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International Collaboration between US and Thailand on a Clinical Trial of Treatment for HIV-associated Cryptococcal Meningitis

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Abstract

Background—International clinical trials can provide scientific and logistic benefits in spite of the many challenges. Determining whether a country, especially a developing country, is an appropriate location for the research should include in-country consultation and partnering to assess its social value for the population; that treatments are relevant for the population under study; and that the research infrastructure and ethical oversight are adequate. Collaboration increases the likelihood of study success and helps ensure that benefits accrue to recruited populations and their community.

Purpose—This paper describes our experiences on a bi-national study and may provide guidance for those planning to engage in future collaborations.

Methods—A Thai and United States team collaborated to develop and implement a Phase II clinical trial for HIV-associated cryptococcal meningitis to assess safety and tolerability of combination therapy versus standard treatment. Clinical and cultural differences, regulatory hurdles and operational issues were addressed before and during the study to ensure a successful collaboration between the 2 groups.

Results—The international multicenter study allowed for more rapid enrollment, reduced costs to complete the study, sharing of the benefits of research, greater generalizability of results and capacity building in Thailand; quality metrics in Thailand were equivalent to or better than those in the U.S.

Conclusions—Conducting successful clinical trials internationally requires early and ongoing collaboration to ensure the study meets sites' requirements and expectations, conforms to varying national regulations, adheres to data quality standards and is responsive to the health needs of studied populations.

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This clinical trial is registered in the National Library of Medicine's registry (www.clinicaltrials.gov) under the registration number NCT00145249.

CONFLICT OF INTEREST STATEMENT

TL Nolen, LO Zimmer, S Pramanpol, ME Walker, D Wallace, P Pappas, P Chetchotisakd: No conflicts of interest

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Keywords

controlled clinical trials; cryptococcal meningitis; international health problems; collaboration

INTRODUCTION

Conducting multinational clinical trials poses a number of scientific, regulatory, ethical, logistic and cultural challenges, while also providing substantial benefits. The challenges include selecting a host country where the research question is applicable and feasible within the country's social and political context, and one that has adequate infrastructure to conduct the study [1–3]. These challenges are particularly difficult to address in studies performed in resource-limited settings. Potential benefits include fostering relationships with clinical investigators internationally, answering questions about drug safety and efficacy in various settings of interest, lowering study costs, and recruiting subjects more quickly in high disease prevalence locations [1,2]. Aside from the usual standards for conducting ethical research including social value, scientific validity, favorable risk-benefit ratio, ethical oversight, and respect for research participants, a collaborative partnership is also required for multinational research [3]. Collaboration reduces the risk of exploitation and is critical in ensuring consideration of local cultural values and social practices [3].

This paper describes the collaboration between US and Thai investigators in developing and implementing a clinical trial of cryptococcosis treatments in the United States and Thailand between 2003 and 2007. Specifically, we outline the challenges and benefits we encountered in performing a study in a resource-limited environment while addressing the above considerations. As a measure of the success of this strategy, the paper also includes a description of the quality of the final study data.

Disease and Trial Background

Cryptococcal meningitis remains a common opportunistic infection in people with acquired immune deficiency syndrome (AIDS) in Southeast Asia and Africa [4], although its prevalence has declined in the US with the increasing availability of prophylaxis and highly active antiretroviral therapy (HAART) [5,6]. Current recommended induction therapy includes the use of amphotericin B with or without flucytosine, although both are known to cause dose-limiting toxicities, and flucytosine is not readily available in much of the world. As such, alternative treatment regimens with improved toxicity profiles and greater availability are needed in developing countries [7,8].

The trial sponsors, the Division of Microbiology and Infectious Diseases and the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID) supported the preliminary study proposal and agreed that insufficient subjects would be available in the United States to enroll the study in a timely manner. Although the research network had previously only conducted trials of therapies for bacterial and fungal infections at US sites, it was agreed that an overseas location that met all scientific, ethical and regulatory requirements be identified.

This phase II study of combination therapy for the treatment of cryptococcal meningitis (BAMSG 3-01) was a randomized open-label trial comparing standard treatment with amphotericin B alone followed by fluconazole with 2 combination treatments of amphotericin B plus conventional or higher-dose fluconazole. Primary endpoints included occurrence of a severe, life-threatening, or fatal treatment-related toxicity and a composite efficacy endpoint where success was defined as cerebrospinal fluid (CSF) culture conversion to negative; stable or improving neurological function; and survival. Additional detail on study design and primary results has been published previously [9].

