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PAPER

Closing the translation gap for justice requirements in international research

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ABSTRACT

Bioethicists have long debated the content of sponsors and researchers' obligations of justice in international clinical research. However, there has been little empirical investigation as to whether and how obligations of responsiveness, ancillary care, post-trial benefits and research capacity strengthening are upheld in low- and middle-income country settings. In this paper, the authors argue that research ethics guidelines need to be more informed by international research practice. Practical guidance on how to fulfil these obligations is needed if research groups and other actors are to successfully translate them into practice because doing so is often a complicated, context-specific process. Case study research methods offer one avenue for collecting data to develop this guidance. The authors describe how such methods have been used in relation to the Shoklo Malaria Research Unit's vivax malaria treatment (VHX) trial (NCT01074905). Relying on the VHX trial example, the paper shows how information can be gathered from not only international clinical researchers but also trial participants, community advisory board members and research funder representatives in order to: (1) measure evidence of responsiveness, provision of ancillary care, access to post-trial benefits and research capacity strengthening in international clinical research; and (2) identify the contextual factors and roles and responsibilities that were instrumental in the fulfilment of these ethical obligations. Such empirical work is necessary to inform the articulation of obligations of justice in international research and to develop guidance on how to fulfil them in order to facilitate better adherence to guidelines' requirements.

INTRODUCTION

Within bioethics, there is a long tradition of identifying and debating the content of obligations that arise in the context of international clinical research, particularly with respect to what is owed to participants and their communities. Responsiveness to local needs and benefit sharing were developed as strategies to reduce the potential for exploitation of research participants.[1 2] Requirements have been described in leading international research ethics guidelines and in the bioethics literature that are intended to advance these strategies. Although there is no uniform articulation across international guidelines, four obligations are commonly cited:

- conducting research that is responsive to local health needs and priorities in host communities and/or countries[3–5];
- the provision of healthcare during studies such as ancillary care (ie, healthcare that is not required for either the scientific validity of a study or to redress study-related harms)[6 7];
- access to post-trial benefits such as medical treatments or practices developed by the study[3 4 8];
- research capacity strengthening in host communities and/or countries.[3 9]

Bioethicists have undertaken considerable work to better articulate the content of these obligations. However, significant debate continues regarding the scope of benefits owed during and after research, the assignment of responsibility for their provision, and the appropriate recipients.[2 10] Two positions regarding the definition of responsiveness exist, with one requiring international clinical research to target health needs that that are also health priorities of the host community and the other maintaining that it is sufficient to target health needs that are simply represented or prevalent in the host community.[5] The scope of ancillary care obligations has been variously defined, ranging from the stance that care for a broad range of conditions is owed to the view that only care related to the disease under study and any diagnoses generated as part of the study are owed.[7 11–13] Whether or not the benefits owed post-trial extend beyond the intervention under study and are owed to not just trial participants but also their communities have been heavily discussed as well.[13–15]

There has been much less focus within the discipline regarding whether and how obligations of justice can be implemented in the research setting. As has been noted, '[c]urrently, little information is available to ascertain what types of research are actually being undertaken in developing countries, how much work is being done, the benefits that studies presently offer communities, and whether research addresses the needs of developing countries, developed countries, or both'.[16] In 2001, Nancy Kass and Adnan Hyder conducted a study exploring the extent to which research ethics guidelines were observed in practice. The study solicited the perspectives of international researchers from the USA and low- and middle-income countries regarding the responsiveness of their projects to local needs, the standard of care provided to participants, the availability of successful study interventions post-trial and research capacity-building.[17] The study showed that ethical requirements for international research are not always observed. It did not, however,

provide information about how requirements, when observed, were implemented. Indeed few studies have sought to collect empirical data on such matters. Recently, the Global Campaign for Microbicides, a civil society organisation working to ensure the ethical development of HIV prevention tools, conducted a study examining the standards of care achieved in six international microbicide trials in Africa. The study also collected data on the ancillary care provided during trials, the capacity-building performed and the steps taken towards creating post-trial access to study interventions.[18] Beyond these two studies, discussion within bioethics does not address questions of implementation, aside from identifying impediments to doing so or characterising the obligations as aspirational or unrealistic.[19–21]

Ethical obligations are often not upheld both because of the complexity of doing so in resource-poor settings *and* because the development of guidelines is largely uniformed by the realities of research practice. Ethical requirements are derived from ethical principles and must necessarily be expressed in general terms. This can mean that insufficient guidance is available when practical difficulties arise in the research setting.[22] Improving the articulation of obligations of justice and developing guidance on *how* to implement them is necessary to facilitate fulfilment of complicated and difficult, yet ethically essential processes. We argue that research ethics guidelines need to be more informed by research practice. Empirical ethics research is vital to this process and to bridging the translation gap. From its outputs, guidance can be developed to assist research groups to meet ethical requirements.

