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Coordination and Management of Multisite Complementary and Alternative Medicine (CAM) Therapies: Experience from a Multisite Reflexology Intervention Trial

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Abstract

Background—Multisite randomized clinical trials allow for increased research collaboration among investigators and expedite data collection efforts. As a result, government funding agencies typically look favorably upon this approach. As the field of complementary and alternative medicine (CAM) continues to evolve, so do increased calls for the use of more rigorous study design and trial methodologies, which can present challenges for investigators.

Purpose—To describe the processes involved in the coordination and management of a multisite randomized clinical trial of a CAM intervention.

Methods—Key aspects related to the coordination and management of a multisite CAM randomized clinical trial are presented, including organizational and site selection considerations, recruitment concerns and issues related to data collection and randomization to treatment groups. Management and monitoring of data, as well as quality assurance procedures are described. Finally, a real world perspective is shared from a recently conducted multisite randomized clinical trial of reflexology for women diagnosed with advanced breast cancer.

Results—The use of multiple sites in the conduct of CAM-based randomized clinical trials can provide an efficient, collaborative and robust approach to study coordination and data collection that maximizes efficiency and ensures the quality of results.

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Conclusions—Multisite randomized clinical trial designs can offer the field of CAM research a more standardized and efficient approach to examine the effectiveness of novel therapies and treatments. Special attention must be given to intervention fidelity, consistent data collection and ensuring data quality. Assessment and reporting of quantitative indicators of data quality should be required.

Keywords

Multisite randomized clinical trials; Complementary and Alternative Medicine; Reflexology; Data coordination and management; Quality assurance; CONSORT

Introduction

In recent years, there has been an increase in the number of multisite trials. [1-3] Multisite trials have several advantages over single-site studies. An obvious advantage is that the involvement of multiple sites allows investigators to achieve the desired statistical power in hypothesis testing or accuracy in estimation of treatment effects through the accrual of an adequate sample of subjects in a shorter period of time than is usually possible in a single-site study. [4-6] Second, multisite studies can also facilitate the goal of reaching diverse populations which usually results in estimates for the treatment effect that have generalizability to the target population. [7;8] Third, since all sites follow a common standardized protocol and adequate quality assurance measures are in place to ensure adherence to the study protocol, the resulting data have a higher level of integrity and quality. [5;9] Finally, multisite studies usually benefit from a larger pool of diverse expertise needed for a successful completion of complex trials. These characteristics are equally applicable to complementary and alternative medicine (CAM) multisite RCTs.

The purpose of this paper is to describe the processes involved in the coordination and management of a multisite CAM intervention trial. To add to this paper's “real world” application, experiences derived from the authors' National Institute of Health (NIH)-funded RCT of the CAM therapy of reflexology will be used as an exemplar. [10] Details about the exemplar study have been described elsewhere. [11] The National Center for Complementary and Alternative Medicine (NCCAM) expects CAM therapies to be investigated with the same rigor as conventional treatments and held to the same standards for quality as put forward by the International Council on Harmonization (ICH) [12] and the Food and Drug Administration (FDA) in order to obtain data on safety and efficacy. [13] Therefore, multisite CAM therapy trials require an appropriate study design and statistical considerations, careful planning and implementation, and coordination between sites to ensure high quality data and reliable findings. [14] In the past, many CAM studies have suffered from the drawback of insufficient sample size and statistical power. [15] Multisite trials of CAM interventions have the potential to overcome this drawback and can provide much needed data on the safety and efficacy of CAM therapies.

The need to study CAM therapies stems from their wide use. In particular, with over 80% of women with breast cancer using CAM therapies for symptom management, [16] the results of well designed and conducted trials can inform clinical practice on appropriate use of CAM therapies during breast cancer treatment, and impact a large number of patients. Therefore, the objectives of this paper are to:

1. Describe key components involved in the coordination and management of a multisite CAM RCT including organization, site selection, recruitment, interviews, randomization, and blinding.

2. Describe data management and monitoring for a multisite CAM RCT including data collection, quality assurance (QA), data cleaning, data safety and monitoring, publications and data sharing plan, and standard reporting guided by the Consolidated Standards of Reporting Trials (CONSORT).

Methods & Results

Study Population

The exemplar study of reflexology included a total of 451 women with advanced breast cancer, who were undergoing chemotherapy. Over the 5-year course of the study, 14 sites were involved across the Midwest, with a maximum of 10 at any one time. The clinical trial had three study arms; women were randomized to (a) reflexology, (b) foot manipulation (placebo), or (c) standard care control. Details about the exemplar study have been described elsewhere. [11]

Study Organization

A multisite trial requires a clear organizational structure, along with well-defined roles and functions for the participating sites. The main purpose is to increase efficiency and uniformity across the sites. [9;17] The key focus of study management is on the implementation of the study protocol [9] and ensuring data quality and patient safety. [18] Key personnel in the exemplar multisite study included the investigators, project manager, study statistician, education coordinator, site recruiters, interveners (reflexologist and placebo providers), interviewers, chart auditors, database programmers, information technology specialist, and student staff.