METHODS

Selection of Overseas Population

Per international guidelines, research in resource-limited countries should be of value to the population in which it is being conducted. As such, the clinical trial should address the health needs of the host country, use products that are locally affordable and available and be feasible given the infrastructure, resources and experience of the host country [2,10–12]. To identify potential overseas locations for this study, we assessed study relevance by examining disease burden, availability of a secure supply of drugs and materials, and national commitment to treating the condition [13].

Based on our research, we identified Thailand as an appropriate candidate for our overseas location. Since the mid-1980s, the Bureau of Epidemiology at the Thai Ministry of Public Health (MOPH) has collected biannual sentinel surveillance data on reported cases of AIDS, opportunistic infections and deaths. In 2004, the MOPH estimated that 572,000 adults and children were living with HIV/AIDS in Thailand, one of the highest prevalence rates in Southeast Asia and the Pacific [14]. Throughout the course of the country's HIV epidemic, cryptococcosis has been one of the 3 most commonly reported opportunistic infections [15]. Fluconazole is readily available at a cost of approximately 10 cents per tablet and thus sustainability of treatment is not a concern. Furthermore, Thailand became one of the first developing nations to provide HAART medication under their Access to Care Program, which was serving over 50,000 patients by early 2005 – a strong indication of their commitment to this serious health condition [16].

Thailand also has access to trained investigators, who in collaboration with various international organizations, have conducted considerable research documenting the burden of cryptococcal meningitis in HIV patients and performing treatment trials [17–20]. These studies indicate that researchers are able to collect high-quality data; report clinical and adverse events accurately; and perform trials consistent with NIAID and good clinical practice (GCP) requirements [1,2]. Further, scientific and regulatory review is available through appropriately constituted site IRBs and the Thai Ministry of Public Health.

Development of Study Infrastructure and Design and Implementation

This study was the first conducted internationally under an IND application by this research network. To ensure that adequate support was provided to the Thai sites and that sites in both countries operated consistently and in compliance with IND requirements, a number of scientific, regulatory, and operational issues had to be resolved. Existing project infrastructure evolved over time as we recognized the need for greater input from local sources. Thus, we began by selecting a Thai investigator to provide study leadership, participate in protocol development and identify appropriate sites. In June 2003, the US and Thai research team began work to develop a scientifically rigorous protocol that could be applied consistently across all sites while addressing the unique treatment settings in the 2 countries. Although we had a US based organization that performed clinical site monitoring for our other trials, we came to recognize that it would be beneficial to have an in-country monitoring group to assist with Thai site management, regulatory approvals, shipping of drug and study supplies, monitoring of data quality and logistics. In November 2003, we selected a Thai company to provide regulatory support, site monitoring and management. This decision was a critical element in the success of the study because the Thai team was able to respond to site concerns more rapidly (given time differences) and had knowledge of local conditions and familiarity with regulatory requirements. Thus, we had 2 sets of clinical site monitors – one for the US and one for Thailand. Both groups were trained at the US investigator meeting to ensure comparability of information received.

While all clinical site monitors were responsible for reviewing subject data for patient safety issues, data accuracy and completeness, and adherence to protocol requirements, the Thai monitoring group also assisted the Thai sites with translation and submission of regulatory documents, organization of site visits and shipment of study drug and supplies. Finally, in March 2004, we added a data and safety monitoring board (DSMB) member from Thailand to provide insight on data and safety concerns with respect to the Thai population.

Figure 1 shows the final organizational structure that the international team developed to complete planning and implement the study. Logistically, the study was organized around the coordinating center, which prepared all study materials, provided day-to-day oversight of the trial, and created the quarterly reports for the DSMB. The coordinating center was responsible to both the leadership team and to NIAID and provided ongoing communications about study status and issues to both. The leadership team oversaw protocol development, while the Protocol Chair and lead Thai investigator responded to sites' clinical concerns and led interactions with regulatory bodies such as the FDA and MOPH.

Protocol Development—To expand the scientific capacity of Thai collaborators, assure an equal partnership, and address clinical or operational issues that might differ between Thailand and the United States, the leadership team included the Protocol Chair in the United States and the lead investigator in Thailand. The Thai lead investigator participated fully in the protocol development process by telephone and provided protocol revisions by email. Given the time difference, calls were scheduled for late in the evening in the US and morning in Thailand.

