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Challenges and Lessons Learned in Conducting Comparative-Effectiveness Trials

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Abstract

The current health-care environment is demanding evidence-based medicine that relies on clinical trials as the basis for decisions. Clinician investigators are more often finding that they are personally responsible for coordinating large, multisite trials. We present strategies for successful implementation and management of multisite clinical trials and knowledge gained through an international, multisite randomized clinical trial. Topics include team composition, regulatory requirements, study organization and governance, communication strategies, recruitment and retention efforts, budget, technology transfer, and publication.

Introduction

Randomized clinical trials (RCTs) serve as a basis for decision making in medicine. The current health-care environment is demanding evidence-based medicine and quality measurement, which often rely on past clinical trials as the basis for the decisions. Proof of efficacy is a priority of the Institute of Medicine (1) and the National Institutes of Health (NIH) (2) as well as the US Food and Drug Administration (FDA) (3). There is demand for higher-quality trials, often with larger sample sizes, as treatment effects may be modest.

RCTs are experiments in which people are randomly assigned to treatments and results are compared with respect to prespecified end points. The RCT has become the foundation of evidence-based medicine. Therefore, methodological validity and ethical conduct need to be ensured across sites, since not only are the results important for the trial but they will also inform practice (4).

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CONFLICT OF INTEREST

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As a result, clinical trials have tended to become larger with multiple sites, resulting in increased costs, bureaucracy, and coordination needs. Industry-sponsored trials often use a clinical trial coordinating center or a clinical research oversight group. However, clinician investigators are more often finding that they are personally responsible for coordinating large, multisite trials. Often these trials fail, for a variety of reasons. The aim of this paper is to review strategies for successful implementation and management of multisite clinical trials and to share knowledge gained through an international, multisite RCT. The information is intended to be helpful to the clinician involved in the project management of a clinical trial. Topics include team composition, regulatory requirements, study organization and governance, communication strategies, recruitment and retention efforts, budget, technology transfer, and publication.

Background

The Functional Dyspepsia Treatment Trial (FDTT) is an international multisite, randomized, placebo-controlled, clinical trial evaluating the efficacy of two antidepressants, escitalopram and amitriptyline, in participants with functional dyspepsia (<http://clinicaltrials.gov/ct2/show/NCT00248651>). Subjects are screened for 2 weeks and then randomized to either one of the antidepressants or placebo for 12 weeks with a 6-month observational follow-up. Patients must have functional dyspepsia with moderately severe symptoms, with no significant comorbidities and no history of depression or major abdominal surgery. The recruitment goal is 400 patients across eight sites in the United States and Canada (5).

The study was funded through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and is managed as a U01 study (6). The U01 multicenter clinical study funding mechanism uses a cooperative agreement award mechanism. The principal investigator (PI) maintains primary responsibility for directing and executing the multicenter clinical study, with NIH staff being involved as a partner with the PI, as described under the Cooperative Agreement Terms and Conditions of Award (7).

In addition to management of the multiple sites and research activities, there is an independent Data and Safety Monitoring Board (DSMB) appointed by the NIH that reviews study progress, adverse events, and any interim analyses. DSMB members provide expertise in areas needed to evaluate the study progress and adverse event patterns. To remain objective, there can be no conflicts of interest between the DSMB members and the study team. A Data Coordinating Center (DCC) gathers data, ensures data integrity, and provides quarterly reports to the DSMB.

The experiences gained from this complex study will serve as examples and lessons learned in the conduct and management of an international, multisite clinical trial. This study exemplifies the complexity of international regulatory requirements, trial governance, and the logistic organization that needs to be taken into account in such studies.

Team composition

One key to success of a multisite trial is the recruitment of interested and invested site PIs who have access to the needed patient populations. A committed research team is needed to initiate the study in a timely manner and to recruit patients. Recruitment of site investigators may rely on professional relationships and/or the ability to recruit patients. Available time, commitment, and ability to recruit should be considered in selecting sites.

Protected time for research is critical for the clinical researcher (8). Younger clinicians may have access to the patient populations in clinic practice, but they may also have competing responsibilities. They may need mentoring if they are not experienced in clinical research.

