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# Implementing Clinical Trials on an International Platform: Challenges and Perspectives

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The importance of conducting medical research on a global or international platform cannot be overemphasized in current times. Sponsors are encouraging international clinical trials for a number of reasons. Globally, clinical trials are under increasing pressure to meet patient recruitment goals quickly and efficiently, at times with very limited resources. Conducting clinical trials in multiple countries increases access to potentially eligible study subjects. It is reasonable to believe that international trials will be completed more quickly and efficiently, leading to more rapid advancement in science and conservation of research-specific resources. Rapid advancement in science can reduce the burden of disease, promote health, and extend longevity for all people. In addition, generalizability, one of the major goals of translational medicine, will increase when recruiting patients from multiple countries and multiple ethnicities. Further, improvement of global health may be possible when certain types of clinical trials are conducted in countries that would not otherwise have access to an innovative drug or intervention.

This manuscript focuses on challenges faced by investigators and sponsors when implementing an international clinical trial and offers a perspective on the current regulatory environment. Observations and opinions are partially based on experiences from conducting the ongoing multinational National Institutes of Health (NIH), National Institute for

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Neurological Disorders and Stroke (NINDS)-funded trial: "A Multi-Center, Single-Blind, Randomized Study Comparing Thymectomy to No-Thymectomy in Non-Thymomatous Myasthenia Gravis (MG) Patients Receiving Prednisone" (MGTX). This multicenter randomized clinical trial aims to determine if the extended transsternal thymectomy (ETTX) surgical procedure plus prednisone versus prednisone alone confers added benefit for patients with the neuromuscular disease myasthenia gravis (MG). The trial has a recruitment goal of 150 patients worldwide. MG's status as a rare disease, the trial's entry criteria that excludes the vast majority of patients, and the requirement that patients be randomized to either receive or not receive a significant surgical procedure, has made recruitment very challenging. In an effort to maximize efficiency, the trial is currently recruiting patients in approximately 57 centers across 16 countries.

## Challenges faced by investigators while implementing a multinational trial

### 1. Conception of the trial or trial design

The planning of a trial normally begins years before the start of patient enrollment. Many site investigators actively contribute to the trial design and protocol; this often leads to multiple investigator meetings and frequent changes to the plan of study. Trial planning can be even more complex when multiple countries are involved. When planning for a multinational study, one must take into account potential differences in the standard of care and cultural practices that could impact implementation of the protocol. For example, in England, the use of contraception cannot be mandatory for women who choose to participate in a research protocol, nor can it be mentioned in the informed consent document. As another example, the MGTX study is using prednisone as the standard medical therapy, however, in some countries, prednisolone is used and prednisone is not available. Although this seems like a trivial difference, it had a sizeable impact on the study design. The rationale for the MGTX trial was, in part, due to the varying preferences among neurologists regarding how to treat myasthenia gravis. In some countries, there was also variation in surgeon opinions regarding the thymectomy approach most appropriate for treating non-thymomatous MG. Thus, modifications to the protocol design may be prompted by issues that arise during peer review at the sponsoring institution and by changes suggested by participating institutions to reflect cultural or local practices. For the MGTX trial, peer review was conducted by the National Institutes of Health (NIH), Clinical Trial Section of the National Institute of Neurological Disorders and Stroke (NINDS) and by the Medical Research Council (MRC) of the United Kingdom.

Selecting research sites usually depends upon the level of expertise available for the disease of interest in that center, estimated prevalence of the disease of interest in that region, the referral network, availability of research infrastructure including administrative and clinical staff, a track record of implementing similar clinical trials, and the willingness of the center to participate. The number of participating centers may change over the years. For the MGTX trial, initially, a total of 89 centers were invited to participate of which 9 withdrew for a variety of reasons. In 2008, the trial was being conducted at 79 centers over 23 countries [1]; currently as of 2011, there are 57 participating centers in 16 countries, of which 43% are in United States (US). The detailed list of participating centers and countries is available at http://clinicaltrials.gov/ct2/show/study/NCT00294658 (Table 1).

### 2. Regulatory burden

There are many administrative issues that can potentially impede conduct of multicenter clinical trials, but there are some issues that are unique to international studies.