This article is an 'empirical ethics' methods paper. It illustrates how information may be gathered from not only clinical researchers but also trial participants, community advisory board members and research funder representatives in order to:

1. measure evidence of responsiveness, provision of ancillary care, access to post-trial benefits and research capacity strengthening in international clinical trials;
2. identify the contextual factors and roles and responsibilities that were instrumental in the fulfilment of these ethical obligations.

To do so, the paper describes how case study research methods have been used to gather data about the implementation of ethical standards in the Shoklo Malaria Research Unit's (SMRU's) ongoing vivax malaria treatment (VHX) trial (http://clinicaltrials.gov/ct2/show/NCT01074905) on the Thai-Burmese border. It explains why the SMRU trial was selected as a case study and describes the recruitment, sampling and data collection methods used. The outputs that this approach generated are described and the main findings are briefly noted.

A METHODOLOGY TO STUDY THE IMPLEMENTATION OF JUSTICE REQUIREMENTS

Selection of research methods

To gather information on how obligations of justice are implemented in international research, a case study research methodology was selected. A case study is an empirical inquiry that investigates a contemporary phenomenon in depth and within its real-life context. It is an appropriate methodology to employ when one's research question seeks to explain *how* or *why* a complex social phenomena works, particularly when that understanding is encompassed in critical contextual conditions.[23]

Case study research generally (but not always) uses qualitative methods.[23] For our project, a triangulation approach was employed that relied on in-depth interviews, direct observation and document analysis. In-depth interviews were conducted with stakeholders involved in the trial being studied because they would bring the experiences and perspectives of the various trial stakeholders into account in significant detail. The interviews were supplemented by an examination of trial-related documents such as the grant proposal, ethics application and protocol and by direct observation at community advisory board meetings and trial sites. Ethical approval for the study was obtained from Mahidol, Oxford and Monash universities.

Selection of a case study

To identify an international research group that consciously designs its trials to fulfil obligations of justice, we relied on biomedical researchers known to us working in the field to recommend a group and facilitate an introduction. SMRU, a field research site of the Bangkok-based Mahidol-Oxford Tropical Medicine Research Unit, was contacted on our behalf. SMRU is located in Mae Sot (Thailand) and since 1985 has been conducting operational research that is designed to improve the health of the Karen and Burmese refugees, migrants and displaced persons living on the Thai-Burmese border.[24] (The Karen are the second largest ethnic group in Burma and have a long history of persecution by the Burmese military government.) It also functions as a health provider, running several clinics that service this border population. SMRU was interested in collaborating with us on the project. Further discussion confirmed that its research fit our main criterion for a case study, ensured that the project was feasible from SMRU's end and determined the actions that needed to be taken before data collection could commence. SMRU then selected its ongoing VHX trial to be the subject of the case study. The VHX trial is funded by the Wellcome Trust. It seeks to describe the epidemiology and compare the efficacy of three treatments for vivax malaria—chloroquine/primaquine, chloroquine and artesunate (http://clinicaltrials.gov/ct2/show/NCT01074905). Trial sites are five SMRU clinics—Mae La, Wang Pha, Mawker Thai, Mun Ru Chai and Mae Kon Ken (each located within an hour of Mae Sot)—and participants are drawn from the border population. There were roughly 410 participants at the time of this case study research.

Sampling and recruitment strategies for in-depth interviews

Participants in the case study were selected from the following categories of VHX trial stakeholders:

- principal and co-investigators,
- trial participants,
- members of the Tak Province Border Community Advisory Board (T-CAB) and
- funder representatives (from the Wellcome Trust's Science Funding Division).

The method of selecting participants was purposive, as it was based on their involvement in the VHX trial.[23] Selection criteria for participants were as follows:

1. being members of one of the aforementioned four groups,
2. being 18 years of age or older and
3. speaking English or Burmese fluently.

The VHX trial principal and co-investigators were identified using the trial protocol and recruited in person at SMRU. Snowball sampling techniques were employed to identify science portfolio advisors at the Wellcome Trust because they were more difficult to access. T-CAB members were identified and recruited for interview by a T-CAB coordinator. Five of fourteen T-CAB members were identified as appropriate

interview subjects because they lived in villages near the VHX trial sites and would, therefore, be most able to describe the impact of the trial on their community.