Seasoned investigators may have interest but less access to patients, necessitating collaboration with clinicians primarily staffing clinics or referring physicians.

RCTs have strict inclusion and exclusion criteria limiting the number of patients who qualify for the trial. While dyspepsia symptoms have been found in as many as 25% of people within a community (9,10), we found that many patients have comorbidities or symptoms that do not meet study criteria. An analysis of recruitment phone calls to a community sample reporting symptoms was conducted at the PI's site. It was found that only 1% of 454 people contacted were recruited for the RCT. The primary reasons were a lack of symptom severity and comorbidities.

It has been difficult to accurately estimate the numbers of patients available at an institution. One suggestion is to ask interested sites to conduct a brief review of patients to estimate whether the needed sample is available at the site. A limitation to this approach is the time and effort required by the site that may not result in participation in the trial. Without payment for such a review, many institutions would not be able to support that effort.

Qualified study coordinators are critical in recruiting patients, conducting the study procedures accurately, maintaining data integrity, and managing reporting requirements. Excellent organizational prioritization skills are needed, as study coordinators are often responsible for several studies, juggling many responsibilities. Face-to-face training of coordinators is often necessary for complex trials. It may be more effective and efficient and less costly to train them initially at the central location. Ongoing conference calls and periodic face-to-face meetings promote teamwork and sharing of successful recruitment strategies and study management.

Regulatory requirements

Regulatory and ethical approvals are required before the study can begin. Conversations about institutional policies and requirements facilitate the timeliness of approvals. Studies investigating drugs often need approval for an investigational new drug (IND) through the FDA (11) or other similar agencies internationally. Studies all require institutional review board or ethics board approval (<http://www.hhs.gov/ohrp/index.html>). These boards are usually specific to the institution and may have varying requirements.

This study involved an IND (11) application through the FDA, and approval was required before the study could begin. Studies involving an unapproved drug require FDA approval. Studies involving an approved drug for an unlabeled indication may require FDA approval depending on whether the study meets IND exceptions. Consultation with the FDA is helpful in those situations. FDA forms, such as 1571, 1572, and 3674, need to be completed. Some require signatures of the co-investigators at each site. The FDA may approve the study or may delay or hold the study. Final approval by the FDA is required before a study that involves an IND or an investigational device exemption may begin.

The primary site is required to maintain the regulatory files, including the FDA application and forms. A roles and responsibilities form is required for each site, outlining the study personnel and their roles. These forms need to be updated each time there is a personnel change at a site or a site is added. The FDA also requires annual progress reports; information to be included in the report is identified on the FDA website. While patients in this study have not encountered any serious adverse events, serious adverse events need to be reported within 24 hours to the FDA, so a call system was put in place at the primary site. A study coordinator, a physician, and an independent safety officer (physician) are available 24/7 to deal with emergency situations related to subjects in the trial at all sites. Should a situation require knowledge of the study medication, only the safety officer is able to make

the decision to break the code in pharmacy. The participant randomization codes are available through the hospital pharmacy and can be accessed 24/7. An extensive data and safety monitoring plan was required by the institution and the NIH that outlined the details of the safety plan and processes.

The FDTT is an international trial and posed some additional challenges as a site in Canada was initiated. An application to Health Canada, similar to that for the FDA, was required for the antidepressants being used. The application process is detailed and complicated, requiring expert knowledge in this area. A pharmacist was hired to complete the form and to work with the suppliers of the drug to ensure that compounding was the same at the Canadian site.

The research pharmacy used for the US sites was not licensed to ship across international boundaries, so extra costs were incurred to have the pharmacy at the Canadian site compound drug and placebo for the study. This process of Health Canada and pharmacy procedures took approximately 6 months and needed to be completed before review at the institution's ethics board. While this is a complex example, each site has had specific details to work out that take considerable time; we have found that we need to allow at least 3-6 months for a site to be up and recruiting patients. Understanding the requirements early in the process can expedite the approval processes.