**Issues common to any multicenter trial—**As is the case for any non-exempt study involving human subjects, obtaining regulatory approval is required for multicenter trials before patient recruitment can begin. NIH-sponsored multinational clinical trials require review and approval by multiple institutional review boards (IRBs) and research ethics committees (RECs), in addition to ongoing safety monitoring by a data and safety monitoring board (DSMB). Many question the ability of these often redundant approval and monitoring processes by multiple IRBs to protect patients[4]. Certainly, the multiple reviews cause increased "idle-time" expenditures by the trial coordinating center(s) which must review and assist with responses to questions from local IRBs/RECs. It is important to realize that these approvals are not just required at the inception of the trial, as most approvals must be renewed annually or semi-annually during the lifetime of the trial.

There is growing interest in simplifying this review process through a centralized IRB/REC, which would assume responsibility for an entire trial and each of its associated site approvals. This lead or central IRB could assume responsibility and oversee reporting of adverse events for the trial. The local IRBs could then be responsible for assuring compliance with local laws, assuring the consent form is relevant to the local language, culture, and local research context. A central IRB/REC could be assigned to a specific study or study group and be composed of members from IRB/RECs from participating research sites or countries. Several logistical considerations for such a model include development of legal and authorization agreements, increased transparency by secure electronic sharing of approval letters, protocol review and amendments, standardized data reporting, subject confidentiality and indemnification and conflict of interest disclosures by the IRB/REC members.

A recent editorial [4] and two thought-provoking articles [2–3] present many of the challenges facing multinational trials for human immunodeficiency virus (HIV) and rare diseases. The publications offer insight into how investigators spend months solving problems and clearing hurdles that have been put into place with the best of intentions, but often without the cost/risk/benefit assessments we expect with therapeutics. In his editorial, Yusuf [4] suggests that training in good clinical practice (GCP) and International Conference of Harmonization (ICH) procedures may actually slow the conduct of clinical trials. He proposes setting up an industry that focuses on the process and ignores the very things all researchers are required to learn when they take university- and IRB-mandated courses in research integrity and human subject protections. Currently, a trial's clinical or data coordinating center will obtain IRB approval for the trial as a whole, while each participating center will need to obtain approval from their local IRB/REC. In addition to the IRB/REC approval, providing assurance of compliance with regulations to protect human research subjects (45 CFR part 46) is required for any US federally funded human research endeavor. This requires that a participating site have a Federalwide Assurance (FWA), the only type of approval accepted by the Office for Human Research Protections (OHRP) for institutions engaged in non-exempt human subject research conducted or supported by US Department of Health and Human Services (HHS). Each FWA must designate at least one IRB/REC registered with OHRP.

**Issues unique to international trials—**The FWA process is built on the US model of the IRB system. In countries that use different structures, such as the UK which uses Multicenter Research Ethics Committees (MRECs) and regional Local Research Ethics Committees (LRECs), the certification processes can be much more complicated [4]. In addition, the FWA certification process requires multiple local institutional commitments and English as the language of communication. In the case of the MGTX trial, many participating sites were required to register their associated REC with OHRP, as there was not a REC already registered with the office registration with OHRP proved to be a time-

consuming process that was addressed on a site-by-site basis due to language barriers and a lack of familiarity with the procedures. The FWA process should be started as soon as possible to avoid regulatory delays. It should also be noted the FWA process must be initiated by the individual centers and not by the trial's coordinating center. The link to register or renew/update a FWA is: http://www.hhs.gov/ohrp/assurances/assurances/index.html. At the host institution, subcontracting processes are contingent upon sites obtaining IRB/REC approvals and FWA assurances.