Trial participants who met the project selection criteria were identified by the SMRU medics who were in charge of the VHX trial at the two trial sites where interviews were conducted. The Mawker Thai clinic and the Mae La clinic were selected as interview recruitment sites because together they captured the diversity of the VHX trial participants. Mawker Thai clinic is used by migrant workers and displaced persons living south of Mae Sot (Thailand) and Mae La clinic is used by refugees living in Mae La camp, which is located 1 h north of Mae Sot.

At the two clinics, trial participants were recruited opportunistically for interviews by the medic in charge of the VHX trial. Trial participants had to wait for 45 min to 1 h for their blood test results as part of their follow-up visits for the trial, so taking part in a 45-minute interview did not considerably extend their clinic visits. Trial participants were compensated by SMRU for transport and a day's work for each follow-up visit as part of the VHX trial. Ultimately, the aim was to sample a range of trial participants, spanning all three treatment groups and who had spent varying lengths of time in the VHX trial.

For all four types of stakeholders, recruitment for interviews continued until every (consenting) member of the stakeholder group had been interviewed or data saturation was reached.

In-depth interview procedures

Nineteen in-depth (semi-structured) interviews were performed with VHX trial stakeholders: investigators (five interviews), T-CAB members (four interviews), trial participants (eight interviews), and Wellcome Trust science portfolio advisors (two interviews). Four interview guides were written, one for each category of VHX trial stakeholder. The interview question guides were developed over three stages:

1. ensuring alignment between the questions and the ethical constructs under investigation,
2. consultation with the Mahidol-Oxford Tropical Medicine Research Unit and SMRU staff in Bangkok and Mae Sot, and
3. pilot testing.

For investigators and funder representatives, a series of open-ended questions was designed such that interviewees were asked to describe, first, their roles and responsibilities during each phase of the VHX trial (funding, design, subject recruitment and data collection, analysis and post-trial) and, second, their perspective on the health impact of the VHX trial on participants and the border population during and after the trial. Follow-up questions probed specifically for information on the VHX trial's selection of research target (disease focus and research question), provision of ancillary care, post-trial benefits and research capacity strengthening (see box 1). Final question guides for T-CAB members and trial participants contained more targeted questions and fewer follow-up questions (see box 2). This was because SMRU staff did not think that trial participants and T-CAB members would know what to say in response to open-ended questions. In order to elicit as much narrative as possible and to avoid getting only yes or no answers in these interviews, the phrases 'Why?' or 'Please provide an example.' were added to the end of questions.

Pilot interviews were conducted with two researchers in Melbourne, Australia and two VHX trial participants at Mawker Thai clinic, and interview questions were modified accordingly. For interviews with trial participants and T-CAB members, three translators were used—an SMRU medic at Mawker Thai clinic, an SMRU medic at Mae La clinic and an SMRU doctor (for T-CAB interviews). These translators carried out the consent process with trial participants and T-CAB members in Burmese in the interviewer's presence. Each interviewee signed two consent forms, one for his/her records and one for ours. All interviews were recorded on a digital tape recorder and followed the same format: the interviewer would ask a question in English, the translator would ask the question in Burmese, the trial participant would respond in Burmese, and then the translator would briefly summarise his/her response to the interviewer in English. Occasionally, the interviewer would ask follow-up questions that were not on the interview guide.

Interviews with VHX trial investigators and Wellcome Trust science portfolio advisors were conducted (in English) as conversationally as possible in order to build rapport. Interviews were an average duration of 72 min, with trial participant interviews generally running much shorter (25–50 min).

Direct observation procedures

Direct observation was undertaken over a 5-week period at four VHX trial sites and at two T-CAB meetings in Mae Sot. We adopted the stance of the *observer as participant*. The observer as participant stance provides the most ethical approach to participant observation because the researchers' activities are known to the group being studied and the emphasis for the researcher is on collecting data rather than participating in the activities being observed.[25]

To collect data, BP travelled to SMRU clinics nearly every weekday over the 5-week period. The first day at each clinic, she performed a walk-through with an SMRU staff member. Based on that walk-through and subsequent observations, she drew a map of the clinic. Each day she visited a clinic, she would observe in the study room during clinic hours from 09:30 to 12:30. Initially, the language barrier made it very difficult to know precisely what was happening at the clinics. Eventually, the main observation strategy was to try and identify VHX trial participants based on the medical tests they were seen receiving, to confirm this with SMRU medics and then to continue observing those individuals in order to determine what study-related and ancillary care they received. Through direct observation, BP was also able to witness the research skills of the Karen clinic staff and observe their training (such as on-the-job training and lectures).