Study organization and governance

"Trial governance" is a term used for the collective oversight bodies formed for the clinical trial (4). Typically, the ultimate oversight responsibility rests with the sponsor in the case of industry-sponsored studies. In the case of this NIH U01 study, responsibility rests with the PI with assistance from an NIDDK director. A number of committees were formed for trial governance, including an Executive Committee, Steering Committee, Data and Safety Monitoring Board, Exemption Committee, Data Coordinating Center, and Study Coordinator Committee. Each of these groups has a role in ensuring that the trial is being conducted in accordance with the protocol and procedures approved by the ethics committees and regulatory agencies.

An FDTT Executive Committee was formed with the PI, biostatistician, NIH director, and support staff. The Executive Committee deals primarily with study progress, site performance evaluation, and budget issues. The Steering Committee is made up of the PI, biostatistician, PI support staff, site PIs, NIH director, and staff, and study coordinators are invited to attend as they are able if the PI is unable to make the meetings. The Steering Committee meetings deal with study procedures (such as clarification of inclusion/exclusion criteria), recruitment and retention issues, publications, and secondary analyses.

The study PI and the site PIs, biostatistician, and NIH director make up an Exemption Committee that votes on exemptions to the inclusion/exclusion criteria. For each vote, three of the site PIs are selected. Additional members who vote include the biostatistician and the NIH director. Members are blinded to the site requesting the exemption. Voting is coordinated at the primary site by a study coordinator. If there is disagreement, a telephone conference is set up. Exemptions assist in clarifying the specifics of the criteria.

The study coordinators also hold a conference call monthly to discuss specific recruitment strategies, study implementation issues, and data transfer issues and provide practical tips and support for one another. They often problem-solve the specifics of the procedures or identify issues related to recruitment or retention of subjects.

In the FDTT, the Data Coordinating Center (DCC) consists of the study PI, the study co-PI biostatistician, an MS-level biostatistician, a study coordinator, a statistical programmer-analyst, and a doctoral-prepared nurse. The role of the DCC is to manage the data related to the study and to prepare reports and analyses. The study coordinator receives data from all of the sites and coordinates data entry. Coding of some of the text data, such as medications, is also completed at the DCC. Data are cleaned and sites contacted for missing data or errors on the case report forms. The DCC prepares the quarterly reports to the DSMB. These reports contain recruitment data such as screening and randomization numbers by site, stratification information by site, and a summary of adverse events.

This committee structure and meetings provide lateral structures that enhance collaboration and communication. Efforts are made to reduce redundancy and to ensure that topics are pertinent. The structure also promotes intellectual challenge. These meetings as well as periodic investigator meetings serve to create a cohesive team.

Team communication

Committee meetings are held by telephone monthly with a face-to-face investigator meeting annually, usually held in conjunction with a major scientific meeting. In addition to the monthly phone calls, e-mail notices are sent as needed. Notes are sent to all study personnel each time a patient is randomized noting the site's number of patients and the total for the study. This serves several purposes: it recognizes the site personnel for the work, maintains awareness of the study, and in some cases encourages healthy competition among sites. Routine types of announcements are sent by e-mail. Site phone calls are made instead if there are complex issues or problems. There is an effort to match the type of message to the medium used. For example, short answers to simple questions are sent by e-mail. Manuscript development is also done through short conversations and then e-mail. However, if there are issues at a site or complex issues, face-to-face meetings, teleconferences, or phone conferences are used. Face-to-face meetings are used for discussion of manuscripts and future projects, and for study coordinators' review of the more complex study procedures. Clear and proactive communication and use of the appropriate medium have been key in keeping concerns and conflict to a minimum.

Maintaining motivation among team members can be difficult in a long trial such as the FDTT. An emphasis on procedures and recruitment of subjects can be discouraging. Realistic recruitment goals with token rewards help to maintain long-term interest and healthy competition among sites. Goals are often tied to dates of professional meetings that tend to be on the calendars and in the minds of the PIs. A congratulatory note (kudos) is sent to all team members noting the PI and study coordinator each time a patient is randomized.

A graph was developed to demonstrate recruitment progress and is circulated monthly. The graph includes the number of days since the last patient was recruited, and color coding is used to indicate institutions that randomized patients in the past 30 days (green), 30-60 days (yellow), and more than 60 days (red). At a glance each team can see where its site's recruitment is in relationship to other sites. Investigator-provided rewards have also been used to recognize efforts. These have been in the form of a small gift card, a food item, or just a card or note acknowledging the effort and success; these are paid for by the PI and not the grant.