The Principle Investigator (PI) has overall responsibility for management of all aspects of the study. (Figure 1) The Co-Investigators (Co-Is) contribute their specific expertise to one or more aspects of the study and collaborate with the PI. Experienced statisticians play an important role in clinical trials/studies. [12;19;20] In the exemplar study, the statisticians not only had responsibility for data analysis, but also supported the other investigators with respect to study design, development, and implementation of the randomization/ minimization schedule.

The project manager reported directly to the PI and coordinated all aspects of the study, including communication and monitoring across the sites. The education coordinator was responsible for the training of recruiters and interviewers. In addition, the education coordinator conducted the general study orientation for all interveners and specific protocol training for the placebo interveners. The lead reflexologist provided training for the reflexology interveners including initial and ongoing quality assurance (QA) checks. The interveners were either lay persons, who delivered the placebo foot manipulation, or certified reflexologists, who delivered reflexology in the respective arm of the study. Interviewers were graduate students trained in the study-specific protocol by the education coordinator to conduct the telephone interviews. The database programmers created the database under the supervision of the statistician, and the information technology specialist maintained the server including daily back up of data. Additional study staff assisted with data entry, data analysis, and day-to-day operations of the study. The site recruiters were employees of the various sites so as to meet Health Insurance Portability and Accountability Act (HIPPA) requirements. The site PIs were either a medical oncologist or a site-based administrator who contributed their time, or a researcher whose time was covered by the study. The site PIs were listed on the human subjects approval forms. The Institutional Review Boards (IRB) of the investigators' university and of each participating clinical site

approved the study. A sub-award was established between each site and the university where the grant was awarded.

Site Selection

It is important that the sites selected for a multisite study have experienced personnel [4] and an adequate infrastructure to successfully perform the research. [17] It is the responsibility of the principal investigator to closely review the qualifications of the site personnel for participation in a multisite clinical trial, which include: credentials, training, and experience to assume responsibility for the proper conduct of the trial in accordance with Good Clinical Practice (GCP) guidelines (see sections 4.1, 4.2 and 5.6). [12] Specific skills include good interpersonal and communication skills to effectively recruit patients; time management skills to adequately meet trial milestones; experience with multisite studies, and ability to obtain IRB approval at their institution in a reasonable amount of time. [12] The principal investigator and site personnel must ensure the adequacy of all facilities for the conduct of the trial and the accuracy of data collection through reliable data management and quality assurance processes. [17] The exemplar reflexology study enrolled study participants from 14 community-based medical oncology clinics throughout the Midwest. Prior to selection, each site PI was asked to provide data on the number of cases that matched the study criteria over the past 12 months. Each prospective site demonstrated they could enroll 2-4 patients per month. A “Letter of Agreement” was signed by both the study PI and the site PI to this effect, and either side could terminate the agreement with 60 days written notice. Second, each site was asked to identify a study recruiter and a backup recruiter in cases of illness or vacations.

Recruitment of patients

Timely recruitment of patients is essential to successful completion of a trial. Interruption and delays in enrollment cause increased workload and cost. [21] About one-third of clinical trials apply for additional funding and/or time extension due to inadequate enrollment based on the original expectations. [22;23]

Factors associated with enrollment challenges in clinical trials can include the type of medical treatment received and patients' distrust of the experimental treatment. [21] Investigators in clinical trials, particularly in cancer, must explain the potential benefits as well as any side effects of the treatment. Popular strategies for improving recruitment in most multisite studies, but not necessary in the exemplar study, include advertising through newsletters, telephone and regular mail. [23] In addition, adequate enrollment begins with clear and comprehensive training of site recruiters.

In the exemplar study, the education coordinator traveled to each site to train the nurse recruiters and provided booster sessions as needed to reduce personnel turnover. Training was based on study manuals developed by the investigators. To assure consistency in the recruitment protocol, training included didactic information, written steps, role-playing, demonstrations, and return demonstrations. [11] After completion of recruiter training, the nurse recruiter identified eligible patients through internal grand rounds and medical record reviews.

Once eligibility was established, the recruiter approached individual patients and described the study to obtain consent. Women could either sign the consent at that time or take the information packet home and mail their consent to the recruiter after thinking about it more. After the recruiter received the signed consent, the patients underwent their baseline interview and then were randomized to one of three study arms. The overall consent rate

was 75.8% out of eligible approached patients; the consent rate varied by site, ranging from 52.38% to 100% (see Table 1).