While observing, notes and sketches were initially jotted down and then expanded upon later on the same day in a separate notebook.[26]

Collection of trial-related documents

Trial-related documents were collected from VHX trial investigators and included: the grant proposal, ethics submissions, trial protocol, T-CAB meeting minutes related to the trial, and trial participant case report forms (CRFs). Information from CRFs was especially useful for identifying the ancillary care that was given to VHX trial participants because CRFs included a form for Concomitant Medications, which listed all medications a trial participant had received for conditions other than vivax and falciparum malaria. At four of the five trial sites, 50 CRFs (200 in total) were sampled to generate a picture of what non-malarial conditions were treated during the trial. CRF data were also used to confirm data from trial participant interviews about their treatment group allocation, the number of vivax recurrences they had experienced and what ancillary care they had been provided with during the VHX trial.

Box 1 Excerpt from trial investigator question guide (follow-up questions are listed below the bullet points)

Questions measuring trial responsiveness to local health concerns:
- Please describe your responsibilities/functions during the trial design and funding phase of the VHX trial.
  - Why and how was the research topic selected? How were the study objectives chosen? Who was involved in this process?
  - Is vivax malaria common in the border population? What burdens are associated with it?
  - Is vivax malaria the biggest health concern in the VHX trial communities or are other diseases of more concern? How do you know this?

Questions measuring ancillary care provision:
- Please describe the health impact of the VHX trial on participants during the trial.
  - Aside from treatment for vivax and falciparum malaria, what healthcare do participants receive as part of the study?
  - Are these types of healthcare necessary for the VHX trial's scientific validity?
  - If not, why are they offered? How is it possible for you to offer them?
  - How did you decide what healthcare to provide as part of the VHX trial?
  - What treatments won't be provided to VHX participants during the study? Why? What happens if participants come to the clinic with these conditions?
  - What are your responsibilities and role in this process (the provision of care and treatment to participants during the study)?

Questions measuring post-trial benefits:
- Please describe how the VHX trial will continue to improve participants' health and health in the border population after it finishes.
  - If the study shows that artesunate or primaquine are better treatment options for vivax malaria than chloroquine, will there be a change in treatment practice?
  - Where, at what clinics? SMRU clinics? Non-SMRU clinics?
  - For whom—trial participants, community? Will treatment be free?
  - How will these changes in treatment practice be implemented? By whom?
  - What will your responsibilities and role be in the process?

Questions measuring research capacity strengthening:
- Please describe how the VHX trial strengthens the research capacity of the border population.
  - What research capacity strengthening was done as part of the VHX trial?
  - Please describe your responsibilities and role in this process.
  - Were SMRU medics trained only to recruit participants and collect VHX trial data? What about training in study design and analysis of results?
  - Have SMRU medics received any other research training from SMRU (outside of the VHX trial)? What did this consist of? Who provided it?

Outputs of case study research methodology

All interviews were transcribed verbatim and translated from Burmese into English (where required). Data were then analysed according to the principles of thematic analysis, with co-coding performed independently by two researchers, in order to determine which obligations of justice were fulfilled by the VHX trial and how this was achieved.[27] Thematic analysis is a method of identifying and reporting patterns (themes) in data.[27 28] Once themes that pertained to an obligation of justice were identified, the final step was to assess whether the collated data extracts from each related theme provided evidence of how VHX trial stakeholders met the obligation.

As this paper focuses on methodology, our discussion of results will be brief. Significantly, our findings demonstrate that the case study approach we employed was able to generate the evidence needed to answer our research questions. Our results

Box 2 Excerpt from trial participant question guide

Questions measuring trial responsiveness to local health concerns:
1. Are you worried about getting infected with malaria? Why?
2. When someone you know gets malaria, do you think they may die?
3. Did many people get sick with malaria in your village in the past year?
4. Are you less worried about getting malaria now that you're part of the study? Why?
5. Are you concerned about getting any illnesses other than malaria? Why?