Site Assessment, Training and Protocol Refinement—In August 2004, a team from the US including NIAID staff, lead clinical investigators, and coordinating center staff visited the Thai sites to foster communication and collaboration and to confirm that sites were able to meet study requirements in terms of GCP standards, facilities, staffing and patient populations. The half-day meetings included a tour of the site and a discussion of logistics and other issues that could affect study feasibility and implementation. US sites involved in the study were established members of the study network and did not receive assessment visits, but were required to complete a study feasibility questionnaire.

All proposed Thai sites had adequate facilities for assessing subjects, performing lab work and storing study medications. However, sites did not have easy access to copy machines and one site lacked file cabinets for storing case report forms (CRFs). Since the study budget did not allow for the provision of copy machines, the team decided to provide 3-part NCR CRFs for the Thai sites. In the US, sites downloaded CRFs from the study website, submitted originals and made copies of all completed pages for the site files.

Prior to implementing the protocol, in-country investigator meetings were held to train site staff and to provide investigators with an opportunity to address any clinical issues that might affect the scientific integrity of the protocol; (April 2004 for the US and August 2004 for Thailand). The investigator meetings included a detailed discussion of the protocol and study procedures, such as website access and randomization, sample shipment, study drug distribution and completion of study forms. The discussion in Thailand was particularly helpful in identifying and resolving both scientific and clinical issues reflecting country differences. For example, Thai individuals are on average smaller than Americans. We revised the protocol to include dosing adjustments for individuals weighing less than 40 kilograms. Additionally, nevirapine is one of the standard antiretroviral therapies in Thailand, but new research from Africa indicated that co-administration of nevirapine and fluconazole could potentially increase nevirapine toxicity [21]. The protocol was amended to exclude subjects on nevirapine at baseline and to recommend that nevirapine use be delayed until completion of the 10 weeks

of fluconazole therapy. Thai investigators proposed substituting efavirenz for subjects requiring HAART therapy prior to the end of the 10-week treatment period.

Study enrollment began in May 2005; a subsequent protocol amendment was implemented in December 2005 as a result of comments provided by the DSMB, study sites and to clarify some inconsistencies in the protocol (see figure 2). A summary of protocol changes was distributed, the study project director and country-specific monitors worked with each site to ensure site staff understood changes, and the updated FDA-approved protocol was submitted to site IRBs and the Thailand MOPH for approval.

Study Materials and Processes—Randomization was performed using a web-based randomization system, which provided the sites simple and flexible access for randomization and allowed the coordinating center to track enrollment easily and efficiently. The system was accessible 7 days a week, 24 hours a day and the randomization system technical support hours were expanded to provide assistance to the Thai sites during their working hours.

Because the investigators and study coordinators in Thailand were reasonably fluent in English, the study CRF was not translated into Thai. However, tools for the use of study participants, such as the subject diary, were translated into Thai and Spanish (for US populations) and reviewed by local native speakers to ensure they met the needs of the study population. The subject diary was intended to help participants document self-administration of fluconazole tablets and to record any adverse events between study visits.

The template informed consent was drafted by coordinating center staff and reviewed by the protocol team for accuracy, clarity, and appropriateness for the target populations. Although the template consent form was translated into Thai by a professional translation service in the US, Thai investigators modified the language to meet the needs of their ethics committees and to simplify the language into a form that was more easily understandable to a lay audience. Consents were then back translated into English to make sure that no substantive information was lost. Thailand's literacy rate (approximately 93%) is not much lower than the US, but the issue of inability to read and understand a consent form was a factor in both countries since cryptococcosis can affect an individual's vision and mental status. As such, we implemented a process that is congruent with both the Thai and US FDA guidelines for consenting a subject who is unable to read. The process involved reading the consent to a potential subject in his/her native language in the presence of a witness, providing the subject and legal representative with any additional information requested, and allowing the subject to sign or indicate with a thumb mark their consent to participate. The subject was then provided with a copy of the consent materials in their native language.

Study endpoints required assessments of toxicities and neurological function. Because lab results were obtained from local laboratories, consistency in the reporting of toxicities was obtained by requiring sites to report adverse event severity and lab grades according to the Division of AIDS table for grading severity of adult adverse experiences. With respect to neurological function, the mini mental status exam (MMSE) was used in the US, while the Thai mini mental status exam (TMSE) was used in Thailand. Although there are some differences between the MMSE and TMSE in terms of content areas, each version has been validated within its respective country. Both versions have the same total score (30 points) and similar cutoff points for impairment levels, and we used intra-subject change in scores to determine whether improvement or deterioration occurred. We anticipated that using the country-specific version for each relevant population would provide consistent results across countries; however, the analysis plan included a comparison of this measure between countries to confirm this assumption.

