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Experiences and challenges in data monitoring for clinical trials within an international tropical disease research network

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Abstract

Background—Models for the structure and procedures of data and safety monitoring boards (DSMBs) continue to evolve in response to issues of new and of old concern. Some authors have called for an open dialogue on these questions through publication of the experiences of DSMBs in addressing them.

Purpose—The goal of this paper is to add to the current discussion about acceptable models for establishing, serving on, and reporting to monitoring committees, particularly those that oversee multiple studies in less developed countries. The paper seeks to do so by describing the establishment and subsequent operation of one such multi-trial DSMB over a five-year period. This DSMB was formed to monitor trials conducted by members of the International Centers for Tropical Disease Research (ICTDR) network of the National Institute of Allergy and Infectious Diseases (NIAID). **Methods** The operational model and experiences are summarized by the authors, who had immediate responsibilities for directing the DSMB's activities.

Results—The board played an active, traditional role in assuring that patient safety was maintained and that current standards for clinical research were met. In addition, both NIAID and the board members viewed education of investigators to be an important role for the board to play in this particular setting. This affected the threshold for identifying which trials would be monitored, and it impacted several procedures adopted by the board.

Limitations—This report reflects the observations of those involved in managing the DSMB, including comments offered by the DSMB and by investigators, but not data gathered in a systematic way.

Conclusions—The operational model described here has allowed the DSMB to fulfill its role in the oversight of the trials. We hope that the ideas we present may help others facing similar situations and may stimulate further critical thinking about DSMB structure and function.

Introduction

Nearly four decades ago, an expert panel commissioned by the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) recommended the use of independent expert committees to monitor ongoing safety and efficacy data from clinical trials [1]. Such committees have been widely implemented to monitor both federally and privately funded trials, and the NIH now requires explicit data and safety monitoring systems for all NIH-sponsored trials; independent committees are required for some trials [2,3]. Following this mandate, the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID) established a data and safety monitoring board (DSMB) in 2000 to oversee DMID-sponsored clinical trials conducted at sites that are part of the International Centers for Tropical Disease Research (ICTDR) network.

The ICTDR network was created in 1991 by NIAID to confront the challenges of international research in tropical diseases by fostering partnerships among US and international scientists and by promoting technology transfer to institutes in endemic areas. The research centers in this network do not, however, operate under a centrally coordinated structure or committee. The program funds individual investigators, organizations and industry to encourage relevant applications of recent scientific advances toward critical issues in international health. More than 20 research centers, each typically involving several studies and multiple diseases, have been in operation since 1991. An overview of current centers and their research areas can be found on the network's website (www.niaid.nih.gov/ictdr).

The ICTDR DSMB was established to more thoroughly and uniformly oversee the diverse clinical trials conducted by these centers. In its five years of operation, the ICTDR DSMB monitored 13 trials (Table 1).

Throughout the years, discussions have continued not only on the need for monitoring committees but also on the operational and ethical aspects of their reviews [4–14]. A book by Ellenberg and colleagues [15] and a guidance issued by the U.S. Food and Drug Administration (FDA) [16] on the creation and operation of DSMBs are great resources for those establishing monitoring committees. These resources, however, have been met with considerable debate, particularly the FDA guidance when first introduced as a draft in November 2001. DeMets and colleagues [17] have identified three main areas of debate: 1) what trials need a DSMB, 2) what level of access sponsors should have to interim data and to DSMB meetings; and 3) whether statisticians presenting interim reports should be independent from study investigators and sponsors. DeMets and colleagues [18] have also written about the pioneering role played by the DSMB for the AIDS Clinical Trial Group in establishing standard operational procedures (SOPs) to simultaneously monitor multiple studies. Some of these procedures have been incorporated into DMID's guidelines on DSMBs [19], which were followed when the ICTDR DSMB was established. Of note, however, is that all of these guidance documents focus their discussions primarily on US and other developed world situations.

The unique characteristics of a research network that focuses on diseases that are serious burdens in less developed countries presented the ICTDR DSMB with three specific challenges for successful monitoring.