Interviews

In multisite clinical trials, it is important to ensure that interviews are conducted in a standard and consistent fashion. Depending on the type of study, various modes of conducting interviews can be considered. These include telephone interviews, face-to-face interviews, and group interviews. [24;25] Providing written instructions in addition to training for interviewers at all sites helps to bring uniformity and consistency to the administration of the interviews. [26]

In the exemplar study, interviewers were trained by the education coordinator using similar educational methods as those used for recruiters. Three interviewers were hired to conduct interviews throughout the study. A bound manual was created for training and used later for reference by each interviewer. Three telephone interviews were conducted with each patient from the study office. The baseline interview occurred after consent and before randomization. Individual patient data from the baseline interview were used in the randomization program. The second interview followed the 4 week intervention at approximately study week 5, and the final interview was conducted six weeks later at study week 11. These interviews collected all outcome data including Quality of Life (QOL), which focused on symptoms and improved physical functioning. [11]

Randomization

Different methods are available for the randomization of patients into study arms. In recent years adaptive randomization also known as minimization has gained popularity. [27;28] At each stage of randomization an adaptive technique analyzes the distributions of the key variables selected as minimization variables with respect to previous assignments to the study arms and adapts the next assignment in such a way that it increases the likelihood of balancing the study arms with respect to the distribution of these predetermined minimization variables. [28] For multisite studies, one of the minimization variables can be the study site in order to control for the variations in care across multiple sites. In addition, balancing the study arms with respect to active sites at any time provides flexibility in terms of adding new sites or dropping poor performing sites during the study. [29;30]

In the exemplar study, the minimization procedure was used for randomization and balanced the study groups with respect to recruitment site, levels of pain and fatigue at baseline, and the goal of therapy. [11] A randomization algorithm was run centrally as opposed to running separate randomizations at each study site. This approach was used since small and insignificant group imbalances at each site could have accumulated and produced a significant overall imbalance among study groups. The minimization algorithm was programmed before patient enrollment began, and was tested on 300 simulated subjects with a subsequent evaluation of the resulting allocation. The test (using simulated subjects) projected distributions of the balancing variables used in the minimization program (algorithm). Levels of pain and fatigue and the goal of therapy (curative, palliative, maintenance or unknown) were expected to have similar distributions across sites. The distribution of patients across sites was not assumed to be the same when testing the algorithm because sizes of the participating sites differed. However, the minimization algorithm ensured that if a particular site enrolled, for example, 10% of the overall sample size, then approximately 10% of the patients in each of the study groups were from this particular site. Once the test run with 300 simulated subjects was completed, chi-square tests were performed to evaluate whether the distributions of balancing variables used in the minimization algorithm were the same across study groups. After confirming lack of

differences, the algorithm was implemented with the actual assignment of patients in the trial arms. As a result, reflexology, placebo and standard care control groups of the trial had the same distribution on level of pain (high versus low, chi-square=0.02, df=2, p-value=.99), fatigue (high versus low, chi-square=0.36, df=2, p-value=.84), goal of therapy (curative, palliative, maintenance or unknown, chi-square=0.54, df=6, p-value=.99), and study site (chi-square=28.81, df=24, p-value=.23). For the Chi-square test by site, site #10, which had a small number of patients (see Table 1), was combined with site #9. These sites represented two clinics within the same system. Not only was the central randomization successful in the sense that it produced balance on the important factors at baseline across study groups, but it also facilitated allocation concealment since the results of the group assignment were not predictable to recruiters and other study personnel at the sites. Allocation concealment is one of the requirements included in CONSORT guidelines. [32-34] The randomization program was designed so that it was easily operated by the project manager. Figure 2 points out the success of randomization in the sense that the rate of withdrawal during the study period and the reasons for attrition (withdrawal) were similar across study arms in part due to the similarity of the characteristics of patients allocated into the study arms. Table 1 demonstrates the rate of consented and attrited patients by site. Overall, 75.80% of the patients approached provided consent to participate in the study. The overall rate of attrition after randomization was 29.87%.

Blinding

The needs of a multisite CAM trial may be different from the traditional multisite drug trials. For example, in a drug trial the blinding is usually coordinated through the packaging of the drug and placebo by the pharmacist; whereas for a CAM intervention trial the statistician plays a central role. For the exemplar study, the randomization program was developed and set up by the study statistician to have a user-friendly interface that allowed the project manager to operate the program. This ensured timely assignment of the interveners (reflexologists or placebo providers) to the patients by the project manager. Prompt contacts with the patient and lack of delays have been shown to be important factors for patient retention in traditional trials. [31] Since there is a paucity in the current literature on attrition in CAM trials, it is unknown if timely contacts help retain patients in a CAM trial. Other predictors of attrition in traditional trials such as poor health have not been shown to be important in the reflexology trial. [32]

In addition, the operation of the randomization program by the project manager ensured blinding of all study personnel (except for the project manager and interveners) to group assignment. In the exemplar study, blinding of the patients was in place in the two active groups (reflexology and placebo) and was achieved by the superficial similarity of the reflexology and placebo protocols (manipulation of the feet for the same duration). Interveners followed the same protocol for limited social interaction with the patient, and if patients asked about their group assignment, interveners responded that this question would be answered after the last study interview. To ensure that the superficial similarity of placebo and reflexology protocols was sufficient for blinding of the patients, one of the exclusion criteria was regular use of reflexology, pedicure or foot massage at the time of enrollment. The necessity of one of the exclusion criteria for blinding is one of the differences between a CAM trial such as reflexology and a traditional drug trial.