The reporting forms for serious adverse events (SAE) were the same for both countries. However, because fax lines were not universally available and faxing documents internationally was considered cost prohibitive, the Thai investigators agreed to fax the SAE forms to the monitoring group in Bangkok. The clinical site monitor, in turn, reviewed the forms, queried outstanding or conflicting information and forwarded the SAE forms to the coordinating center. This process provided an added level of quality control, but it did impact the timing of adverse event report receipt at the coordinating center.

Shipping of Drug and Supplies—Amphotericin B was supplied by each site's pharmacy. Fluconazole study drug was sent to the sites from a central site in Asia (for Thai sites) and the United States (for US sites). A company in Asia that had experience in importing and distributing experimental medications was contracted to handle this component of the study. Unfortunately, we experienced delays in drug importation because of inadequate paperwork and the selected company's lack of familiarity with the Thai custom clearance process. In these situations, we learned it was essential to have a representative in Thailand who could negotiate the process and ensure all local requirements were met. In response, the Thai monitoring group agreed to handle the importation and distribution of study drug.

Ethical Oversight

Study procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The training and requirements for compliance with GCP as well as local institutional review board review provided a level of ethical oversight and assurance that the rights, safety and well-being of trial subjects were protected. While most of the Thai sites had their own IRBs, one site was overseen by the Ministry of Health IRB, which also provided an umbrella review for all studies conducted in Thailand. One key difference between the US and Thailand was the requirement for annual review of the study in the US. Since this was not a requirement in Thailand, we had to track annual expirations closely in order to ensure that US regulations were met. Additional safeguards were provided through ongoing site monitoring and oversight by the DSMB.

Ongoing Oversight of Site Performance

Clinical site monitoring occurred at both Thai and US sites; however, site visits occurred more frequently in Thailand because Thai staff enrolled a greater number of subjects. US based coordinating center staff provided instructions on when monitoring should occur – based on enrollment or site performance – and developed a detailed monitoring plan so that data and regulatory document review was consistent between countries. While the coordinating center staff maintained ongoing contact with US sites, the Thai monitoring group handled communications with Thai personnel, since most of the study coordinators were more comfortable using Thai. The Thai monitoring group and coordinating center staff interacted frequently to resolve logistic or process issues and ensure consistent information was disseminated to all sites.

The inclusion of the Thai physician in the DSMB proved invaluable during the study monitoring process. At numerous meetings, the US DSMB members raised concerns about discrepancies in lab values and differential incidence of adverse events between patients in the US and Thailand. For most of these concerns, the Thai physician was able to provide insight into the HIV-positive population in Thailand as a whole, as well as at each hospital, which explained the disparities, thereby addressing the concerns of the rest of the DSMB.

Fatal or life-threatening SAEs were to be reported to the coordinating center within 1 day of the site identifying the event while all other SAEs were to be reported within 3 days. The

additional time required to send these reports through the Thai clinical site monitors was a potential concern for meeting these requirements. To assess the reporting lag time, the coordinating center and DSMB tracked time from SAE onset to report receipt by the coordinating center (figure 3). Since sites may not have identified SAEs at their onset, it was expected that some of these lag times would be greater than 3 days. The DSMB and coordinating center considered tracking lag time as the time from when the site became aware of the event but felt that this calculation could seemingly reduce sites' accountability for ensuring that subjects were being monitored closely and might therefore negatively impact how quickly SAEs were reported. Based on data through July 2006, the DSMB became concerned about the SAE reporting lag time for the Thai sites. Discussions about this issue with the Thai clinical site monitors revealed that the Thai sites were holding reports in order to make them as complete as possible, rather than submitting the first information available. The coordinating center clarified with the sites that early reporting should be prioritized over completeness. Once the sites understood the importance of submitting preliminary reports within FDA designated timeframes, lag times diminished overall with the exception of 2 SAEs with large reporting delays due to events occurring after hospital discharge.

