modifications were made in the manual when deemed appropriate. The codes and sub-codes were then used in analysis of all of the interviews.

To protect confidentiality, especially given the sensitivity of the information provided, we have not identified respondents by country or nationality. Each speaker is identified by an ID number and by status as a researcher (RES), local REC member (REC) and/or a member of a government agency or government REC (GREC).

RESULTS

In many host countries with emerging economies, MOH or other government agencies serve as review bodies whose approval is required in order to conduct human studies; in this way, these agencies play pivotal roles and can profoundly affect the research review process (Figure 1). As shown on Table 2, several themes and subthemes emerged regarding the considerations that these agencies may take into account. These considerations are both related and unrelated to research ethics review as, commonly practiced elsewhere. Challenges arise related to differing definitions of national interests; prioritizations of particular diseases, treatments or interventions; perceptions of the value of prevention (vs. treatment); desires to uphold national reputation and avoid potential exploitation and stigma of the country's population; low resources; poor organization; inconsistent review processes; limited expertise; and problems storing biospecimens. Poor communication and tensions may exist between sponsor and host countries, impeding optimal interactions and reviews. Agencies may be influenced by political priorities and power dynamics. These factors can affect whether, when and how protocols get approved.

ROLES OF MOH/ GOVERNMENT RECS

Of the 15 interviewees, 14 said the MOH or another government agency played a role in reviewing and regulating research. In general, both local and foreign researchers expressed frustrations dealing with governmental bodies for logistical and political reasons. In some countries, a national, central REC exists, which may be located inside or outside of the MOH. Across countries, different government agencies may be involved in reviewing and/or overseeing US sponsored HIV-related research – MOH and/or other agencies concerned with drugs, biosafety, scientific affairs or research.

Differing definitions of national interests

The MOH or similar governmental body, when its approval was required, tended to factor national interests into its decision-making process. But what qualified as "national interests" was not always clear. One interviewee stated, "Their definition is their definition … There is no definition." **(RES #2)** Other interviewees, however, described specific national interests. An agency's concern may be that sponsors ensure post-trial access to medication for subjects, if the drug under investigation proves more efficacious than the current standard of care in the country. This concern sometimes appeared twofold: an economic concern with funding to provide newer drugs to citizens after the study ends, and an ethical and medical concern about continuity of care:

> With a discordant couples study [i.e., when one partner is infected with HIV and the other is not], you undertake a study that proves that 96% of infection can be averted and prevented by giving anti-retrovirals. But in this country, at this point in

> time, anti-retrovirals would not have been indicated for use as prophylaxis in discordant couples. So, once you've proven efficacy, discordant couples in the country ethically could be provided with the drugs to prevent transmission within the couple. That puts pressure on [government agencies] to provide these drugs when they do not have the budget to do so. Therefore, they are increasingly forcing you to include in your proposal how you are going to fund and provide supplies of therapies that the study demonstrates to work. (**RES #9)**

Another national concern was the relevance of research results for the country in question; but what is deemed to be important can vary over time.

> It's more the relevance for the country. The REC deals more with the ethical issues. But the [government committee], depending on who's sitting on it at any point, may raise ethical issues as well. **(RES #12)**

The government agency may pressure local RECs to insist that local researchers be involved in foreign-funded research due to "skepticism of [Western researchers] coming to do research, and taking all the data from the country without having local people involved." **(RES #9)** This pressure has caused foreign researchers to include "ghost investigators" on protocols for review – i.e., local investigators whose names are included on the studies without a true or significant contribution to the research:

> Very often, you may not have a local investigator with the capacity to undertake and participate in the research. Sometimes, that can be a reason to delay, or to include ghost investigators who are local, but would not in themselves be participating in the research. They may be physically present, but would not have the full expertise to contribute significantly to the research. But because the local IRB wants these people to be involved in the research, you have no choice, if you want to get your protocols approved. That is an area that we've been working on with them. We want local investigators who have the capacity and the knowledge of the protocols, before we include them. Much like: if you're going to say somebody is going to be a co-author on your paper, they should have participated in the research. **(RES #9)**

Is research a priority?