In addition to FWA assurances, all countries outside the US that contain a participating site, must be formally cleared through the US State Department before federal funds from the sponsor may be transferred for research activities. To facilitate this process, a complete list of countries participating in the trial should be submitted to the sponsor as soon as possible in order to obtain approvals efficiently. The clearance process involves obtaining documentation from the study sponsor showing that the US State Department approves of the trial within a specified country. In addition, the US State Department approval also signifies that the specified country's own government is agreeable to the trial being performed in that country. The trial's coordinating center often assists indirectly with the State Department approval process that is primarily handled by the sponsoring agency. It should be noted that for certain countries approval may take months to obtain. Furthermore, many countries require an approval from their own health departments prior to starting a multinational clinical trial involving human subjects. The process may be complex and the use of local clinical research organizations (CROs) familiar with the approval requirements, documentation, and language may improve efficiency. While launching recent stroke trials ('Albumin in acute ischemic stroke trial' and 'Insulin resistance intervention after stroke'), researchers realized that it was essential to use local CROs in some of Scandinavian countries and Israel in order to obtain approval in a timely fashion. Although this adds to the financial burden for the sponsor, CROs may be invaluable to expedite trial initiation.

The overall regulatory environment can be overseen by the data coordinating center. The data coordinating center for MGTX is responsible for routine communications, contract management, assisting with regulatory approvals, maintaining IRB/REC and FWA approvals, and State Department clearances, in addition to its primary role of data management and statistical analysis.

From a global perspective, the lack of common rules, procedures, and research ethics board configurations adds significant cost and inefficiency due to trial delays and resolution of rule variations and/or interpretations [2–4]. It is clear that standardized regulations would simplify and expedite regulatory processes. During the MGTX trial, the mean time for non-US centers to achieve regulatory approval was much longer (13.4+− 0.96 months) than for US sites (9.67 +− 0.74 months; p=0.0175, t-test)[1]. Efforts toward centralization have been initiated in Europe by forming the European Clinical Research Infrastructure Network (ECRIN) and European Network of Research Ethics Committees (EUREC) to address the heterogeneity and complexity of existing regulatory requirements in European Union (EU) nations. In Europe, trials have to adhere to the European Union (EU) Clinical Trials Directive (2001/20/EC) and EU GCP Directive (2005/28/EC). However, different countries interpret the regulations differently when transforming them into law. Several reports have suggested that the directives conversely had an adverse effect on implementation of non-commercial trials conducted in EU [2]. Hence, despite the best intentions of these research networks, more work is needed to streamline the process by identifying and eliminating redundancies, define or simplify the respective roles of RECs, simplify safety information provided to RECs, and explore the possibility of a single EU authorization for multicenter investigations [5, 6]. Although these efforts may simplify the regulatory process for conducting

trials in Europe, they do not address the regulatory challenges in other countries of the world. An ideal situation would be to employ a model with a central regulatory entity, with global representation, that is responsible for comprehensive regulatory approval for multinational trials. This entity would ideally conduct rigorous scientific and peer review, as in NIH-funded trials, and thereby minimize critiques of a study's scientific rigor by individual ethics or regulatory bodies.

Heterogeneity of insurance and indemnification requirements is a common issue that needs to be considered while conducting an international trial. Study compliance often requires coverage by a local malpractice insurance policy that provides negligent-harm coverage for investigators. Some noncommercial insurance policies may only cover non-negligent harm only or contain other restrictions, such as refusing coverage for HIV studies, certain geographic areas, or children. As a result, regional or global standardized indemnification and insurance requirements, which may be trial-specific or group-specific, could benefit research infrastructure [e.g. Children's Oncology Group (COG)]. Existing models are the United Kingdom (UK) National Cancer Research Institute (NCRI) common insurance that provides no fault clinical trial insurance and covers non-negligent harm and the UK National Health Service's indemnity for patients participating in the trials. However, funding insurance premiums for such a standardized model across country borders could be a limiting factor.[8]

As more clinical trials assume an international scope, regulatory authorities in all countries need to recognize and address these major hurdles in multinational investigation. The regulatory burden contributes to protracted timelines that potentially impact the relevance of the scientific question being addressed. Such delays could that negatively influence enthusiasm at sites and bias the recruitment of countries participating in the study.