Recruitment and retention

For an RCT to be successful, it must be adequately powered to answer the research question. One of the most common causes of failure of a clinical trial is the inability to recruit an adequate number of subjects. Trial samples may be too small for subgroup analyses that are

important to the study (12). Attention to recruitment, recruitment strategies, and retention are key to a successful study.

Recruiting patients from a number of international sites poses some issues related to covariates, including the site itself. Web-based dynamic randomization was used to ensure balance on a number of important covariates (e.g., sex, dyspepsia subtype, and anxiety status). Treatment assignments are made sequentially to balance the marginal distributions of each of the *a priori*-chosen balancing factors (covariates). A newly recruited patient is thus assigned a treatment based on the treatment group balance (number of subjects in each treatment arm per category of each factor) summed across all balancing factors (treatment arm score) using the assignments of prior patients. The treatment assignment for any patient is to the treatment group with the smallest score (simple random assignment if scores are equal across treatment arms). This method ensures that each treatment arm has approximately equal proportions for each balancing-factor category (e.g., the same percentage of men and women in each treatment arm) (13). The chosen covariates are included in the screening process. The study coordinators enter the data on the website, and the randomization assignment is made available to pharmacy staff.

Recruitment of patients for a clinical trial can be challenging. Early in the study, we found that functional dyspepsia patients were concerned about being started on antidepressants and thought there were implications regarding their mental state. This issue was discussed with the site PIs and study coordinators, and the approach and message being conveyed to patients regarding the use of these neuromodulators were standardized. Consistent messages and a clear understanding of the rationale behind their use have reduced patient concerns and refusals to participate. In addition, the word “antidepressant” was taken out of the study title, and work was done to create an acronym for the study, FDTT (Functional Dyspepsia Treatment Trial).

The inclusion/exclusion criteria for clinical trials are strict in order to reduce any confounding variables. The FDTT subjects are required to have functional dyspepsia with no comorbidities, no prior use of antidepressants, and no history of depression and to have significant symptoms. Although symptoms of dyspepsia are common in community surveys, with as many as 25% reporting symptoms (9,10), people who meet the study criteria have been difficult to find. For this reason, a number of recruitment and advertising strategies have been used, with varying results depending on the location and timing. All sites have used flyers, posters, and employee advertisements at the academic medical sites. Additional recruitment strategies have varied depending on the site and regional environment. At one site, the number of functional dyspepsia patients is limited at the clinic, so the site PI relies on referrals from regional physicians. To make them aware of the study, educational sessions such as grand rounds have been provided in addition to letters to referring physicians. This strategy has been successful in obtaining patients from the surrounding area. Another site has found great success in running a free advertisement in a medical-center publication mailed to patients and families. That site has also had success with a local radio advertisement resulting in as many as 80 phone inquiries. However, in a large metropolitan area, radio and newspaper advertisements can be cost prohibitive, running as much as \$20,000 for a small advertisement in a weekend edition with broad circulation. As some strategies are very expensive, recruitment advertisements are approved before funding of that expense; the approvals are made by the Executive Committee of the study.

A new recruitment strategy was piloted for this study involving study advertisements and links to study information on Google. Advertisements were linked to searches for words such as “dyspepsia,” “stomach pain,” and others. The advertisements were targeted to a 120-mile radius around each of the study sites. Males and females within study ages were able to

see the advertisements. Charges for the advertisements are based on the number of people who click on the actual advertisement. Over the course of approximately 2 months, a total of \$1,000 was spent on the advertisements, which ranged from approximately \$0.80 to \$4.00 per click. Although the use of this technology was interesting, no recruits could be identified as having come from this source of advertising, and the advertisements were discontinued. Additionally, video information about functional dyspepsia and the FDTT was recorded by the PI and other study personnel and placed on YouTube. The advertisements contained links to the videos. Although there has been discussion about a social networking presence, possible issues related to inappropriate postings were thought to be a limitation, and the method was not pursued.