Government agencies appeared to vary in how much they considered research itself to be a priority. One interviewee noted that a national research agenda existed, which included some governmental interest in research. The agency assessed how closely proposed studies aligned with the government's specific objectives, and the government approved a few studies outside this agenda. An agency employee said:

> We actually look at the national research agenda. We actually encourage researchers to look at what we have written down there as our priorities, and study those. We've allowed [the researchers] a little freedom to maybe look into other things that are not in the agenda, but the majority are mostly looking within that research agenda. **(REC/GREC #5)**

By contrast, another interviewee noted that research as a whole was not a priority in the country, because the government was still struggling to meet basic needs, such as providing clean water, sanitation, and education, and eradicating poverty:

> Development of our basic infrastructure for research has to also have a contribution from the local, host country, and the [government agencies] of that country. They have to invest in it…But that hasn't been the case. The priorities have very often been elsewhere. I can understand sometimes why. Instead of investing your money in research, you want to use those dollars for education, clean water, sanitation, and eradicating poverty. Those are the government's priorities. So I sometimes understand, with the competition for meager resources, why research suffers. But on the other hand, one would argue that you can invest in that research to inform how best to address and eradicate a particular disease, and develop programs. **(RES #9)**

Specific diseases or interventions as priorities

Government RECs may approve certain non-HIV studies more quickly than US-funded HIV studies:

> The problem [researchers have] is primarily HIV-related trials. We work with malaria, and those studies just go right through quickly – we have the complete support of the Ministry. There's cooperation – no delays. It's different. OB, cancer, and surgery studies go right through. HIV has its particular issues. You wouldn't think that there would be such a big difference. **(RES #2)**

Although this researcher believed that the government agency appeared to be reluctant to approve HIV research, as compared to studies on other diseases and conditions, agencies in other countries may prefer HIV treatment over HIV prevention. Government funding may thus get directed toward anti-retroviral (ARV) treatment research over prevention studies:

> There's a very powerful ARV Treatment Committee in the [agency] that sort of rules all policy. There is not a Prevention Committee! No one in the [agency] is a champion of HIV prevention. **(RES #2)**

This interviewee perceived a relative lack of support for prevention trials. Another researcher echoed this perceived bias against HIV prevention studies, and thought it resulted from of a fear of promoting risky behaviors:

> Most of the studies that we're having problems with are HIV prevention studies, because a few people in the [agency] think that HIV prevention studies are asking participants to get involved in risky behaviors. **(RES #3)**

Avoiding stigma

One interviewee thought that the government agency's caution might arise from a fear of stigmatizing the country's population:

> It's just suspicion that a report will come out about the genetic makeup of a population in the country – that their genetic components will be used for something odd. It's more of what a global perception would be. **(RES #2)**

Another country's government agency appeared not to want world media headlines to announce results of HIV risk studies that the agency had not vetted:

> …one of the [agency's] concerns was they didn't want things to appear in the news one day that a study was done in their country, and they didn't see it. That's partly why they demand to see all these studies: they're afraid they'll be published in a newspaper…it's almost like a control issue. **(RES #2)**

In particular, this interviewee explained, studies might show high rates of HIV among certain groups in the country, which could be stigmatizing.

Storage of biospecimens

Some government agency RECs had concerns about particular aspects of a study's conduct, especially storage of samples, and hence sought to have biological specimens stored inside, as well as outside the country. An agency might allow specimens to leave the country only in the case of very specific and compelling research objectives. One agency did not allow samples to leave the country, and insisted that they be processed locally: "They basically don't want samples to leave the country, period." **(RES #9)** This interviewee said that the agency would approve international processing, but only with significant hesitation, if researchers argued for the need to reduce laboratory error and ensure uniformity of processing: "with some of those explanations, they do relent, and provide the approval. But they tell you that we prefer that some of the work processes begin regionally." **(RES #9)**

Fears of exploitation

Several interviewees described governmental concerns that foreign-sponsored research may exploit the host country's citizens. For example, one interviewee stated that the government agency's committee reviewed all foreign-funded research grants. This extra review process did not occur with locally funded trials:

> If it were a study, funded by in-country resources, we would not have to go to the [agency] committee. But if it is an internationally-funded trial, whatever country it may be, it is then submitted to the [agency] committee. **(RES #8)**

In another country, legislation required that any foreign-funded study also be conducted in the sponsor country, in order to protect against a double standard:

> We are very wary of a double standard. No study would be approved if it would be conducted differently in the sponsor country. Our legislation demands that the study has been approved and conducted in the country of origin. If not, the explanation must be very good, because we cannot accept these double standards… This is a *sine qua non* point. **(RES #6)**

However, another interviewee from the same country found fault with this policy:

> Sometimes they have a very paternalistic view. This is a problem. They think that if the study's not conducted in the country that planned the research, there's something wrong with it. This kind of thinking is very naïve. **(RES #15)**

This researcher felt that certain studies (e.g., of malaria) may be more appropriate in the host, rather than in the sponsoring country.