The first and most obvious was the need for the board to sufficiently appreciate the conditions and cultures in which the research was taking place. Second, was the great diversity among network investigators not only in the diseases they studied but also in their data management, statistical support, site resources, and other aspects of study conduct. Third, tropical diseases are not commonly studied by industry, so before the ICTDR DSMB was created in 2000, even though investigators in the network were experienced scientists, most had not experienced the scrutiny regulatory agencies or by interim data monitoring committees. Furthermore, the standards for clinical research and its oversight have changed dramatically in the last decade. The International Conference of Harmonization Guideline on Good Clinical Practices was released in May 1996, an NIH policy on monitoring committees was issued in June 1998, and a revamped clinical terms of award [20] – a document that lists the requirements NIAID expects on clinical grants – was published in June 1999 stipulating compliance with these new monitoring standards. Therefore, investigators in the network had to learn and adapt to the new standards as NIAID moved toward increasing the oversight of the trials it funded.

Here we provide an overview of the operational model developed for the ICTDR DSMB within this challenging context. Much of the presentation focuses on issues for which data monitoring and international trials in resource poor settings intersect. We also discuss how our model addresses the common points of debate mentioned above. We hope that this will add to the current discussion about acceptable models for data and safety monitoring and will help guide others in establishing, serving on, and reporting to monitoring committees, especially those that oversee multiple studies in less developed countries.

DSMB composition and structure

The size of the DSMB was initially set at six full voting members. Included were four clinical scientists with a wide range of expertise in infectious disease research areas including malaria, HIV, pediatrics, tropical virology and tuberculosis; one biostatistician with experience in clinical trial methodology; and a bioethicist. An additional biostatistician later joined the board as a full voting member. At least one full member with tropical disease expertise was required to be from a less developed country, and the bioethicist was required to have experience with the conduct of research in less developed countries; in fact, the bioethicist who served for the last three years was from a less developed country. From among the full members, a chairperson was appointed by DMID and continued as chair throughout the five years of the DSMB. To provide continuity in study monitoring, DMID requested that board members serve for a minimum of three years. Also, to ensure that the board's independence was maintained, conflicts of interest were assessed when a candidate was considered for membership and on a study-by-study basis at every meeting.

Full members were augmented by study-specific members when additional, specific expertise was needed to monitor a trial. This was particularly important for handling the

diverse research agendas of the centers in the network and the diverse cultural contexts in which the trials were conducted. During the five years of operation, six study-specific members were appointed to provide expertise in particular disease areas, but no need was identified for additional experts regarding local factors. Instead, the DSMB was able to rely on accounts by foreign site investigators, clinical monitors and NIAID program staff and contractors who visited the sites. For any given study, the study-specific members had to be free of conflicts of interest and had the same voting privileges as full members.

The leadership of monitored ICTDR trials always involved US and local collaborators who facilitated interactions among the DSMB and other oversight bodies. For example, in a study conducted in Southern Africa, in addition to involving local institutional review boards, investigators also involved a community advisory board (CAB) in discussions regarding study conduct. However, no particular issue was ever identified that needed more direct communications between the DSMB and the local CAB during the conduct of this trial. In another study in East Africa, the DSMB was involved in discussions regarding the care for a study participant who experienced a particularly serious adverse event. Issues regarding differences in the standard of care between the US and the local site, and issues regarding sponsor responsibility, were discussed at length. Investigators kept the local IRB informed of DSMB recommendations and no areas of contention were reported.

Our DSMB model also included a coordinating group of four additional, non-voting individuals who were integral to DSMB functioning. An executive secretary served as a liaison between the DSMB and DMID, overseeing and coordinating the administrative aspects of the DSMB's activities. These included orienting new members, developing agendas, requesting materials that were needed for reviews, and preparing meeting summaries for approval and dissemination. Assisting the executive secretary was an administrative assistant, who coordinated all logistical aspects of the meetings, and later, a note-taker. The executive secretary was a staff member from another component of NIAID, while the administrative assistant and note-taker were members of the International Clinical Studies Support Center (ICSSC), a center under contract with DMID dedicated to providing technical assistance to DMID-supported investigators.

The fourth nonvoting individual was an additional statistician who acted as the main liaison between the DSMB and the study teams. This statistician, who was also an ICSSC member, assisted ICTDR investigators in submitting appropriate reports to the DSMB. The ICSSC statistician worked directly with investigators and their study statisticians, educating and advising them on developing interim reports, establishing procedures and time-lines for generating their reports and preparing their presentations for DSMB meetings. The ICSSC statistician also provided any needed clarification of the board's recommendations, and helped the study teams develop monitoring procedures as suggested by the DSMB. For example, in one study involving severely ill children, due to the occurrence of deaths early in the study, the DSMB recommended closer monitoring. The ICSSC statistician helped the study team define proper trigger points indicating an overall excess risk for mortality and serious adverse events among study participants. After further modification and approval of the plan by the board, the study team adopted the plan, which called for halting recruitment and preparing a full interim report any time a trigger point was reached.

