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The MGTX experience: Challenges in planning and executing an international, multicenter clinical trial

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Abstract

We present our experience planning and launching a multinational, NIH/NINDS funded study of thymectomy in myasthenia gravis. We highlight the additional steps required for international sites and analyze and contrast the time investment required to bring U.S. and non-U.S. sites into full regulatory compliance. Results show the mean time for non-U.S. centers to achieve regulatory approval was significantly longer (mean 13.4±0.96 months) than for U.S. sites (9.67±0.74 months; $p=0.0175$, t-test). The delay for non-U.S. sites was mainly attributable to Federalwide Assurance certification and State Department clearance.

Keywords: Myasthenia gravis; Thymectomy; Regulatory approval

1. Background

This manuscript describes our experience in the planning and launching of an international, multicenter, clinical trial funded by the National Institute of Neurological Diseases and Stroke (NINDS) of the National Institutes of Health (NIH) to study the role of thymectomy in myasthenia gravis (MG). By summarizing our experience, we hope to assist other investigators who are organizing clinical trials that will involve international collaboration.

MG is a chronic autoimmune neuromuscular disease that fulfills established criteria as a rare disease. Prevalence rates range from 0.5 to 20.4 per 100,000 (Phillips, 2003). No regions of particularly high or low incidence or prevalence have been identified, but most studies have focused predominantly on Caucasian populations of western European descent. Studies of South African, African American, and Asian populations suggest that there may be differences in racial susceptibility (Chiu et al., 1987; Phillips et al., 1992; Wong et al., 1992; Heckmann et al., 2007). Clinical investigation of MG is further complicated by the presence of disease subgroups based on the presence of antibodies against the acetylcholine receptor, muscle-specific kinase or absence of detectable auto-antibodies. Age of onset, presence of thymoma, and the presence of pure ocular versus generalized disease appear to define other patient subgroups (Compston et al., 1980).

The thymectomy trial for non-thymomatous myasthenia gravis patients receiving prednisone (MGTX) is an NINDS cooperative multinational, multicenter, two-arm trial that is currently enrolling patients. The study aims to determine if extended transsternal thymectomy plus prednisone compared to prednisone alone results in a greater improvement in MG

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weakness, a lower total dose of prednisone, and an enhanced quality of life by reducing adverse events and symptoms. The study was funded by NINDS in September 2005, approximately five years after planning of the trial began (Wolfe et al., 2003). An international trial undergoes extra scrutiny at NIH. In order to fund a grant with a foreign Principal Investigator, a special justification has to be made regarding the added value of international sites and leadership to the Advisory Neurological Disorders and Stroke Council meeting and must be approved by the Director of NINDS.

To achieve adequate recruitment for a sufficiently powered study in a reasonable timeframe, the MGTX organizers assembled a large group of investigators from both in and outside the United States. The multinational composition of the study group was deemed necessary given the relatively small number of centers with clinical expertise in MG in an individual country or continent, and the need for a vast referral network of patients in early stages of disease. Further, when confronted with testing an intervention that has been utilized for over 50 years in MG, a small number of centers declined participation.

At the time of study initiation, 70 centers were invited to participate. Nine centers dropped out for a variety of reasons. In the second quarter of 2007, an additional 18 centers were invited to join the study to boost the rate of recruitment. Of the 79 participating sites, 43% are in the U.S. Table 1 lists the 23 countries and distribution of MGTX study sites.

Patient recruitment plays a key role to the success of any clinical trial. However, prior to launching a study, months to years are now required to navigate the ever-increasing paperwork, the body of regulatory approvals, building infrastructure and data management solutions, and the training of personnel on the protocol. For an international study involving multiple centers worldwide, the planning phases are even more challenging as a result of additional regulatory requirements, differences in approval policies between institutions and countries, language barriers, and regional customs.

Table 1
Distribution of centers by country

Country	# of centers
Argentina	1
Australia	2
Brazil	3
Canada	5
Chile	1
Germany	4
Greece	1
Holland	1
Ireland	1
Italy	4
Japan	2
Mexico	1
Poland	1
Portugal	1
Romania	1
Serbia	1
South Africa	1
South Korea	3
Spain	2
Taiwan	1
Thailand	1
United Kingdom	7
United States	34

2. Center selection and pre-award preparation

Formal planning for the study began in October 2000 under the direction of the late John Newsom-Davis. He assembled a group of investigators based on personal assessment of their expertise and ability to participate in a long, demanding, complex study that would require patients to be randomized to surgical plus medical therapy versus medical therapy alone (Newsom-Davis et. al., 2008). The initial meeting took place in Boston, MA, during the annual convention of the American Neurological Association. Three more investigator meetings were held in 2001 in Philadelphia, London, and Chicago. Based on feedback from these meetings, the protocol underwent several modifications. Further revisions to the study plan were made in response to peer reviews of grant applications to the Medical Research Council of the United Kingdom and the National Institutes of Health in 2001, and following a March 2002 meeting with the clinical trials section of the NINDS. The University of Alabama at Birmingham was enlisted as the Data Coordinating Center in the February 2004 NIH grant submission, and following a revised proposal in October 2004, the NINDS Council recommended funding for MGTX.

3. Regulatory approval

For participating sites, obtaining regulatory approval is the first and a critical step for any clinical trial for several reasons. First, all regulatory documents must be in place before recruitment can begin. Second, most sites will not receive subcontract approval until regulatory paperwork has been approved. In our experience, regulatory approval was the major source of delay. Although project summary and consent form templates are provided by the coordinating center, each site must negotiate with their own institutional review board (IRB) or ethics committee on regulatory language, patient protections, and a variety of local issues and preferences while preserving the overall framework of the protocol. In the U.S. there are local IRBs and centralized IRBs. University-based centers almost exclusively require local IRB approval for federally funded studies. In the United Kingdom both local and Multicentre Research Ethics Committee (MREC) approvals are required before launching recruitment. Ethics boards or committees govern such investigation in other countries.

The duration of IRB approval ranges from 6 to 12 months in the U.S. before another IRB review takes place in order to continue the study. Ethics committee approval outside the U.S. usually lasts for the duration of the study; it is 5 years for MGTX. As a federally funded study supported by the U.S. government, each institution is required to register their ethics committee and apply for Federalwide Assurance (FWA) through the Office for Human Research Protections (OHRP)