Data Management and Monitoring

Consort

The CONSORT statement provides important guidelines with respect to the reporting of clinical trials. [33-35]The key elements stated in the CONSORT include: (a) participants, (b)

intervention, (c) objectives, (d) outcomes, (e) sample size, (f) randomization procedure, (g) blinding, and (h) statistical methods.[11] While the CONSORT has helped standardize reporting of RCTs, it does not report indicators of data quality, a description of quality assurance (QA) procedures, or data monitoring. In a multisite study, these are also important considerations.

Data Management

Data management involves the development of processes to ensure systematic and efficient handling of research information.[4;36] For multisite trials this often begins with the development of a computerized information system that ensures timely reporting of accurate data as well as uniformity in methodology for collection of data by study sites. [37;38] A computerized information system provides innovative tools to improve data accuracy and timely data collection procedures as well as storage and retrieval of data. Recent research shows that the development and use of efficient electronic data management and data collection systems with audit trail capabilities can improve data quality while decreasing the cost. [39;40] The system should be user-friendly while maintaining capability for disallowing entry of invalid data into the system. Univariate and multivariate rules should be developed for identifying and correcting potential invalid data.

In the exemplar study, several members of the team contributed to the processes of data management. The study statistician led the data management team and worked closely with the database programmers during the first year to establish a system with the necessary fields for the various types of data to be collected. A web-based information system was developed with separate parts corresponding to study components: recruitment, interviews, intervention, and medical record audit with access to each area limited to the appropriate study staff. For example, recruiters only had access to the recruitment portion of the database, and interveners were only authorized to use the intervention portion. All log-ins were documented, and all data entered or modifications made were date and time stamped in addition to the name of the person who made the change. Some fields in the database were required, including fields corresponding to inclusion and exclusion criteria, and date of consent or refusal. When any of the inclusion criteria were not satisfied, an alert message was displayed for the recruiter, and the database application would not proceed to the consent page until all eligibility criteria were met. The levels of pain and fatigue and the goal of therapy were required fields in the interview since these were used as balancing variables for the randomization program. The dates of all intervention sessions or reasons for missed sessions were documented by required fields in the database. Other fields in the database were programmed to only accept data of specific types (numerical, text, check all that apply or check one).

To ensure security of data, two separate servers were involved in database operations. One was the web server that hosted the application for data collection and entry. The second server was used to store the data. Both servers had firewalls, password protection and automatic daily backups. The study statistician coordinated data needs between the database programmers, information technology specialist, the project manager, and the graduate student with statistical expertise.

Quality Assurance (QA)

Quality assurance includes the development of processes that ensure optimal data management, personnel performance, data quality, and easy access to information in terms of secure storage and retrieval. [36] The main objective of QA processes [35] in clinical trials is to minimize errors. [41] These processes involve development of Standard Operating Procedures (SOP), manuals of procedures (MoP), codebooks, testing the data

collection system, and all accompanying computer programs that help to avoid doubtful practices in implementation of the intervention or data collection. [41;42] Any misconduct or protocol deviations must be documented and appropriate actions taken to address the underlying concerns.

Designing clear forms [36;38], training of personnel, double data entry, checking data integrity and consistency, establishing inter-rater reliability, providing training, performing calibration, conducting site monitoring, and audits are all ways to maintain data quality. [35;41] In developing these processes, simplicity and efficiency should be kept in mind by incorporating only what is actually needed for a specific study.

Monitoring

In multisite trials regular site monitoring is conducted. These monitoring activities are designed to improve data quality and performance at all study sites. [43] Typically, a monitoring plan is developed that encompasses all issues that require monitoring at the sites. These could include a range of clinical activities as well as data monitoring. Though site monitoring can be expensive, experience has shown that clinical and data monitoring improves the quality of data collected at all sites. [35;41;43]

In the exemplar study, conference calls with the sites were scheduled quarterly and on an as needed basis with all sites to review recruitment and any associated problems. Recruiter monitoring was managed through site visits conducted by the site liaison (site monitor). Site visits occurred approximately every three to six months or as needed. During the sites visits, the focus was on reviewing recruitment procedures, identifying difficulties and ways of handling them for the particular site, and resolving questions specific to the sites. The site liaison took with her information from the data quality assurance reports regarding anything unique to the specific site, as well as summary information on the numbers and percents of patients approached, consented, and attrited from the site. Strategies to enhance recruitment and minimize attrition that could be successful at the site were discussed. Following the site visit, the liaison completed a site visit summary form, and this summary was discussed at the regular team meetings. A recruitment newsletter was also distributed quarterly from the main study office with pointers on what was working best for the various sites. The top recruitment site was asked for ideas for the newsletters.