As needed, the ICSSC statistician also provided other general statistical support to the ICTDR network, including help with protocol development and training. Once a study began, however, the ICSSC statistician was not expected to be part of the decision-making process for the study. Decisions affecting the data and study conduct were the responsibility of the study statisticians and investigators.

Given the complexity and many details involved in preparing for a DSMB meeting at which multiple studies will be reviewed, the coordinating group developed an SOP listing all responsibilities of each member of the group, specific steps for implementing them and expected timelines.

Managing the monitoring of multiple trials in this diverse network of investigators has been challenging, but establishing a coordinating group with clear communication lines to the sponsor and the investigator groups and developing SOPs for that group's activities have been essential for managing the DSMB.

Determining which ICTDR trials require DSMB

The question as to what trials needed to be independently monitored was not an issue for the ICTDR. NIH guidelines [2,3] required that all Phase III trials conducted within the network be monitored by a DSMB. The guidelines also stated that selected Phase I and Phase II trials, depending on the risk of their interventions and the vulnerability of the populations they targeted, should be overseen by a DSMB. Almost all of the populations that the ICTDR network targeted could be considered vulnerable, as they were almost always economically disadvantaged. Many of the trials also recruited children, who are vulnerable by nature. Furthermore, the relative lack of experience of investigators with respect to standards for clinical research that had been advancing in the United States made it important that smaller trials, or those that would otherwise be considered less risky, also be monitored. For this reason, in addition to monitoring all Phase III trials, the ICTDR DSMB was assigned to monitor all Phase II trials in the network. Phase I trials were usually monitored by the study investigators, or their monitoring could involve an independent safety monitor [21] or a small safety monitoring committee [22].

DSMB meetings

The ICTDR DSMB met regularly twice a year and scheduled additional meetings or teleconferences when necessary. Meetings were held near DMID offices in the United States, since the majority of board members were from the United States and because the research being monitored was not conducted in any one region in the less developed world. For nearly all studies, two types of review meetings were scheduled: one for a study preview and another for monitoring reviews.

Preview meetings

The FDA guidance and DMID's DSMB guidelines both recommended that an initial DSMB meeting be scheduled before each study started, to familiarize DSMB members with the study they would monitor. That is the board's chance to raise any ethical, scientific, or

practical concerns that could interfere with successful study conduct or data analysis, particularly those that could affect the board's ability to monitor a study as planned. Discussions during these preview meetings also focused on ensuring that adequate safety systems for identifying, recording and reporting adverse events were in place. The DSMB's procedure was to have DMID program officers bring a DMID-approved trial to the executive secretary, who then made plans for a study preview at the next regular meeting of the board. Preferably the study preview occurred before the study was initiated. Otherwise, it was held as soon as possible thereafter.

A written guidance was developed to outline the expectations for presenting a new trial at a DSMB preview session. The materials needed for a preview meeting included a protocol, informed consent forms, and any available case report forms. The board also required that certain details of the monitoring plan, including the expected frequency and content of interim reports, statistical methods that would be used for interim analyses and stopping guidelines, be provided. In these preview meetings, the DSMB requested changes in the data and safety monitoring plans in all 13 trials it monitored. Changes ranged from improving data presentation to establishing more formal monitoring guidelines to abandoning collection of burdensome ancillary data.

The entire study preview process – from the first time a study is presented to the DSMB for preview to the first monitoring review – has proved extremely useful in defining expectations and requirements of the monitoring process and in orienting study teams to the specific issues they must consider and steps they must follow.

Monitoring meetings

To review interim reports, DSMB meetings followed the general format outlined in DMID guidelines with open, closed, and executive sessions as originally proposed by the AIDS Clinical Trials Group [18]. During open sessions, general study conduct and progress were reviewed, and, if so agreed, safety and efficacy data for combined treatment arms were presented by investigators and discussed. During closed sessions, safety and efficacy data were reviewed by study arm. Closed reports as well as closed sessions were divided into two separate parts: one to review safety data and one to review efficacy data, the latter having more restricted access.