## 3. Financial/Contract Issues

Obtaining adequate financing is an ever-present issue in clinical trials and in science in general. Sponsors desire efficiency without compromising data quality. Investigators generally accept the cost structure of the trial when it is presented or choose to not participate. There are many models of payment, but in a typical arrangement, the clinical or data coordinating center oversees the issuance of subcontracts to each participating site. This process can be quite complex and time-consuming. Usually, IRB/REC approvals must be obtained before the contracting process can begin. Since contracts are usually reissued on an annual basis, the coordinating center governing many sites should be prepared for a significant workload. In addition, there are situations in which the contract will need to be translated into another language. At the host institution, it is critically important for investigators to meet with grants and contracts officials at the initiation of the trial to review the subcontracting process and associated timelines. Contract negotiations can be very time consuming, so any modifications to existing contractual agreements must be clearly communicated to all parties involved. In the MGTX trial, contract execution averaged 8.7 months for non-US sites (median = 6.2) with a range of 2.5 to 24.9 months; for US sites, the average was 7.9 months (median = 6.6) with a range of 2.5 to 17.2 months[1]. The major stumbling blocks for US sites were issues related to indirect cost recovery, which is not offered for direct patient care costs, and issues related to indemnification. For foreign sites, major issues included the translation of contracts into local languages and currency and other payment issues.

Payment mechanisms can vary from trial to trial. In a pay-for-performance model, common to the pharmaceutical industry, sites are reimbursed for procedures completed on a per-patient basis. In a pay-for-participation model, subcontracts are issued for time and effort of the research team with an expectation that sufficient subjects will be enrolled. From one

perspective, the latter model could be considered less desirable since underperforming sites would receive the same budget as those sites with the best performance. However, in most accounting systems, this latter pay-for-participation arrangement is easier to negotiate and manage for the host institution. The former pay-for-performance arrangement is more complex and requires that invoices be received with documentation of work completed, per unit of time, in order to reimburse for work completed under the contract. This requires ongoing interaction between staff at the clinic and adjudication with what has been received at the coordinating center. One approach to make the process easier and more cost-effective is to have invoices prepared by the coordinating center and then forwarded to the participating sites. Sites then sign the invoices and return them to the coordinating center for payment. However, payments to foreign sites are not always simple. Paper checks can be inconvenient and costly to deposit, if they are even accepted. Currency transfer also can be difficult to manage due to the fluctuating exchange rate of the currencies. This is best tracked using wire transfers. It is also advisable to specify up front that all payments will be made in US dollars for federally funded studies.

## 4. Study drug accessibility

If a trial drug is to be used, care must be taken to ensure that it can be used in a participating country. Even if a drug cannot be imported into a specific country, an equivalent substitute may be available. For example, one of the issues encountered during the MGTX trial was related to prednisone. Some countries, including Japan, Taiwan, and the United Kingdom would not permit importation or use of prednisone manufactured in the United States. Therefore, another form of corticosteroid (locally obtained prednisolone) is being used. Since local drug was being dispensed, pharmacists had to be trained to ensure that the system used to track dosing matched that of the trial protocol[1]. This unexpected issue added further burden and delay in trial initiation at those sites. However, in some situations, an equivalent drug may not be available. In addition, if the drug is to be supplied from a central location, shipping regulations should be thoroughly vetted before the trial is launched. The study drug or intervention may be subject to additional local regulatory approval and different labeling requirements in terms of language, temperature control, etc. An import license may be needed and high custom costs may result. The drug importation process itself could interrupt the randomization sequence for some trials[8]. It is also worthwhile to note that regulations could change during the course of a trial, especially one that has an extended duration; flexibility by the trial leadership and coordinating centers and the ability to adjust are critically important.

## 5. Quality of data and safety monitoring

In a multicenter international trial, timely transfer of the data from the sites to the data coordinating center and the data and safety monitoring board (DSMB) or independent data monitoring committee (IDMC) is extremely important for monitoring safety of the study participants and maintaining data quality and integrity. The DSMB or IDMC will meet to monitor the ongoing safety of the trial. These committees meet at least once a year since many IRBs/RECs use DSMB recommendations as a part of their continuing review.

A DSMB meeting will have open sessions, which include trial investigators, and closed sessions, which involve only the unblinded trial statistician(s) or the DSMB alone. The trial sponsor will typically appoint the DSMB members. While serious adverse event (SAE) reports also go to local IRBs and RECs, the DSMB is usually responsible for actual safety monitoring. The local IRBs/RECs can make requests for additional information from the trial leadership; these requests are often referred to the DSMB. DSMB members should understand that differential time zones may create a challenge for real-time adverse event reporting. A plan should be established to deal with any events that occur after-hours.