In March 2006, when approximately 40% of the subjects had been enrolled, an additional meeting with investigators was held in Thailand to review study status, obtain site feedback and address any data collection issues the sites were experiencing. For example, the protocol required that fluconazole be adjusted or discontinued due to QTc prolongation or decreased creatinine clearance and early data suggested that not all subjects were being dose adjusted appropriately. A call was held with US sites to review these same issues.

QUALITY OF STUDY RESULTS

Measures of Study Implementation and Subject Disposition and Compliance

Figure 2 displays the timeline for development and completion of this study. The first version of the study protocol received NIAID approval in March 2004; however, to respond to a request from the FDA to incorporate ECG monitoring and to input received from the Thai investigator meeting in August 2004, study initiation was delayed until September 2004 when version 2 of the study protocol was approved by NIAID and FDA. Further delays were experienced in completing contracts, receiving IRB approval and collecting site regulatory documents. Delays specific to Thailand included the need to translate regulatory documents into English and to obtain documentation that all Thai investigators were currently eligible to practice medicine since medical licenses do not expire in Thailand.

In all, 5 Thai sites and 9 US sites participated in the study between May 2005 and August 2007. While average enrollment rates per site met expectations (4 and 1 subjects every 3 months for Thai and US sites respectively), study enrollment took longer than originally planned (22 vs. 18 months) due to staggered completion of site contracts, IRB approvals and initiation. A total of 99 subjects in Thailand and 42 subjects in the US were enrolled and received study therapy. Each Thai site enrolled and treated between 6 and 50 subjects and each US site between 0 and 16 subjects. Completion of key assessments was fairly high through day 70 and approximately equivalent between countries with the Thai sites performing slightly better numerically in all assessments (table 1).

As the primary composite efficacy endpoint was measured at days 14, 42, and 70, compliance with study medications, fluconazole and amphotericin B, was summarized for days 0–14, days 0–42, and days 0–70 (table 2). Amphotericin B was administered via IV on an inpatient basis; as such, compliance was high for all subjects. Fluconazole was administered orally via pills with the majority of treatment being taken on an outpatient basis. Subjects were instructed to bring all unused pills to each visit and compliance was measured using pill counts. For days

0–14, compliance was high for subjects in both countries (>80%); however, compliance dropped sharply thereafter for the US subjects (<60% for days 0–42 and 0–70) while remaining relatively high in the Thai subjects (typically around 90% at all time points. A portion of the low reported compliance can be attributed to subjects not bringing in remaining pills or diaries to study visits thereby hindering the sites' ability to record compliance accurately. Ten US subjects and 3 Thai subjects were reported as failing to bring in pills to a visit or were lost to follow-up; for these patients, we were unable to ascertain stop dates for study therapy.

Because neurologic function was part of the primary endpoint and was assessed using 2 different versions of the mini-mental status exam, the comparability of these exams was assessed by summarizing total scores at baseline and subsequent changes from baseline to day 14 by country (table 3). The scores appear to be comparable between countries at baseline indicating similar average neurological function. Additionally, the changes from baseline to day 14 appear to be similar between countries. Other measures of neurological function, including Karnofsky scores and other functional tests, were also comparable. As such, the evidence suggests that the mini-mental status test instruments provided a consistent measure of neurologic function between countries.

Data Submission

To allow for adequate oversight of the study, CRFs for each subject were submitted at 3 time periods: the first batch after the completion of the primary efficacy assessment at day 14, the second after the completion of study therapy at day 70, and then all remaining pages after study completion on day 168. CRF pages recording AEs occurring and concomitant medications received on or prior to each of these visits were to be submitted with each batch. Because the additional time required for the CRFs to be routed through and reviewed for completeness by the Thai monitoring team prior to submission to the coordinating center for data entry was a concern, the coordinating center monitored CRF submission times throughout the study. Figure 4 presents the number of days each CRF submission was overdue by country. Even with the additional steps, the average number of days CRFs were overdue was lower for the Thai sites than the US sites for each submission period.

Data Quality

Data quality measures implemented throughout the study included the clinical site monitor visits discussed above and automated univariate and multivariate checks of the data as they were entered into the clinical database at the coordinating center. Queries were generated and sent to the site for any questionable data noted during these reviews. On average, the number of queries issued was considered comparable between the two countries (29 and 36 queries per subject for a 110 page CRF for Thailand and the US, respectively). Additionally, because one of the Thai sites enrolled and treated over a third of the total subjects (50 subjects), an on-site audit of the site's data and study documentation was performed by the coordinating center to assess data quality and demonstrate the site was compliant with US FDA regulated research activities and GCP. The auditors reviewed regulatory documents and CRFs and source documentation for 20% of the subjects enrolled at the site (including informed consent and randomization documentation, study eligibility criteria assessments, reporting of protocol deviations, and primary safety and efficacy endpoint assessments). Overall, the auditors found few issues, confirmed the site was compliant with US FDA regulations and guidelines, and determined the site's collection and reporting of the data was of high quality.