Generally, investigators and other members of the study team participated only in open sessions. DMID program officers overseeing trials generally attended open sessions and closed sessions in which safety data were reviewed but did not attend closed sessions in which efficacy data were discussed. The interim reports discussed during closed sessions were presented using treatment codes (eg, A and B), with any needed unblinding done in an executive session of voting members only. The executive secretary kept sealed envelopes containing treatment decoding information for all monitored studies. These envelopes were available to members for each study being reviewed at a meeting. DSMB members began to consider the arguments for fully unblinded reviews [23], and began to move toward more easily unblinding reports. However, members did not achieve a clear position regarding automatic unblinding of reports. Discussions of the issues are to be continued.

We believe that the presence of DMID representatives during closed sessions in which safety data were reviewed has contributed greatly to DSMB deliberations and led to improved safety-reporting systems for some studies. The discussions on safety led to halting of recruitment for four of the 13 trials until more complete safety reports were provided and safety systems were improved. After further assessment by DMID, one of the studies was not allowed to re-open, while the three others were re-opened following review of more complete data and completion of recommended alterations to the protocol or study procedures. For one additional study, a phase II open-label randomized trial, the DSMB recommended more frequent interim safety monitoring because of the unusual safety profile emerging from the control group, which was assigned to a standard treatment. The discussions on safety eventually led to the early termination of the trial by the study team, and important safety data regarding the standard of care was effectively disseminated.

DMID and the DSMB decided to split the closed session into two separate sessions in response to the long-standing debate about participation of sponsors during closed session reviews [17]. The FDA guidance advises that no sponsor have access to unblinded interim data. However, we believe this is an area in which the differences between industry and government sponsors need to be recognized, as others have also argued [24]. The DSMB and DMID acknowledge the risks of allowing DMID staff to access unblinded interim data, as their knowledge of this information could potentially influence subsequent protocol modifications that could introduce bias. However, DMID personnel are not normally involved in the management of trials, except when safety issues arise. Also, both DMID and board members agree that DMID program officers overseeing trials face fewer conflicts of interest than representatives of industry sponsors may face (or appear to face). In addition, since none of the monitored studies were large Phase III trials, the tensions related to potential unblinding of DMID staff and early termination were much lower. Finally, DMID staff saw only safety data by coded treatment arm, not efficacy; the group identity for safety results were not revealed to them; and they were not allowed in executive sessions during DSMB formulation of sensitive recommendations.

Having the closed session divided into two sub-sessions has been a useful extension of the common meeting format of open, closed, and executive sessions and might be useful for other groups to consider. Of course, making this distinction is not always possible, such as when primary safety and efficacy endpoints are identical. As DeMets and colleagues [17] pointed out, trials within NIAID use different models for staff participation in DSMB meetings, and even though our model was applied consistently for ICTDR trials, we acknowledge it adds to the diversity of approaches for staff participation currently used. Effective arguments have been made that a more uniform guidance on this issue would be useful.

Educational role of the DSMB

Though educating investigators is not a traditional role of a DSMB, the ICTDR DSMB agreed to adopt an educational approach when possible, while still maintaining its independence. This explicit acknowledgement seemed to engender subtle but important shifts in members' attitudes during interactions with investigators. However, it did not entail

any lowering of standards. The interest in education was also evidenced in specific activities. For example, to help train investigators and to ensure better initial data reviews, the board requested that the proposed content and format of interim reports be discussed with and approved in advance by the DSMB. To facilitate this process in a setting with considerable diversity among study teams in both research experience and area of expertise, investigators were directed to refer to board-approved templates to help them develop their report plans. Study teams were, however, allowed to adapt the templates to the monitoring needs of their studies. The templates helped provide investigators with clear expectations for the DSMB's review, prompting investigators to consider and discuss such monitoring concepts as blinding, type I error inflation and stopping rules. The templates developed for the ICTDR network and adopted by the ICTDR DSMB can be found on the ICSSC website (www.icssc.org/templates_resources.htm).

The preview process itself was a great opportunity for education and led to better understanding of monitoring requirements among investigators and to improvements in data management, statistical systems and safety oversight of participants, all which can affect study outcomes as well as their dissemination and credibility.