Questions measuring ancillary care provision:
1. Have you gotten sick since your initial treatment for vivax malaria?
2. How many times? What illnesses?
3. Did you go to the clinic when you got sick? Why?
4. What did the medic do to you at the clinic?
5. Did you get medicines? What were they for?
6. Were there any times when you got sick that you didn't come to the clinic? Why didn't you come to clinic?

show that SMRU generally upheld its obligations of justice in the VHX trial. Trial investigators confirmed that vivax is now the most common form of malaria in the border population and SMRU has the data to support this assertion. Vivax can result in significant morbidity over time. As the vivax parasite has liver stages that can remain dormant for weeks, each infection is associated with multiple relapses, which can result in chronic anaemia. Nevertheless, vivax does not typically cause severe illness and, as a result, is not considered the top health concern of the border population. According to Investigator 01,

> Vivax is a problem but not a serious—I would not put that as the number one priority in terms of health in the population. It probably goes after respiratory infection, diarrhoeal disease and in terms of public health, tuberculosis is emerging as a big problem. Of course, if you look at just the sheer numbers, of course, we still treat many more cases of vivax than we treat tuberculosis, but it's difficult to compare because one is a disease that almost you would, you know, could compare as a flu, as a mild flu, except that in young children, in very young babies, then it can be dangerous and in pregnant women it's not very good, but in adults it's like a flu.

Trial investigators consider vivax to be a health priority but not the top health concern of the host communities. Similarly, T-CAB members and trial participants identify vivax as a health concern because it can affect their ability to work, deal with family matters and engage in social activities. However, many trial participants report concern for falciparum malaria because it can affect the brain and cause death. T-CAB members and trial participants also identify other illnesses such as cancer, dengue, diarrhoeal disease and tuberculosis as significant health concerns.

To measure the health needs and priorities of the border population, SMRU relies on four main strategies: epidemiological surveys, following prospective cohorts, clinic data collection systems and information from local clinic staff and T-CAB members.

Interview data, direction observation and CRF analysis also confirm that ancillary care beyond the disease under study is provided to VHX trial participants. However, ancillary care is not provided for all health conditions and is mainly limited to care for acute illnesses that are inexpensive to treat and that fall within the skill set of the SMRU medics and nurses, who are from the Karen and Burmese border population and provide the majority of care. Trial investigators are generally only called on to deal with complex cases. Since SMRU runs the clinics that serve as the VHX trial sites, this healthcare is provided to community members as well. Referral networks for other health conditions are already in place between the clinics and the nearest Thai and Burmese hospitals, but CRF data show that they have rarely needed to be used during the VHX trial.

Interviews and direct observation data show that the research capacity strengthening performed as part of the VHX trial was carried out mainly at the individual level. It consisted of training SMRU laboratory and clinic personnel from the border population to perform the assays and clinical tests required to conduct the trial. At some clinic sites, medics and nurses with limited research experience assumed management roles and gained leadership skills. The majority of the training was led by one of the VHX trial co-investigators, with assistance from other VHX trial co-investigators, who also served as her translators.

Finally, our data indicates that there is a high likelihood that post-trial benefits will be provided to VHX trial participants and their communities. Although the trial was still collecting data during our research, we were able to ask investigators how trial results would be translated into health benefits for the host communities post-trial. We discovered that, as the VHX trial was not testing a new drug, the most likely health impact would be a change in treatment practice for vivax at SMRU clinics and other medical NGOs on the Thai-Burmese border. Following a subsequent trial to optimise the treatment regimen for the border population, primaquine may be provided as the standard vivax treatment at SMRU clinics, with funding from the Global Fund. One investigator described how such changes would be implemented:

> If we change the treatment policy, we have the Malaria Handout and it is revised every year, every two years, so we need to revise that Malaria Handout and then all the clinics along the border use that Malaria Handout. So to revise the Malaria Handout it is the job of Andrew* and the other [SMRU] doctors who are treating the malaria… So we have the malaria meeting and malaria workshop every year, at least once a year. So in that workshop we invite all the NGOs, all the medics, so the Mao Tao clinic and other NGOs or some other associations and then they try it. So we distribute the handouts and then sometimes they advise me to go there and then give the training at the workshop. (*Name changed for confidentiality reasons)

Where SMRU research results suggest that a study regimen is more effective than that which is used in current clinical practice, revisions are made to the Malaria Handout (ie, the treatment guidelines for malaria written by SMRU) by SMRU doctors. These doctors then train SMRU clinic staff to implement the changes in their daily medical practice. Other medical NGOs on the border are also informed and trained to implement the changes at an annual malaria meeting. Thus, the fulfilment of obligations of responsiveness, ancillary care and post-trial benefits is facilitated by SMRU's long history of combining health services and research with the active involvement of the border population (its staff).