DISCUSSION

Developing and implementing an international clinical trial provides greater challenges than implementing a clinical trial domestically and requires additional planning, oversight and

extensive ongoing communications to ensure scientific and ethical integrity through partnership. The study was successful as evidenced by the ability to complete study enrollment and the high quality of data obtained. Equally importantly, we achieved a reasonable level of collaboration: partnering in the planning, conduct and oversight of the research; respecting the community's values and traditions; capacity development; and sharing in the financial and other rewards of research [3]. This collaboration allowed use to realize many of the benefits of international research; however, the study team did identify areas where improvements in collaboration were possible.

Benefits

The study has been immensely successful at fostering relationships between investigators internationally. Thai personnel provided input into protocol development, modification of study procedures, problem solving and monitoring of performance. At the final study meeting in Thailand, investigators identified manuscripts of interest and volunteered to take the lead on these topics. Thus, Thai investigators were intimately involved in the analysis and writing of study papers, on some of which they were the lead or senior author. This study provided the opportunity for more junior investigators to gain experience in GCP trials and expectations for study implementation through feedback from the leadership team, monitoring group, coordinating center and the DSMB. As a further measure of the success of this collaboration, the principal investigator is pursuing a subsequent phase III trial in which many of the investigators from the phase II trial have expressed interest in participating.

Other benefits of international collaboration included the collection of data from two countries related to drug safety and efficacy and the acceleration of study enrollment as the Thai sites enrolled at a much faster rate [7]. Finally, while some additional costs were incurred by including Thai sites (e.g. more expensive costs for shipping CRFs and samples, international travel for three meetings, translation of study documents), these costs were minimized via the use of the study web-page, e-mail, fax and teleconferences as a means of transmitting information as well as bulk shipping of CRFs and samples. Since payments to investigators should reflect costs needed to conduct a trial locally and be consistent with in-country economics in order not to be coercive, the incurred costs were far less than the savings obtained via lower per-patient costs of subjects from Thailand compared to US and lower monitoring rates for Thai monitors compared to US monitors [2].

Challenges

Although we had a committed and well-organized study leadership and management group and country-specific study leadership in the form of a local clinical site monitoring group and a Thai lead investigator, more frequent face-to-face communication would have helped to ensure that adequate support was provided to all sites and unexpected issues identified and addressed in a timely manner. It was not until the in-person meeting that a rapport was established between the US and Thai study team members that allowed for all team members to comfortably express their concerns and questions. The meeting resulted in necessary modifications of the study materials but delayed study progress due to its timing.

In retrospect, earlier identification of the Thai collaborators and more frequent in-person interaction among the study team would have facilitated earlier resolution of some of the issues that occurred. Specific deficiencies included our failure to select the Thai monitoring group until halfway through protocol development (figure 2); the Thai DSMB member was not included in the DSMB review of the draft protocol (only in active study monitoring); and CRFs were only pilot tested by US study coordinators. Additionally, although the lead Thai investigator was involved in protocol development, an in-person meeting that included Thai investigators was not held until after the first version of the protocol had been FDA approved.

These factors delayed the time required for protocol drafting, review and approval and thus, study initiation. Furthermore, using in-country investigator knowledge to help vet local representation is strongly recommended. We assumed that a company with offices in Asia would be familiar with Thai drug importation regulations. This assumption was unfounded; fortunately, we were able to expand the Thai monitoring group's scope of work to handle this critical study function.

The success of this study relied on ongoing monitoring of study status provided by the coordinating center, site monitors and DSMB. However, due to language and clinical practice differences, we initially had issues with dose adjusting appropriately, failing to grade labs according to study requirements rather than local standards, and SAE reporting delays. Additionally, there were vastly different reporting practices with regards to what each site considered a 'screened subject' making interpretation of this information difficult. These issues were identified through ongoing study monitoring; however, an improvement to study status monitoring would have been to obtain input from Thai investigators on the status report content, as this input may have led to earlier identification and resolution of issues encountered. With respect to training, early evaluation of CRF completion and reinforcement of CRF completion training is critical for all studies but was especially pertinent for our study for sites where English was not the first language. When sites had completed the first 1–2 CRFs at their site, scheduling a call to review the items they had questions about and the items about which they are being queried greatly reduced confusion and lessened rework. These post-completion meetings were inconsistently implemented in this study; however, for the sites where the meetings occurred, they tended to have greater impact than the preliminary CRF training provided at the investigators' meeting.