Intervener QA—In multisite CAM trials, a concerted effort must be made to ensure intervention fidelity. [44;45] In the exemplar reflexology study, interveners were responsible for adherence to the study procedures throughout the trial. A concerted effort was made to assure rigorous intervention fidelity including intervention dose consistency, provider consistency, delivery consistency, and receipt consistency. [44;45] If any deviations from the protocols were detected, the PI and Co-Is were notified immediately. The investigation team determined if any portion of the protocol was violated and how such a violation could be prevented in the future.

While reflexology is a safe and non-toxic therapy and no adverse events occurred during the study, procedures were in place to notify the sites, including physicians, as appropriate. All interveners (placebo and reflexologists) were retrained and their performance checked for quality using the established intervention fidelity check form for quality assurance every six months.

Data Entry QA—Entirely manual and optical character recognition (OCR) are two popular methods for data entry. Regardless of the method used for data entry the procedure must deal with identifying and correcting problem data in order to ensure quality control of the entire process. [46] In the exemplar study the data were entered manually. All data from

interviews were checked to ensure their completeness and any missing fields were discussed and corrected at the regular data meetings. A weekly run computer program flagged all interviews due to be completed within 2 weeks. The computer program's output contained a list of patients due for interviews. This output was given to the project manager who assigned tasks to the interviewers. Data quality reports were produced every 6-8 weeks that indicated whether or not the rate of errors or skipped fields during data entry did not exceed the recommended error rate of 0.3% (3 per 1,000 entries) [47]. All errors identified on the reports were corrected by the interviewers who entered the interview data or by the project manager.

Interviewer QA—The quality of information obtained during interviews is important but few RCTs report their method for ensuring interview quality. Educational background and quality of prior training and clinical experience impact interview quality. [26] In the exemplar study, refresher (QA) training using tapes and role-play occurred every six months as needed. To assess the need for refresher training, QA checks were completed on 10% of each interviewer's taped interviews. The study statistician provided a computer-generated random schedule for recording 10% of all interviews. [26] Prior to recording, the interviewer obtained verbal permission from participants to record the interview. Participants were informed that the information they provide will be kept confidential and only authorized research staff will view/listen to the tapes. In addition, the participants were assured that the QA evaluation only focused on the interviewer, not on the participants' answers. The tapes were reviewed and evaluated by the education coordinator who reported the summary of evaluations at monthly data quality assurance meetings attended by all investigators. A QA reporting form was developed at the beginning of the study and was used for the duration of data collection. The components listed on the evaluation form included items such as the interviewer's pace and voice quality, enunciation and diction, use of appropriate prompts, and the interviewer's adherence to set procedures such as contacting patients at the appropriate time dictated by the study protocol, and patient availability.

Chart Audit QA—Some multisite clinical trials rely on information obtained from medical records. Chart audit is a method to ensure the quality of data obtained and submitted by the sites. [36] For the exemplar study a chart audit QA was performed for 10% of each site's total completed chart reviews. The charts selected for the QA were determined from a set of random numbers generated by the study statistician. A set of 120 random numbers between 1 and 10 was generated and saved. The chart audits were sorted by site and date received. Once a site had reached 20 completed chart audits, the first random number generated determined a chart audit out of the first 10 in the ordered list to be checked. The second random number on the list determined the chart from the next 10 (charts 11-20 sorted by date at each site) to be checked. Two charts selected for audit were reviewed by a nurse at the study site who was different from the nurse who conducted the original chart audit. The QA nurse had a printed copy of the data recorded in the database during the original data collection. A standardized chart review QA form was followed and included the number and specific fields where differences appeared between data recorded in the database and what was found in the chart. The completed review form was then submitted to the central research office. The hard copy of the study medical chart review which was downloaded from the database was saved with the patient's records in a secure locked file cabinet at the site or destroyed if the site had an electronic medical records system. Throughout the duration of the study, the error rate ranged from 0.1 to 0.4 % (1 to 4 errors found in 1,000 fields).

Data Cleaning

Chapman (2005) highlighted the need for conducting data quality checks at all steps of data management, [48] but some data managers may not fully appreciate the consequences and impact of data quality on the research findings. Errors and uncertainty are inherent in all data, and any errors may affect the final results and research findings. However, there are few published articles that actually report the error rate and methods of data quality assurance in their research. [49] Therefore, a data cleaning plan to improve data quality must be an essential part of the data management plan.