Government agency committees may be suspicious of foreign funding due to a fear that foreign, rather than local, researchers would then be in control. In such instances, government RECs may strive for more control:

> The [government committee] thinks that because we [researchers] have money, we want to do whatever we want – that we want to have things our way, that the [international project team] wants it the way they want it. The [agency committee] believes in local control. **(RES #3)**

Host country concerns about exploitation often appeared to be directed particularly toward US sponsors. One US researcher based in an emerging economy expressed this anti-American sentiment:

> If we were a British institution, we would be much better off, because the Brits have always been there, and there's more trust of the Brits than of the Americans. They think the Americans are out for their own advantage at the expense of the host population. **(RES #2)**

Other interviewees mentioned this "anti-Yankee" feeling as well. One interviewee thought that though the government as a whole did not share this sentiment, the government agency involved in review of foreign-funded studies did:

> The [review agency] is plagued by the left-wing people, linked with the socialists in the past. They have this view that Americans are bad…The government now is much more open and not anti-American. So the [review committee] doesn't really necessarily reflect what is in place at this point." **(RES #15)**

This respondent felt that suspicion toward American researchers has led the agency to approve research on new applications of pre-existing drugs, rather than research on new drugs. Mistrust can exist and strongly affect the review process. "There is still awareness that some researchers can or may use our population for their sake." **[RES #15]**) He thought this suspicion is specific to the US and that research funded by other countries such as Great Britain and France is seen as "benevolent."

Other obstacles

Low resources—Researchers expressed frustration with slow approval processes that resulted from poorly-resourced government agencies and local RECs. Communication with the agency REC could be difficult because it had "low resources and little access to technology like e-mail." **(RES #3)** Another researcher thought that his country's government REC was understaffed because the agency as a whole had budget cuts. As a result of the country's financial problems, the agency had not replaced empty positions:

> Because of the financial crunch in the country, they haven't replaced people who have resigned. There's been a freeze on new hires within the [agency]. **(RES #9)**

Another researcher felt that his country's review body is "swamped with work" because poor funding has had several ramifications, including poor staff training and refutations and procedures.

> If the [agency] were better funded, it would be able to apply, not a higher caliber, but people with more experience in dealing with clinical trial regulatory work. If you pay better, you can retain staff. And I think they are swamped, overwhelmed with the applications that come through. There's a lack of procedure – just checking that the five attached documents have everything in order and are up-to-date. But sometimes, they don't have things as simple as operating procedures or checklists in place that could aid people in the work they do. **(RES #12)**

He felt, however, that despite being underfunded, there is a general resistance to receiving outside help, for fear of appearing corrupt:

> …Getting simple things, like we've bought fax machines in the past. But as a department, they're not allowed to accept these things, because there would be perceptions that we're trying to bribe them to get applications through quicker. **(RES #12)**

Poor organization—In addition to financial issues, interviewees have also perceived that poor organization of the government REC or review body can contribute to inefficiencies in the review process. One researcher felt that the agency REC has no clear rules or regulations in place, leading to inconsistencies in review processes. Administrative confusion can ensue – e.g., concerning needs to purchase insurance for subjects:

> We kept saying, "Please tell us what that means, and where to get it, and we will get it." The [agency] didn't really know themselves. They just heard that at some conference or some meeting…It was months and months of torture. We finally got them to get on a call with the insurance company. By that time, they had shifted, and said they not only need no-fault insurance, but insurance for participants after they exit the study – for the rest of their life…We need to give them some money at the time of leaving the trial that would compensate them for possible harm in the future…That is not only impossible, but it's unethical. NIH was able to cover part of it, up to when subjects exited the trial, but would not cover any insurance after subjects exit the trial. So, now we're stuck with that bill…The insurance coverage is not for the individual, but for the whole trial…We're paying for three years of enrollment and follow-up, and five years of post-trial coverage. If we need it beyond that time, we're going to have to go back and get it adjusted. **(RES #2)**

Nearly all researchers thought that their government agency review processes were too slow. One interviewee **(RES #11)** said that the REC "argued that [it] met too infrequently to review all the protocols they received quickly." Another investigator said that though the agency had an expedited review process, it existed only on paper, and in fact was much slower:

> They meet only every two months, and there's not much of an expedited review system. It is on paper, but not in reality. So the review process can be quite lengthy.