Since the recruitment strategies vary by geographic site, study coordinators have been asked to have the patients who call identify the source of their information about the study so the effectiveness of each strategy at each site can be evaluated. The information field was added to the recruitment log required in the study. The majority of the subjects are being recruited from specialty gastroenterology clinics despite the variety of advertising strategies.

The recruitment logs proved useful in negotiating additional funding for payment of parking and travel for participants. The number of patients who declined participation the first year because of travel expenses was significant. A decision was made to pay the government rate for medical travel and to provide parking for study visits. The study visits were also consolidated to the minimum possible to reduce the time required of the participant.

Effective strategies for retention and compliance with the study reduce barriers for the subjects. As noted, efforts have been made to decrease the number of study visits as much as possible, allowing subjects to complete surveys by mail and to have blood drawn locally. Study coordinators are in weekly telephone contact with the participants while they are on a drug. Another barrier to retention is drug side effects. Patient information was developed before implementation providing guidance to deal with known side effects of the medications. Subjects are encouraged to contact the study coordinator to work out any issues. For subjects who are unable to tolerate the side effects, a stop-trial protocol was written by which the drug can be stopped and restarted. A case report form was developed for clear documentation of the stopping and starting dates. Side effects may be reported as adverse events and are tracked and analyzed by the study team and the DSMB. Early intervention and an invested study team can keep dropout rates to a minimum, thereby reducing the numbers to be recruited.

Other retention tools, such as payment for transportation, flexible scheduling (including Saturday visits for those working Monday through Friday), and remuneration, are also important. In addition, the FDTT provides a water bottle with the FDTT logo on it as the person starts the study. Other examples from various studies include coffee or snacks at the end of appointments, birthday or holiday cards, carrying bags, study identification cards, and appointment reminders (8).

Study integrity

Clinical trials often entail physiological testing, blood work, and surveys as well as other procedures. Standardization of the procedures across sites is critical to data integrity. The FDTT uses numerous surveys (symptom, quality of life, eating disorders, sleep, and trauma), physiological testing (nutrient drink test, gastric emptying scintigraphy, and gastric accommodation at select sites for standardization), and blood samples for DNA testing. To ensure that the study was implemented in a standardized way at each site, several strategies were used. First, an investigators' meeting was held at the beginning of the study during which the site PIs and study coordinators reviewed the study, inclusion/exclusion criteria,

study procedures, and data transfer processes. Standard operating procedures were developed for each study visit, including physiological testing, adverse event reporting, and medication stop rules. Although tedious and time-consuming to develop, the standard operating procedures have provided consistent guidance and the foundation for discussions for changes if needed. They have also served to document decisions by the study team that either clarify or modify procedures.

As sites have been added or personnel have changed, site visits have been made by the PI and lead study coordinator to orient study staff and to gain institutional buy-in. Study procedures are reviewed with study staff. In addition, the NIDDK director and/or PI provide grand rounds and other informational sessions for staff. The NIDDK director, if present on the site visit, also meets with institutional leadership to gain support for the study.

Blinding of subjects and research study personnel is crucial. In the FDTT, study drug is provided to US sites by the institution's research pharmacy, with one drug and placebo being compounded by the pharmacy, and the other drug and placebo provided by industry. The pharmacies compound the medications in such a way as to ensure that study personnel and patients remain blinded. Since two medications are used in this trial, an initial suggestion was to encapsulate each; however, opening the capsule would unblind the patient and study staff. The research pharmacist devised a system by which each patient has a capsule and a tablet to ensure continued blinding of all involved. Although this is more complicated for the patients, it ensures blinding. Detailed instructions on medication administration are provided, as there is a 2-week ramp-up for the amitriptyline. The research pharmacy supplies medications to each site for each randomized patient and has ensured that pharmacy regulations are met and has provided the necessary forms and procedures for compliance. Medications are provided in childproof containers or blister packs. Patients sign a waiver to obtain the blister packs. Patients also complete a medication diary noting the date and time they took the medication, which is checked against the remaining medication each month. Sites are required to maintain accountability logs and environmental logs provided and managed by the research pharmacy. The accountability log lists study personnel who may be handling the drug and are therefore accountable for the medication or placebo. The environmental log provides a record of temperature and humidity each day. This is required by the Joint Commission in the United States if the medication is not maintained in the pharmacy.