Data cleaning has four major aspects: screening, diagnosis, editing, [49] and cost considerations. Screening: The screening phase is characterized by identifying data peculiarities, such as missing data, outliers, unusual response patterns or unforeseen results. Diagnosis: The purpose of the diagnostic phase is to understand the origins of sporadic findings, troublesome response patterns or peculiar results. Possible diagnoses may include error, true extremes or idiopathic, where no justifications can be found. Editing: Once data issues have been screened and diagnosed, the next step is to reconcile discrepancies. Researchers are generally limited to correcting or deleting, or leaving data elements unchanged. These decisions are based on the types of errors found and whether certain assumptions can be made about why problematic patterns have been detected (e.g., whether data are missing at random or not). [49] Cost considerations: The cost and availability of trained resources are major determinants of the extent of data cleaning conducted for clinical trials. If the data-cleaning process is planned in a way that queries are generated and automated comparison of successive datasets are implemented early in data collection process, then this may result in lower costs and speed the process. [49] It is important to keep in mind that while high quality data are centrally important to the success of clinical trials, perfect data may not be necessary and indeed, may be difficult if not impossible to obtain.

Defining, generating, and applying validation rules for data cleaning and validation are time-consuming and labor intensive. Therefore, it is important to weigh the effort invested in data cleaning and validation with the improvement in data quality and ultimately on trial results. An acceptable data quality level is one that can be considered good enough to not materially affect the results or conclusions. [50] Achieving this may be challenging, since an acceptable data quality level has never been defined in regulatory guidance documents or in the literature. Further, the threshold for data quality may depend on the complexity of the trials. More complex trials may need more rigorous tests of data quality to assess their impact on the findings. Additional methodological research is required to define acceptable data quality for clinical trials. Setting the standard for data quality, requiring a report of the data cleaning process, and providing indicators of data quality as part of clinical trial evaluation, will result in more robust and reproducible findings. In the exemplar study, data cleaning techniques included computer programs that were written to flag inconsistent data (such as indication of the absence of a symptom yet presence of severity rating), as well as missing data on the outcomes. These tools were applied periodically to the data downloaded from the server, and provided easy access to the audit trail information by saving all error reports and documenting the correction of these errors through date and time stamping and documentation of all logins to the database. Further, the project manager took notes during the data meetings and the investigators indicated which items needed to be communicated with the sites regarding resolution of missing, discrepant, or questionable data. These efforts resulted in 100% completeness of the outcome data in the sense that the only missing data were from the patients who dropped out and did not complete the interviews.

Data and Safety Monitoring Committee (DSMC)

In addition to regular monitoring at the sites and regular team meetings for clinical trials, a Data and Safety Monitoring Committee (DSMC) is established with an oversight role for patient safety, data quality, and weighing risks versus benefits in continuing clinical studies. [51;52] Since we did not expect adverse events (AEs) in our exemplar study, an internal DSMC provided oversight for data management and monitoring, interviewers' QA, chart audit QA, interveners' QA, and recruiters. The DSMC met every four to six weeks to discuss progress on various aspects of the trial. The data team members produced a data summary for each DSMC meeting in the form of a CONSORT chart. These data included the number of patients approached, consented and attrited patients to date (overall and by site), reasons for refusal to participate (overall and by site), and the number of patients who completed baseline, 5 and 11 week interviews (see Figure 2 and Table 1).

Data Sharing and Publications Committee

It is important to develop procedures for the utilization of multisite data. [9;18;42] Such procedures include the development of data sharing guidelines for publication and dissemination of multisite findings. For the exemplar multisite study, the data sharing committee comprised all study investigators and relevant members of the study team, such as interested site PIs. Various investigators on the team have taken the lead on publishing different aspects of the study. [11;32;45;53]

Discussion

The RCT is considered the standard design for the assessment of clinical interventions in relation to their efficacy/effectiveness. [54] Even though about one-third of CAM studies in breast cancer are designed according to RCTs, [7] there remains some concern about a lack of rigorous methodology. Using RCTs with sound methodology in CAM studies will lead to the most robust findings. [54]

Multisite CAM studies provide opportunities for recruiting an adequate sample size to achieve appropriate statistical power. [4-6] In addition, multisite studies will improve the standardization and consistency of procedures, assure higher data quality, and provide appropriate infrastructure for a well coordinated study. [5;9]