> We have…worked with that office to try to help them with filing and streamline some of their administrative work to make it more efficient. And that has had some effect. **(RES #2)**

Moreover, since the agency review committee met only once every two months, applying for an expedited review may even impede researchers, by causing them to miss the deadline for the regular review committee, if the expedited review committee does not approve the protocol swiftly or on time:

> They meet on [one set day] each month. Expedited review only makes sense in the two weeks before that, because any new protocol or any response for the main committee has to be sent out [a month before the meeting]. So if you put it in for expedited review, and they say it's going to get expedited, they send it for expedited review to the chair and two committee members. But if those letters don't get sent out in time, or if they don't review it in time and get the response back, it doesn't get into the main pile that will be reviewed in the main meeting, which will be in a month. And so sometimes you don't get either review. **(RES #2)**

Poor organization could also make a national review committee inconsistent. This researcher said,

> The most outstanding characteristic of that committee is that it's unpredictable! It's never clear what they will focus on in reviews from meeting to meeting, which makes it very hard to anticipate if a study will be accepted, and what the anticipated ethical issues may be. Sometimes they aren't really ethical issues, they're more political, or personnel issues that really don't relate to the well-being of the participants. **(RES #2)**

Low expertise—Several researchers felt that government agency reviewers at times lacked expertise, delaying research. One interviewee perceived a lack of scientific knowledge on the committee:

> Not many of them are really science-driven people. They are from the church, or other institutions that have nothing to do with research – especially with clinical research. **(RES #15)**

Difficulty finding a reviewer with specialization in a research area could slow down the review significantly. Another researcher reported,

> For specialist areas, sometimes they have problems finding appropriate people to review applications. Sometimes, if it's a very specialized area, and there's one person in the country that could probably review it, that person's timelines are going to end up being your timelines. **(RES #12)**

Perceived power dynamics—Several researchers felt that politics could affect the approval of research in several ways. "The official relationship and the letters we get back are sometimes insulting," making it "hard for us to understand where all that comes from." **(RES #2)** This interviewee thought that the agency's focus was on "political" rather than ethical issues. **(RES #2)**

Other interviewees felt that the governmental agency committee was at times difficult because it sought to exercise or display its power. One interviewee felt that review members had to "show service" and asked "stupid questions" just to demonstrate they were contributing. The committee could write:

> I suggest that this language should be like that. They would just present endless different ways of saying the same thing, just to be able to say that they're contributing. **(RES #15)**

Researchers often tried to change the agency REC, but with little, if any, success. One tried seeking help from the nation's leaders, but was still unable to alter the situation ("We and others asked at the level of the vice president of the country." **[RES #2])** Positions on a national agency REC may have are no term limits. Hence, these committee members' power may be unchecked. "I wouldn't say it's corrupt," one researcher explained, but rather, "a place that people go to show their power." **(RES #3)**

An agency REC member interviewee also acknowledged the presence of power dynamics. He acknowledged researchers' antipathy toward the agency, but he believed that toughness was essential.

> We're one of the most hated institutions in the country by the researchers. We're mean with them. But it's a fact of life: if they don't call us names, then we're not doing a good job. **(REC/GREC #5)**

He explained his rationale:

> They need to understand that we have to protect the participant as well, while encouraging good science. Unfortunately, most of them think of that as a hindrance, that we just stand in their way, or just slow them down in their research. **(REC/GREC #5)**

He thus felt that he, not the researchers or the local RECs, protected participants – that local RECs may not be able to address these issues as effectively as government review agencies or government RECs.

Several interviewees felt that politics and power dynamics affected the agency's structure, and that appealing an agency review was difficult, if not impossible, because of conflicts of interest. The chair of an appeals board may, for instance, also oversee the review process. Such individuals may have added power since they often hold the same positions for long periods of time.