Strengths and limitations

The methodology we describe in this paper has a number of strengths. Most critically, it was able to generate the evidence needed to address our research questions from *multiple* perspectives. By conducting in-depth interviews with not only funder representatives and investigators but also trial participants and T-CAB members from host communities, we obtained both emic and etic accounts of community health concerns and the benefits created by the VHX trial for participants and their communities. Spending five weeks on-site in Mae Sot, attending T-CAB meetings and going to SMRU clinics with trial investigators helped establish a pre-existing level of familiarity with the interviewer that was essential to building rapport and trust during interviews with trial stakeholders (which were largely conducted in the latter three weeks of the visit). This meant that interviews were better able to generate authentic insights into interviewees' perspectives on the VHX trial. Our methods were also sensitive to drawing out important contextual conditions. In-depth interview guides are continually revised as informants provide new information that researchers have not previously identified.[29] We, therefore, incorporated new insights into our question guides throughout the interview process and re-interviewed trial stakeholders (using the added questions) during the final week of data collection in Mae Sot. In effect, we captured rich details (not discernable from the VHX trial protocol) on the complex processes that culminated in SMRU's adherence to ethical requirements and the contextual conditions underlying their achievement. Examination of trial stakeholders

in their natural setting enhanced our comprehension of how the trial processes described in interviews worked in practice.

Direct observation over a prolonged period facilitated a broader understanding of SMRU's operations, the local health system and the relationship between the two. This was highly important to grasping how the VHX trial topic and outputs fit into SMRU's overall research strategy and would supplement existing health services. Triangulation of methods, data sources and analysts demonstrated that converging conclusions could be generated by different data collection methods, data sources within methods (eg, accounts from different trial stakeholders) and analysts who reviewed the findings.

Although it may be argued that an ethnographic methodology would provide greater insight and understanding of the VHX trial's fulfilment of ethical requirements, ethnography typically involves data collection over a lengthy period (ie, 1 year or more) and considerable time for data analysis. Developing practical guidance for research groups entails gathering data about different international clinical trials in a multitude of settings. Relying on ethnography would be an inefficient way to collect this data and would require a significant investment of resources for each trial studied. The case study research methods we describe can generate the required evidence in a much shorter time frame.

Despite the strengths discussed above, there were a number of limitations to the case study methodology we employed in our research. First, we did not interview members of one significant category of VHX trial stakeholder—the Karen and Burmese medics who were responsible for running the trial. Logistical issues (availability of translators) limited our ability to interview members of this group. As a result, we did not get first-hand perspectives on, for example, research skills learnt and ancillary care provided as part of the VHX trial. Second, the language barrier made conducting in-depth interviews and direct observation difficult. Some degree of miscommunication and misinterpretation of events was unavoidable, particularly in initial interviews with translators. Despite training, translators occasionally became confused by questions during interviews. Where this occurred, the interviewer would re-explain the question briefly during the interview and again more comprehensively after it finished. Third, as the VHX trial was ongoing, measurement of post-trial benefits was limited to T-CAB members and investigators' descriptions of what would happen if the trial was successful, rather than their description of actual post-trial processes that could be observed.

To address the first two of these limitations, it would have been useful to have a bi-cultural Karen-Australian research assistant (who could speak Burmese).[30] This would have obviated the need to rely on busy SMRU staff as translators and lessened the difficulties associated with the language barrier in interviews and during direct observation. Measurement of post-trial benefits could be enhanced with a follow-up site visit after the VHX trial concludes.

CONCLUSIONS

The case study research methods described in this paper represent one way of generating empirical data to measure whether and how obligations of justice are translated into international research practice. As evidenced by SMRU's VHX trial, responsiveness can be assessed through interviews with investigators, trial participants, and community advisory board members; ancillary care provision through interviews with investigators and trial participants, direct observation, and CRF analysis; research capacity strengthening through interviews with investigators and direct observation; and post-trial benefits through interviews with investigators and community advisory board members. This methodology also yields strategies for implementing these obligations such as conducting epidemiological surveys to facilitate responsiveness and integrating research and health services to facilitate the provision of ancillary care and post-trial benefits. Case study research can, therefore, ensure that research ethics guidelines are better informed by international research practice. It can be employed to improve the articulation of guidelines' requirements and to develop guidance on how to implement them, which is essential to boosting research groups' adherence to justice requirements.

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