Study resources vary across sites, affecting study feasibility, data integrity, and cost. For example, an institution with a clinical and translational science award has resources that supplement a study funded by the NIH. Study procedures being done on a clinical studies unit can be controlled to a greater degree than a number of clinical studies across sites. We have found that the quality, resources, and costs vary by institution even though descriptions of such units may be similar.

Study budgets

Budgeting a long-term, multisite study is challenging. The NIH requires annual budgets and contracts with each site. Institutional finance/contract staff can be most helpful in getting budget information from the multiple sites; however, the PI is still responsible for allocating and managing available funds. This study was budgeted on the basis of personnel percentage of effort and patient care costs. An advantage of this method is that the institutions know what the personnel costs will be each month; however, a site may charge for personnel time spent on recruitment of patients, increasing the average per-patient cost for the study. Another method is to calculate per-patient cost for each institution and to pay for randomized patients. This puts the responsibility on the participating organization to manage

its time accordingly. A disadvantage is that a site may not put in any time and not recruit patients, resulting in failure of the study due to lack of recruitment, a common reason for study failure.

Research spending tends to be front loaded with significant costs to begin a study. Costs to consider are start-up costs such as institutional review board fees, administrative start-up charges, and indirect charges. In the case of the NIH grant, indirect costs are paid according to the rate negotiated by the institution with the NIH, so each may vary. The NIH has a specified rate for international sites that can be found on its website. Notably, this rate is considerably lower than what is allowed for US sites. In considering the budget, data entry, analysis, and publication costs need to be included as well.

Payment systems may vary as noted above. Some studies require completed data sets for the subject prior to payment, while others invoice actual costs. Invoices for the FDTT are reviewed by central study staff at the primary site. Review includes not only the amount but the types of charges, as the NIH has very specific rules about how funds may be used. Finance personnel also assist in assuring compliance with effort certification and charges. Use of a spreadsheet comparing the budget to actual expenses and enrollment can be helpful in monitoring the budget.

Data transfer and entry should be considered and processes developed as the study begins. For the FDTT, the PI's site serves as the data coordinating center, entering data and ensuring accuracy. Data are entered by a double entry method for quality assurance. Because of the technology at the various sites, most of the case report forms were being copied and sent. Now, nearly all the sites have copier-scanners that allow electronic transfer of the data. To ensure consistency in the readings of the gastric emptying procedures, a file-transfer system was set up for data to provide for consistent interpretations of the tests by a single individual. Interpretation of the research exams is completed at the primary site.

Publication

Publication can be a source of dispute if not addressed early in the study (8). McPhaul and Toto strongly recommend that the PI meet early with the study team to determine authorship and to consider who will write up the primary and secondary questions. In the FDTT, authorship discussions occurred at the first investigator meeting for orientation to the study. Conversations have continued at each of the Steering Committee meetings and investigator meetings, where manuscript ideas are generated and primary authorship negotiated. Study team members are offered participation in manuscripts and abstract. Not all team members are authors on each paper. Those who have contributed to the design and execution of the secondary analysis and who have helped with the manuscript are included as coauthors.

Typically, hired or support staff are not authors, but there may be exceptions depending on their contributions (8). While support staff may be acknowledged for a single-site trial, it may not be realistic to acknowledge all support staff in a large, multisite trial.

Conclusion

RCTs will continue to be a definitive mechanism for evaluating the effectiveness, risks, and costs of new therapeutic treatments in medicine (4). RCTs continue to be the gold standard for evaluating new therapies. To answer the clinical questions, especially for less common diseases, multisite trials are needed; however, RCTs pose substantial methodological and practical challenges. The international regulatory burden is likely to continue. The role of the electronic health record and developing technology in RCTs is yet to be explored fully. The use of social networks for recruitment of subjects is yet to be evaluated. Internet-based

interventions and data collection methods are being used, but their full role in RCTs and possible cost savings have not been fully realized.

This is an exciting and challenging time to be involved in RCTs. Management of an international multisite RCT can be frustrating but rewarding if managed well. Opportunities exist to more fully realize RCTs in a cost-effective manner with improved quality and generalizability.

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