DISCUSSION

There is an enormous amount of multinational collaborative US-sponsored research conducted abroad, but ethical reviews of these studies can face barriers that need to be understood and appreciated more carefully. Needs for cultural sensitivity and awareness of broader issues involved in conducting research abroad have been discussed, but our data highlight that investigators (as well as sponsors and funders) must examine and appreciate how host country local governmental agencies may impact multinational collaborative

international research. MOH and other government agencies can vary widely between countries in regard to expertise, effectiveness and outlook, complicating the research approval process and making it, in many cases, unpredictable.

The roles of MOH in delivering primary health care and public health services have been explored, but not related to these agencies' involvement in research ethics.[35,36] Several articles have discussed ethical challenges posed by studies in emerging economies, and a handful of these reports have mentioned MOH in passing, but have not examined the range of issues and complexities involved.[37] One article, for instance, mentioned simply that "politics" may be involved in REC decisions.[38] Focus groups in Botswana suggested that having protocols approved by both a university REC and an MOH committee caused "inordinate delays."[39] Another article mentioned the MOH only to say that researchers in Ghana were able to consult with the chiefs and residents of a district with approval of the MOH.[40] Macpherson[41] described a study in which the local REC approved a study, but the MOH did not. She suggested that the MOH and the local REC interact more, that the REC include members of the MOH, and/or that the MOH create an internal REC.[42] In a Swaziland study, a host country collaborator suggested getting MOH approval to avoid political repercussions.[43] The MOH then limited the topics to be explored to those that were not politically sensitive, and stated that the researchers could show the informed consent document to participants but not copy or distribute it.

Our data shed important additional critical light on these issues, substantially expanding the range of issues concerning interactions, and the intricacies involved. On the one hand, government review bodies can play valuable roles, enhancing the appropriateness of research for particular countries. If local institutional RECs have non-financial conflicts of interest (e.g., wanting to help colleagues bring research funding to a local institution) and/or lack resources to review studies optimally, national government-level input can be helpful, correcting for these issues. These agencies can hence facilitate optimal review, and benefit the country and research in key ways. Governmental prioritization of certain diseases and research can aid citizens and the local research community, facilitating allocation of resources for particular purposes that bolster public health, heightening attention to specific diseases or problems of national concern. For instance, government agency emphasis on post-trial access from foreign sponsors can help protect research subjects, and mobilize additional foreign aid.

On the other hand, some may argue that government agencies can at times impede research that can benefit many citizens. Governmental agencies may have other competing priorities that can at times influence how they review studies. A government may, for instance, prioritize economic development over research. National or agency agendas, power dynamics, political tensions, exercise and abuse of power, and structural issues can all potentially affect the review of a study. These obstacles may involve both the content and the process of review. For instance, requirements to include, as PIs, additional local investigators who have not contributed to the research can create problems, violating ethical and professional guidelines concerning authorship, as presented by the International Committee of Medical Journal Editors (ICMJE).[44] Though not mentioned explicitly by these interviewees, anecdotally, some agencies have also forbidden secondary use of research

data. Other obstacles, including poor capacity and low resources, can also make the approval process inefficient and slow. Poor organization and communication can pose difficulties for researchers, in part since applications of rules may then be inconsistent.

These competing priorities may be legitimate, but differ from the priorities of local IRBs and RECs in several ways. IRBs, RECs, researchers, sponsors and funders need to be aware of these differences in order to address them as best as possible. Moreover, national agencies may define and weigh these competing priorities in ways that are subjective and opaque – rather than transparent – and can be affected by external political, economic and personal factors, including possible corruption.

Some of the problems described here concerning agency reviews are similar to those that researchers face regarding US IRBs as well (e.g., "wordsmithing" documents), but other concerns here (e.g., regarding competing national priorities) are more unique to government agencies or government RECs reviewing proposed research. While local RECs may focus on individual participant-researcher interactions (e.g., informed consent), government agency committees may emphasize more system-level issues, such as obtaining insurance to cover potential harms – in part given limitations in the national health care system. These broader concerns are reflected in international guidance documents, but agencies may see these system-level issues as matters of national policy, and hence emphasize these more than do local RECs. In part since these concerns reflect international guidance, researchers should strive to anticipate and address these issues clearly in their protocols, and sponsors and funders should anticipate, in study budgets, the costs of addressing these concerns in order to secure approval to conduct a proposed study.