Language barriers may also create obstacles and translating reports from one language to another may add to the delays. We should add that all international investigators involved in the MGTX study have the ability to speak and converse in English; this is likely to be shared by other international endeavors.

It is critically important to routinely monitor site activities as the study progresses. Web-based data entry systems allow for real-time form completion and data quality monitoring. In the MGTX trial, within 24 hours of a serious adverse event (SAE), investigators are required to utilize the trial's data entry system and enter information about the event. The notification is immediately circulated to a predetermined list of recipients, which usually includes an independent medical monitor and the DSMB. SAE follow-ups are prompted by reminders until the event is considered resolved. Back-up fax systems may also be established in the unlikely event that the data entry system is inaccessible. Web-based systems are more efficient and cost-effective than providing centers with their own laptops. In addition, data entry mistakes are minimized when using electronic systems as a result of real-time prompts and questions that occur when an unrecognized or illogical response is identified. Face-to–face time with a representative from the coordinating center helps with compliance and can significantly improve investigator morale.

**Management of protocol deviations—**When dealing with a complex protocol or disease, the trial should be able to handle deviations quickly and consistently to minimize the potential impact on trial continuity. Flexibility among personnel is necessary when conducting trials in different countries. Many of the exceptions or deviations occur because they were not considered in advance. Some cultural differences can create minor deviations. Other deviations can occur due to scheduling issues, which produce results out of the time window originally planned. Items that could impact patient safety must be handled more carefully in comparison to other study items. These issues must be considered when developing the inclusion and exclusion criteria when designing the trial.

## 6. Personnel training and research education

Personnel training are important to minimize variation in data collection so that all study information is obtained and reported in the same way across all participating sites and countries.

**Physician/surgeon certification—**Training programs should be established to ensure that investigators are well-versed in the trial's protocol and procedures and that they understand what must be done at each time point. Traditionally, this is accomplished by arranging central or regional investigator meetings. The timing of the investigator training(s) is very important. Training a research team far in advance of the beginning of recruitment could create a situation in which investigators need to be retrained. In the MGTX trial, recruitment was delayed an average of 14.88 months (median = 14.67) in non-US sites and 12.08 months (median = 11.5) in US sites due to regulatory processes[1]. Despite the fact that a number of the pre-recruitment processes were completed simultaneously, almost one year of funding was expended in the process of bringing the team to the point of trial initiation. Knowledge of the study procedures and rules is enhanced through group discussion and training. Logistical inconsistencies and differences in practices between sites can be identified and planned for when group training occurs. However, scheduling a large number of researchers for training meetings can be complex and must be done well in advance.

Effectively implementing information technology and using online training systems may mitigate training complexities. In addition, using regional video conferencing and online video training sessions with post-training electronic testing and certification could save time

and money. However, the value of in-person meetings should not be underestimated. Budgeting for project monitors who can work with investigators should be available throughout the trial duration. Additional provisions should be made for retraining of existing centers that are not performing adequately or who experience investigator/staff turnover. For the MGTX study, in-person training sessions were conducted over two days in San Francisco, US and Oxford, England to accommodate investigators from various geographic locations. However, as new sites were added, training physicians and staff at their locations by a project manager, complemented by video training via internet and online administration of a multiple-choice certification test, proved to be a cost-effective strategy. Similarly, surgeons were required to review a printed manual and a video illustrating the extended transternal thymectomy prescribed by MGTX followed by a multiple-choice certification test and a surgical agreement form[1].

Trial personnel also need human subject protection training. While cooperating non-US sites will be covered by their Federalwide Assurance, particular emphasis should be placed on the informed consent process. While local customs dictate what is or is not acceptable in the informed consent process, investigators should demonstrate a clear understanding of the process.

**IATA training and certification—**International Air Transport Association (IATA) training and certification is important if the trial involves shipping international biological samples. Web-based training is available for this material. IATA certification helps to ensure that center staff will be able to properly prepare and ship biological samples. Most large institutions have laboratory personnel who are IATA certified. Despite the presence of IATA rules and regulations, some countries prohibit importation or exportation of biological materials and will be unable to provide these samples. Sites that cannot provide samples could possibly enroll patients if the primary endpoint is not dependent on these samples.