Most attention to date has focused on data monitoring, with less attention has been paid to assuring data quality and procedural adherence. Formal quality assurance procedures help to improve efficiency and minimize errors. Establishing formal data cleaning processes as part of QA helps to detect and correct errors, resulting in better data quality. This requirement of the establishment and documentation of the QA procedures is not present in the CONSORT statement, and consequently little attention has been made to require indicators of data quality when reporting the results of clinical trials following the CONSORT guidelines. Even though CONSORT is not used as a quality assessment instrument, [34] adding a requirement of reporting indicators of the data quality would result in more robust findings in clinical studies, including CAM trials. [42] The need exists for starting a process of discussions among academia, industry and regulatory groups for adding potential indicators of data quality to the CONSORT statement. Multisite trials need to establish rigorous procedures for ensuring data quality by providing manuals, training personnel (including interveners and interviewers), establishing guidelines for data entry, data collection, conducting quality control procedures and appropriate methods for data analysis. [18]

It is important to note that the more complex and novel the intervention, the more important the need to provide rigorous testing of its effects. Additional methodologic research is required to investigate the role of data quality on the assessment of various effects for

clinical trials. Setting the standard for this field as a clinical trial evaluation will challenge methodologists but benefit the medical and consumer communities. Since CAM multisite trials can have unique features and present challenges, it is necessary to consider the key areas of data management and monitoring as an essential component of coordinating any CAM multisite clinical trial. The use of an exemplar reflexology trial has allowed the real world application of principles for a rigorous RCT to be demonstrated in a multisite CAM trial.

Implication for future research

This research highlights the importance of reporting quantitative indicators of data quality (e.g., error rate in data) for all trials, including CAM studies. These requirements are not included in the current version of CONSORT, but could make a significant contribution. Multisite RCT designs offer the field of CAM research a standardized and efficient approach to examine the effectiveness of novel therapies and treatments. Even though most clinical trials conduct data management and monitoring, few trials report indicators of data quality and associated error rates in published reports from trials. As multisite CAM trials (interventions) gain widespread acceptance, increased attention to study coordination and quality assurance procedures will lead to rigorous reporting of trial effects, and by extension, improve the overall integrity of empirical evidence in CAM research.

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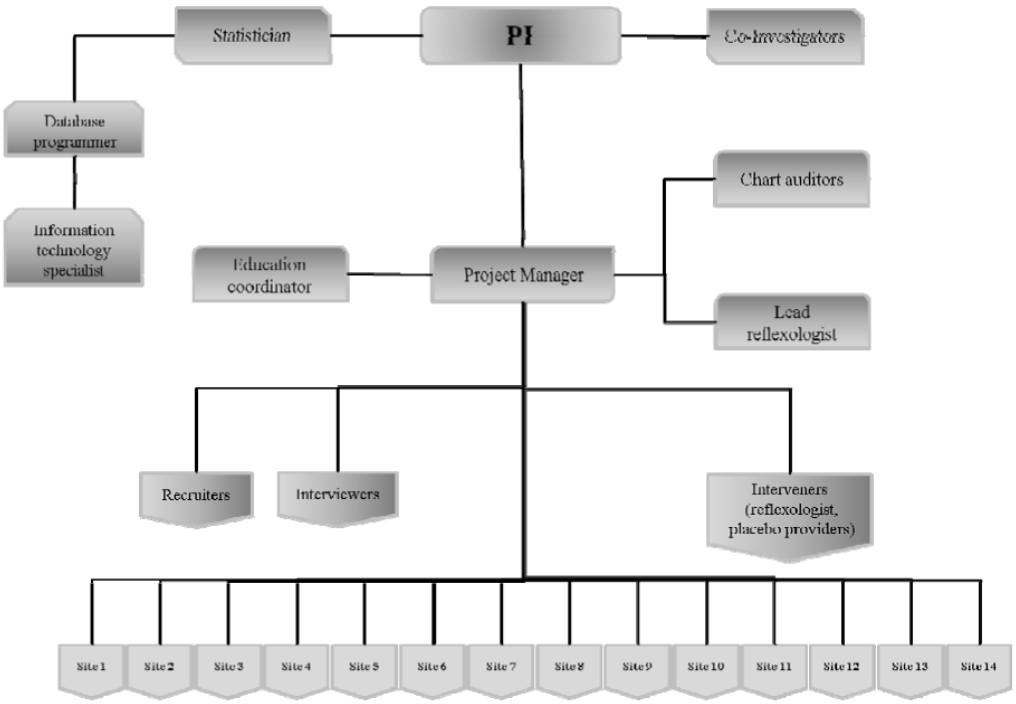