Government and local committee reviews can differ due to process issues related to not only the lack of training and resources, but the exercise of political position and power. Moreover, both sponsor and host country local or institutional RECs have often already reviewed and approved a study before the agency assesses it. Thus, this additional, national level of governmental review can take additional time and resources. An agency may take long periods of time (e.g., up to a year) to review a study, yet may not significantly alter the protocol or improve subject protections. Investigators should plan appropriately to allow sufficient time for these processes.

These data should be interpreted with several potential limitations in mind. First, these data are based on a relatively small number of in-depth interviews with researchers who conduct multi-national collaborative HIV-prevention research in emerging economies, and with REC personnel outside of the US. We did not include direct observations of governmental or MOH meetings, or investigate MOH or governmental written records. Future research might consider using such approaches; yet these additional data may be hard to obtain, given the politically and culturally sensitive nature of these topics. In the US, for instance, some IRBs have often been reluctant to agree to be observed as part of research. Five of the 15 respondents were members or chairs of IRBs. Many of the interviewees are researchers presenting their points of view that understandably favor research. While researchers' complaints about MOHs may be known to some observers anecdotally, they have not been described in the academic literature. Such publication is crucial in order to facilitate their

consideration and examination by researchers and scholars in a variety of fields, policy makers, funders, and others. These data are thus, to our knowledge, the first published on this topic. Moreover, researchers have had extensive interactions concerning these issues – their views and experiences are thus valuable to examine in and of themselves. The perspectives of other MOH staff may differ in ways that future studies can begin to explore further. Moreover, these data appear to have certain face validity. Though the number of themes identified in these interviews may seem relatively high, each of these interviews probed respondents about numerous issues and studies. Future studies should investigate these issues among larger numbers of respondents from additional countries, involved in HIV as well as other kinds of research. These interviews also probed respondents' experiences and views based on their past experiences. Future research might be conducted prospectively .

These findings have important implications for future studies, education and practice. Investigators from sponsor countries who conduct research in emerging economies would benefit from being aware of, and prepared to address, these content and process issues. Anticipating these structural, resource and attitudinal issues might improve the efficiency of having studies reviewed. Researchers from host countries, too, may benefit from heightened appreciation of these factors. Given post-colonial histories, some governments and their RECs may be cautious about foreign sponsors, particularly US and other OECD-based sponsors and funders, fearing exploitation; and see themselves as playing important roles in determining and pursuing what they perceive to be national interests. Hence, US and host country researchers may need to be particularly sensitive about these issues, in order to ameliorate tensions, and improve collaboration and relationships. These investigators, along with sponsors, research networks and local researchers, should not only plan adequate time for agency review, but consider contacting these agencies beforehand to anticipate and communicate about questions and concerns that might arise, explicitly addressing possible agency concerns (e.g., explaining exactly how research on a particular disease, using a particular prevention strategy, can indeed serve that nation's interests). Poor communication and deeply-rooted tensions may exist between sponsor and host countries. Further awareness and investigation of these strains may help to improve relationships between these parties.

Host country government agencies may also benefit from becoming more aware of researcher perspectives on these processes, to ensure that review processes are as optimal as possible – e.g., including individuals with appropriate scientific expertise, if possible, and recognizing that facilitation of protocol reviews might benefit the country in vital ways.

Efforts by sponsors, funders and researchers to enhance dialogue and interactions to assist host countries in improving the quality of agency reviews and oversight can also be helpful. The HIV Prevention Trials Network (HPTN) Ethics Working Group has published ethics guidelines for research presenting a series of guidelines that should be considered.[45] The Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT)[46] has recently developed important suggestions as well.[47]

Future studies can examine aspects of these issues in more detail, probing perspectives and experiences concerning agency reviews among researchers, local and government agency

REC members in other countries, related to other diseases as well. Barriers and facilitators of agency review can be investigated further – e.g., exploring the significance of factors unrelated to the research protocol per se that may affect agencies' suggested revisions and relationships with researchers and RECs.

These data can also be used to aid practice in other ways, too – e.g., in developing a list of "best practices". Policymakers in host countries could potentially clarify the roles and appropriate purviews of governmental reviews, and be as aware as possible of both the benefits and costs of their decisions.

As international collaborative research becomes ever more prevalent, better understanding of the full range of issues that may influence research ethics review should aid in expanding appropriate global scientific progress and collaboration.