### 7. Other issues

These include language barriers, availability of translators and funding for translations. In our experience during the MGTX trial, the issue of translating the consent forms from English to other languages and vice versa can pose a significant challenge. Maintaining regular communication to boost morale and enthusiasm of the clinical sites is important. However, teleconferencing with all investigators and in- person investigator meetings are challenging due to time differences and the need to travel internationally. Hence, for the MGTX trial, we send an electronic newsletter approximately every six months to all participating sites, which have proven to be a useful strategy for conveying information related to the study's status and other important issues.

## Discussion/Conclusion

Multinational clinical trials have the ability to efficiently provide highly generalizable information for the medical and scientific communities. Trials that are implemented in multiple countries are especially valuable for rare diseases. However, there are multiple challenges may be encountered while implementing a clinical trial in multiple countries (Table 2). Despite these challenges that can make implementation of such trials difficult, time-consuming, and costly, they are feasible with appropriate funding, thorough planning, and adequate administrative support, The NIH/NINDS-funded MGTX trial, which is being conducted at approximately 57 sites in 16 countries, has enrolled 115 subjects and screened more than 6300 patients as of September 2011. Considering that myasthenia gravis is a rare disease and the study involves a surgical intervention, this is a notable accomplishment. We can also learn from examples in other fields. In 2008, the European and American

Osteosarcoma Study Group (EURAMOS) formed through collaboration by the Children's Oncology Group (COG), the Cooperative Osteosarcoma Study Group (COSS), the European Osteosarcoma Intergroup (EOI) and the Scandinavian Sarcoma Group (SSG) enrolled 901 patients from 249 institutions in 16 countries (as of 2009). In fact, the chemotherapy trial EURAMOS-1 has proven to be both the fastest accruing and largest osteosarcoma trial and is ever conducted[7]. Such examples are not limited to rare diseases and several large-scale trials in cardiovascular disease can be held up as models of successful international collaboration [9, 10]. The clinical research enterprise needs to be forward-thinking in order to simplify, harmonize, and improve the efficiency of multinational studies. A few practical considerations include effective project coordination, utilization of telemedicine and translational technologies to improve multidimensional communication, adoption of effective recruitment and retention strategies, global drug availability mechanisms, centralization of adverse report monitoring, development of web-based common form databases, and utilization of organizations with established working relationships and experience with international sites, reciprocity of contract and protocol approval by various regulatory bodies, and online education of trial personnel. Potentially, these are all goals that can be achieved in the short term.

Centralization and standardization of regulatory agencies including IRB/REC approvals at a global level, improved working relationships among funding agencies, and development of sponsor models to accommodate standardized insurance and indemnifications are goals that can be achieved in the long term. Development of an infrastructure with operationally structured management approaches by central clinical and data coordinating facilities is also possible. These efforts will help build a global infrastructure for the future to conduct multinational trials efficiently and effectively.

The leadership of the federal and regulatory agencies, in partnership with governmental and regulatory agencies from other countries, must work together to facilitate the advancement of science and clinical care. In addition, it is important to establish partnerships between government, industry, and patient groups with corresponding multinational trial groups. Establishment of multinational collaborations among investigators, and funding and regulatory agencies is indispensible to the advancement of science and the improvement of patient outcomes on a global scale.

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**Table 1**

MGTX trial: Distribution of centers by countries (as of September 2011).

| Country | Number of Centers |
|---|---|
| United States | 25 |
| Argentina | 1 |
| Australia | 1 |
| Brazil | 3 |
| Canada | 1 |
| Chile | 1 |
| Germany | 4 |
| Italy | 3 |
| Japan | 2 |
| Mexico | 1 |
| Netherlands | 1 |
| Poland | 1 |
| South Africa | 1 |
| Taiwan | 1 |
| Thailand | 1 |
| United Kingdom | 4 |

**Table 2**

List of challenges to consider while designing and conducting an international clinical trial

| | |
|---|---|
| **1** | Complex trial design |
| **2** | Regulatory burden |
| **3** | Financial and contractual issues |
| **4** | Study drug accessibility |
| **5** | Quality of data and safety monitoring |
| **6** | Personnel training and research education |
| **7** | Other issues like language barriers and time differences |