Figure 1. Organizational Chart

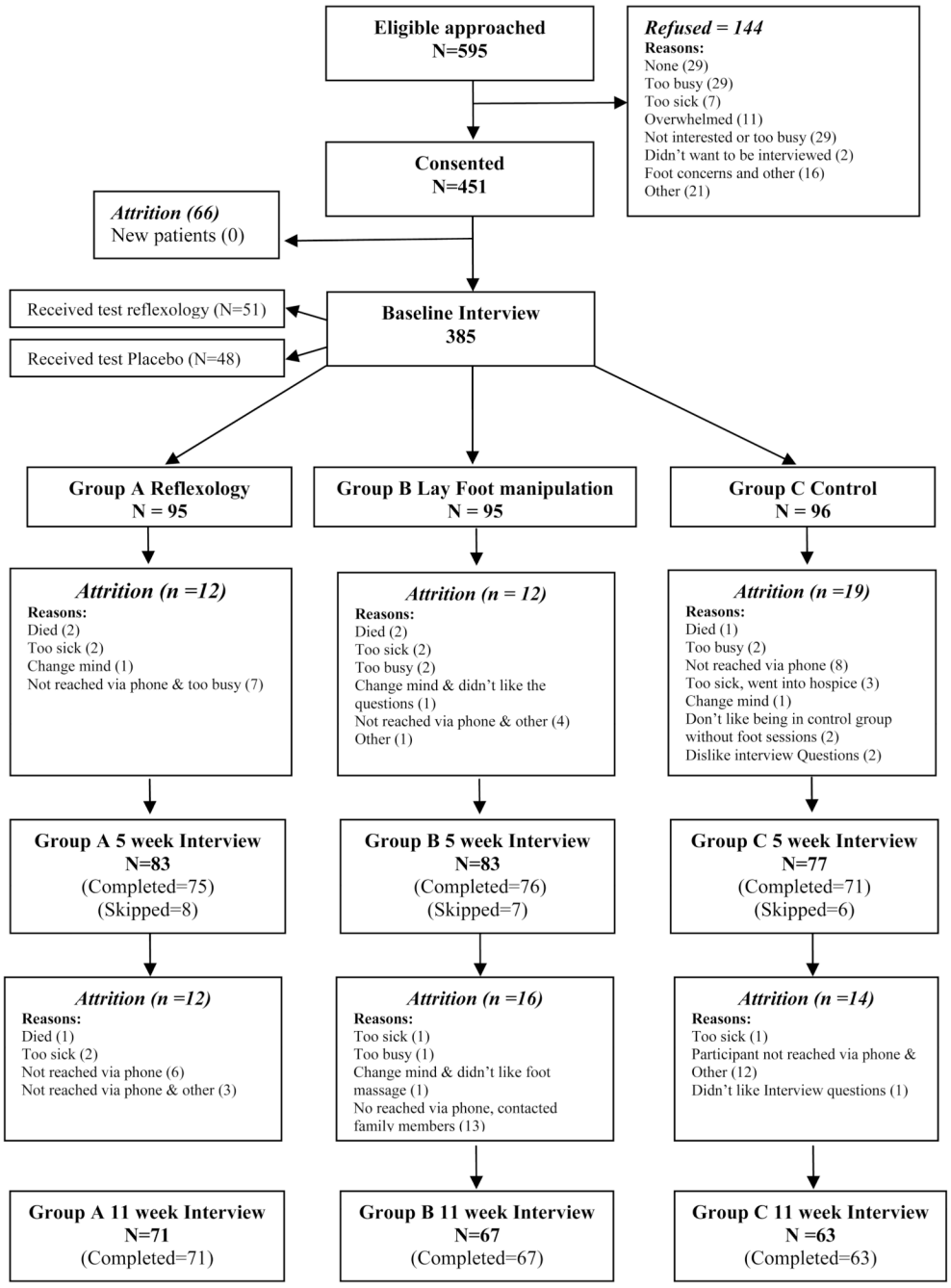

Figure 2. CONSORT Flow chart indicating the number of patients assigned to each study arm

Table 1

Summary of approached, consented, and attrited patients overall and by site.

Recruitment Site	Number approached by site	Number consented by site	Percent (%) consented out of approached at each site	Number attired before randomization by site	Percent (%) attrited out of number consented at each site	Number randomized by site	Number attrited after randomization by site	Percent (%) attrited after randomization out of those randomized at each site
Site 1	77	61	79.22	8	13.11	53	12	22.64
Site 2	55	43	78.18	8	18.60	35	9	25.71
Site 3	58	31	53.45	3	9.68	28	5	17.86
Site 4	27	27	100.00	2	7.41	25	11	44.00
Site 5	22	17	77.27	3	17.65	14	3	21.43
Site 6	55	35	63.64	2	5.71	33	11	33.33
Site 7	98	84	85.71	14	16.67	70	19	27.14
Site 8	21	11	52.38	0	0.00	11	2	18.18
Site 9	81	56	69.14	5	8.93	51	21	41.18
Site 10	5	4	80.00	0	0.00	4	1	25.00
Site 11	4	4	100.00	1	25.00	3	0	0.00
Site 12	15	11	73.33	3	27.27	8	4	50.00
Site 13	35	26	74.29	6	23.08	20	6	30.00
Site 14	42	41	97.62	11	26.83	30	11	36.67
Overall	**595**	**451**	**75.80%**	**66**	**14.63%**	**385**	**115**	**29.87%**