In both its preview meetings and its monitoring meetings, the board furthered its educational role by providing detailed minutes of both its deliberations and its final recommendations. Its recommendations were often explicit, such as suggestions of helpful references or of additional assistance from the ICSSC, if other resources could not be identified. In addition, on a few occasions, one or more board members were assigned to provide post-meeting feedback directly to investigators to ensure that the board's concerns were fully appreciated.

Independent statistician

No issue in the FDA guidance has provoked more discussion than that of the use of an independent statistician. [5, 24–32] Generally agreed upon is that knowledge of unblinded interim results can introduce bias into study conduct, so no one involved in the study decision-making process should have access to interim reports, even in open-label studies. Study statisticians are normally consulted on decisions affecting study design and data collection and analysis. For this reason, the FDA guidance recommends that a statistician who is independent of both the sponsor and the investigator group prepare interim reports and present them to the DSMB.

After discussing the possibility of using an independent statistician to prepare and present closed session reports, the ICTDR DSMB originally decided to determine the need for an independent statistician on a study-by-study basis. Later, however, the DSMB changed its approach and recommended an independent statistician for all studies it monitors. Although this approach was not required, deviations from it had to be justified by the study team and approved by both DMID and the DSMB. Regardless of whether the final decision was to use an independent statistician, procedures for maintaining the confidentiality of reports had to be specified. If an independent statistician was charged with generating the reports, justification of his or her independence and a description of implementation procedures (eg,

data transfer and analysis) had to be provided. The DSMB then reviewed the proposed plans during the study preview meeting and either approved them or recommended modifications.

DMID recognized that using an independent statistician added some expenses to trials, which were typically already on tight budgets. Also, investigators frequently mentioned that additional statistical help was not readily available to them. To address these concerns, DMID assisted investigators by providing statistical support through existing resource contracts if necessary. For the ICTDR network, the ICSSC statistician was a natural choice to fill the role of the independent statistician. Both DMID and board members also believed that the ICSSC statistician was in a unique position to interact with the DSMB and study teams, as he had adequate knowledge of the studies, was already involved in the preview process, and could properly maintain confidentiality of interim reports.

The actions of the ICSSC statistician, in his role as the independent statistician for a study, were guided by an SOP describing steps to ensure that he became familiar with the study, interacted with the study statistician regarding report contents, and tested computer programs and procedures for generating interim reports in a timely manner. The SOP was also used to guide investigators who wished to choose an independent statistician of their own. Investigators, and even study statisticians, often do not know that an independent statistician is an option or understand the implications of having one. In such cases, the ICSSC statistician assisted some study investigators and their appointed independent statistician in establishing appropriate procedures to maintain confidentiality of interim reports. The SOP specified that the independent statistician be qualified to review study results for statistical soundness (eg, check assumptions of models). Once interim data had been reviewed, the independent statistician was not to be involved in discussing potential changes to the protocol including changes in study design, study size, entry criteria, methodology for interim monitoring, or primary endpoint definitions. In general, he or she also was not to be involved in managing the study. The SOP advised the study management team to explicitly define procedures for building proper firewalls to limit interaction among the independent statistician, DMID program officers overseeing the study, and the study team regarding interim results. It also advised that the independent statistician be provided with full data sets and detailed data set documentation so that he or she could conduct additional analyses if the DSMB requested it.

Concluding remarks

The unique characteristics of the ICTDR network required developing an operational model that could accommodate the challenges of monitoring safety and efficacy data from multiple international trials conducted in less developed countries. Through the DSMB's work in its five years of operation, we have identified several aspects of its operation – mainly regarding its composition, meeting format, preview meetings, and educational efforts – that have played a major role in its success. Furthermore, the fact that it set uniform standards for all trials in the network has been of great significance.

Central to our presentation is that DMID recognized the need to educate investigators and build capacity to improve the quality of international research in tropical diseases. To some

extent, the board could not escape playing this educational role, and in fact we believe that education became an essential part of the board's legacy. Investigators have gained experience through interacting with the DSMB – experience that many of them acknowledged would improve the conduct and quality of their studies and resulting publications and also help them tremendously as they work toward more pivotal studies. In fact, one of the factors that led to the decision to have the ICTDR DSMB monitor all phase II studies, some of which might not have been monitored by a DSMB in other settings, is the apparent educational needs of the ICTDR network investigators. DSMB members have repeatedly acknowledged that these were important and worthwhile uses of their efforts.