Site assessment and training in Thailand required consideration of cultural differences between the US and Thailand. Specifically, knowledge of holidays of all involved cultures when scheduling training and assessment visits is important. Our first investigator meeting and site assessment trip in Thailand overlapped with the Queen's birthday, which is celebrated as a public holiday, making scheduling of the site visits complicated. Additionally, it is important to be aware of country-specific customs, including but not limited to dress etiquette, social hierarchy, and meeting etiquette. As with many Asian cultures, rank and status are important in Thailand and conflicts with senior authority figures are generally avoided [22]. Thus, obtaining suggestions for study modifications or raising concerns about proposed procedures requires gaining the trust of local collaborators. While the Thai monitoring group provided helpful recommendations to the US study team members regarding these customs, communications remains a key to successful collaboration.

CONCLUSIONS

This study demonstrates that study-specific solutions can successfully address the scientific and ethical challenges of conducting research in resource-limited settings. However, general learnings critical for success in multi-national clinical trials include the following:

1. Identifying appropriate resources and implementation partners early in study development reduces the potential for study delays [23].
2. Close monitoring of administrative and procedural aspects of the trial is needed for early detection and resolution of issues [24].
3. Multiple coordination mechanisms are needed ranging from informal contacts, email and telephone communications to formal in-person meetings [23].
4. Awareness of, and sensitivity to cultural norms, is essential to full collaboration.

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Figure 1.

Diagram of Study Coordination Organization: ^aA lead Thai investigator was selected to help identify additional sites for the study and to provide in country guidance to the Thai sites. ^bA Thai member was included in the DSMB to provide input from a Thai perspective on study issues and potential resolutions. ^cThe clinical site monitors for Thailand were responsible for more activities than typically expected.

Figure 2.
Study Timeline

Figure 3.

Lag Time Between SAE Occurrence and Reporting to Coordinating Center by Country over Time

Figure 4.
CRF Days Overdue by Submission Period and Country

Table 1

Subject Disposition by Country

	Thailand (N=99)	US (N=42)
Baseline Opening Pressure Obtained	99 (100.0%)	33 (78.6%)
Completed Day 14 Visit ^a	99 (100.0%)	39 (92.9%)
Completed Day 42 Visit ^a	94 (94.9%)	36 (85.7%)
Completed Day 70 Visit ^a	91 (91.9%)	37 (88.1%)
Completed First Follow-Up Visit ^a	88 (88.9%)	33 (78.6%)
Completed Second Follow-Up Visit ^a	69 (69.7%)	25 (59.5%)

^aIncludes subject that completed visit or died prior to study visit.

Table 2

Treatment Compliance

	Thailand (N=99)	US (N=42)
Amphotericin B (%)		
Overall		
Mean $\pm$ SD	116.3 $\pm$ 14.59	104.3 $\pm$ 36.74
Median	116.3	114.1
Fluconazole (%)		
Days 0–14		
Mean $\pm$ SD	104.8 $\pm$ 38.1	81.1 $\pm$ 47.0
Median	100.0	91.3
Days 0–42		
Mean $\pm$ SD	92.7 $\pm$ 31.0	62.5 $\pm$ 39.4
Median	100.0	59.1
Days 0–70		
Mean $\pm$ SD	88.2 $\pm$ 31.3	56.1 $\pm$ 35.6
Median	96.8	59.3

Note: Percent is calculated as 100 times the dose received divided by the planned dose the subject should have received during the treatment period. For subjects who died prior to end of treatment period, planned dose only includes doses prior to death.

Table 3

Neurological Assessment: MMSE vs. TMSE

	Thailand (N=99)	US (N=42)
Baseline Total Score		
Mean $\pm$ SD	25.3 $\pm$ 5.13	24.9 $\pm$ 6.06
Median	26.0	28.0
Change from Baseline to Day 14 in Total Score		
Mean $\pm$ SD	1.8 $\pm$ 5.04	1.3 $\pm$ 6.78
Median	1.0	0.5