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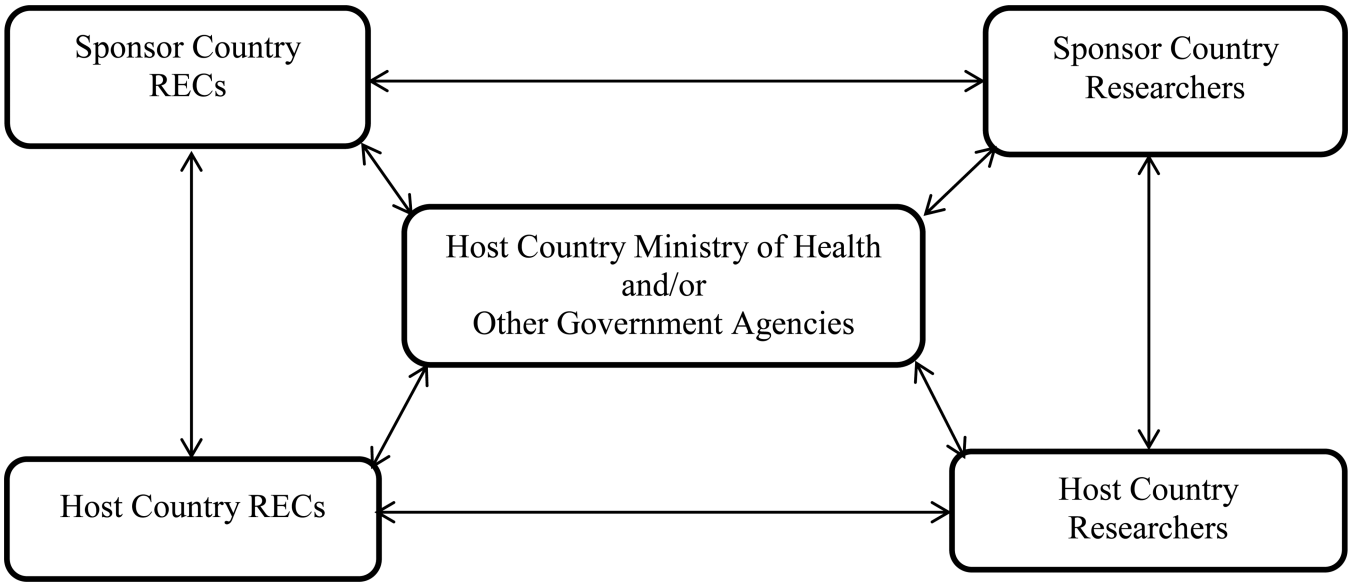

Figure 1.
Relationships between government agencies, researchers and IRBs/RECs.

Table 1

Interviewee Demographic Characteristics

Characteristic		**N**	**(%)**
Gender	Male	8	53%
	Female	7	47%
Role*	Investigator	12	
	Chair or Member of Local or Government Agency IRB	5	
	Researcher and IRB Chair/Member	2	
Region	Sub-Saharan Africa	7	47%
	Asia	4	27%
	Latin America & the Caribbean	4	27%

* Note: Some respondents had multiple roles.

Table 2

Themes concerning roles of government agencies in protocol reviews.

- Differing definitions of national interests: Government may
  - Prioritize certain diseases and/or treatments or interventions over others
  - Not always prioritize research
  - Prioritize national reputation
    - Seek to avoid stigmatization of a country's population.
  - Fear exploitation by US funders
  - Be wary of storage of biospecimens and data in sponsor countries
  - Draw on perceived national priorities in reviewing research design and subject protections
- Low resources
  - Limited financial support
  - Suboptimal equipment (e.g. fax machines, Internet access)
  - Suboptimal computerized systems
  - REC members may have little ethics education
  - REC staff may be untrained or hard to retain.
- Poor organization
  - REC members may have limited research and scientific expertise
  - REC meetings may be infrequent
  - Rules for review may not be clear
    - Can lead to unpredictable reviewer feedback on protocols
    - Can lead to inconsistent review
  - Expedited review processes may exist in name, but not in practice
- Perceived power dynamics
  - Term limits may not exist
  - Agency and personnel members may feel needs to justify their positions
- Politics within the MOH/governmental review body structure
  - Conflicts of interest may exist
  - Same officials may oversee both reviews and appeals