Initially, discussions were held about whether it was appropriate to establish a single DSMB to monitor such a diverse group of trials. The alternative – establishing several DSMBs to each focus on a limited area of research – was considered. However, the use of a single DSMB has helped ensure uniform oversight of trials. Also, we expect that managing multiple DSMBs would require considerably more staff efforts. The clinical research, biostatistical, and ethical expertise of the ICTDR DSMB cuts across all research areas. The diversity of diseases studied within the network can be managed by inviting one or more study-specific members to monitor studies for which additional types of expertise or knowledge of local settings is needed. An added advantage of a single DSMB is that the members develop a broad perspective of trials and so can provide recommendations that affect the entire network. This helps promote a sense of unity and fairness among the different investigator groups. It also promotes DMID's vision for the ICTDR program to strengthen these groups by drawing on their commonalities in conducting research on tropical diseases.

All of the procedures mentioned here were important for the successful monitoring of trials conducted within the ICTDR network between 2000 and 2005, and many of them continue to be important in the monitoring of the network's trials. We believe that this operational model has allowed the ICTDR DSMB to fulfill its role in the safety oversight of study participants and in ensuring the quality of the research. To our knowledge, no major safety issues were overlooked. However, we acknowledge a limitation of our presentation is that it reflects our own observations, which include comments that investigators and DSMB members made to us but which were not gathered in a systematic way. Furthermore, just as the rest of the scientific community continues to adjust its models for the operation of monitoring committees and strive toward consensus regarding these committees, the operational models used in NIAID are continuing to evolve.

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Table 1

Randomized clinical trials monitored by the ICTDR DSMB, 2000–2005

Disease under study	Treatment intervention evaluated	Region	No. of sites	Sample size	Duration ^a	Study population
Bancroftian filariasis	Diethylcarbamazine and albendazole	Northern Africa	1	50	24 months	Men and women ages 18 years or older with microfilaria counts >80/mL
Diarrhea	Vitamin A, zinc, and micronutrient mixture	Southern Africa	1	516	18 months	HIV-infected children; HIV-uninfected children of HIV-infected mothers and HIV-uninfected children of HIV-uninfected mothers. Ages 4–6 months
Diarrhea	Vitamin A, zinc, oral glycine, oral glutamine	South America	1	280	3 years	Children ages 2 months to 8 years with low height for age Z-score
Diarrhea	Alanyl-glutamine 24 g Glycine 25 g	South America	1	108	5 weeks	Hospitalized children ages 3 to 36 months with persistent diarrhea or malnutrition
Hantavirus cardiopulmonary syndrome	Intravenous methylprednisolone 8 mg/kg (up to 500 mg) in 100 cc D5W	South America	11	60	38 months	Individuals 2 years old or older with suspected hantavirus infection
<i>Plasmodium falciparum</i> malaria	Azithromycin in combination with either artesunate or quinine	South East Asia	1	120	12 months	Men and women ages 20 to 65 years with acute, uncomplicated <i>P. falciparum</i> malaria
<i>P. falciparum</i> malaria	Amodiaquine + sulfadoxinepyrimethamine, amodiaquine + artesunate, or artemether + lumefantrine	East Africa	1	600	3 years	Children ages 1 to 10 years with acute, uncomplicated <i>P. falciparum</i> malaria
<i>P. falciparum</i> malaria	Chloroquine + sulfadoxinepyrimethamine, amodiaquine + sulfadoxine-pyrimethamine, or artesunate + amodiaquine	East Africa	1	400	28 days	Children ages 6 months to 10 years with acute, uncomplicated <i>P. falciparum</i> malaria
Pneumonia	Zinc adjuvant	East Africa	1	600	hospital stay + 6-weeks after discharge	Hospitalized children ages 6 to 36 months with acute pneumonia
Subarachnoid cysticercosis	Two lengths of albendazole therapy	South America	4	120	360 days	Men and women ages 18 to 65 years with subarachnoid cysticercosis
Tuberculosis	Multivitamin supplement containing vitamins B, C and E adjuvant	East Africa	1	400	2 months	Children ages 6 weeks to 5 years with tuberculosis
Tuberculosis	Micronutrients adjuvant	East Africa	1	600	24 months	Men and women ages 18 to 65 years with tuberculosis
Tuberculosis	Rifampin/pyrazinamide; rifapentine/isoniazid	South America	1	720	4 years	A household contact of a pulmonary tuberculosis case who was at high risk for developing tuberculosis

^aDuration includes treatment and follow-up periods.