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Randomized clinical trials

Jeffery A Dusek, Jane Sherwood

This chapter summarizes the goals of research design in randomized clinical trials of prayer and healing and current unresolved issues that arise in designing and executing such studies, including conducting multisite investigations.

Randomized clinical trials (RCTs) are considered the gold standard for determining if a treatment works and is safe and effective. As discussed in the previous chapters in this book, considerable preliminary work using other methods is needed before a properly conducted RCT can be constructed. Premature execution of an RCT risks presenting irrelevant or misleading evidence. Once prepared, conduct of a RCT is a complex task, especially in multisite studies, in order to assure that proper quality control is maintained. **WBJ**

INTRODUCTION

This chapter focuses on the practical issues associated with the design and conduct of double blind randomized controlled trials (RCTs) in evaluating the possible benefits of an intercessory prayer (IP) intervention. The purpose of this chapter is not to completely review the procedures required for conducting a standard RCT of pharmaceutical interventions – others have already done so (Friedman et al 1998). Rather, the goals of this chapter are to highlight the similarities and differences between RCTs of pharmaceutical interventions and RCTs of IP, identify the specific challenges that occur during the design of an IP clinical trial, as well as to review procedures necessary for the implementation of a multicenter RCT of IP. The chapter is organized

chronologically with trial design specifics addressed prior to issues of trial implementation.

CURRENT STATUS OF IP RESEARCH

Research into the possible beneficial effects of IP in medical populations is a relatively new phenomenon in modern American medicine. Recently, several independent investigations have demonstrated beneficial effects of IP (or distant healing) in cardiac coronary care unit (CCU) (Byrd 1988, Harris et al 1999), AIDS (Sicher et al 1998), and infertile (Cha et al 2001) patient populations. However, others report no effect in chronic illness (Joyce & Whelldon 1965), leukemic children (Collipp 1969), psychological well-being (O'Laire 1997), major depression (Greyson 1997), rheumatoid arthritis (Matthews et al 2000), chronic pain (Abbot et al 2001), kidney dialysis (Matthews et al 2001), and cardiac (Krucoff et al 2001), and cardiac CCU patients (Aviles et al 2001). Importantly, two studies display negative effects of IP with increased alcohol abuse in chronic alcoholics (Walker et al 1997), and on the size and number of warts in a sample of healthy volunteers (Harkness et al 2000). Finally, results from an un-blinded study, in which participants were aware whether they were receiving distant healing or not, show improvement on health in a heterogeneous group of chronic illness patients (Wiesendanger et al 2001).

Physicians, statisticians as well as clergy have questioned the variable quality and specific methods used in these published single institution RCTs (Goldstein 2000, Hamm 2000, Hammerschmidt 2000, Hoover & Margolich 2000, Karis & Karis 2000, Pande 2000, Price 2000, Sandweiss 2000, Sloan & Bagiella 2000, Smith & Fisher 2000, Van der Does 2000, Waterhouse 2000). Still others question the ethical limitations or relevance of conducting such clinical trials at all (Cohen et al 2000, Halperin 2001). Although the reports of positive results are intriguing, the failure to make *a priori* decisions identifying a single primary end-point as well as statistical irregularities have severely limited the medical and scientific communities' acceptance of the reported beneficial effects of IP.

As systematically reviewed by three independent groups (Abbot 2000, Astin et al 2000, Roberts & Ahmed 2000), the published data from completed IP trials are equivocal. Nevertheless, all three reviews conclude that the overall positive trend justifies further investigation using established clinical trial methodology. Thus, as traditional medical practitioners and the American public become increasingly interested in the results of studies exploring the efficacy of IP, this additional scrutiny necessitates the careful planning, implementation, and conduct of RCTs evaluating the effects of IP.

It should be stated from the outset that, in our opinion, RCTs of IP are not designed to put God to the test. Nor are they able to determine whether God exists, whether God does or does not respond to IP, whether it is possible to evaluate the presence of God in a controlled clinical trial, or whether God would withhold treatment from any study group. Rather, we believe that well-designed and carefully implemented RCTs of IP can be used to examine the possible effects of a clearly defined IP intervention on a predefined end-point in a restricted patient population.

STUDY DESIGN

Study Personnel

Prior to evaluating the effects of any intervention (including IP) on the outcome after illness, study investigators need to establish a study protocol that includes: a specific objective and hypothesis; a validated and clearly defined primary end-point; a defined and described intervention; strict eligibility criteria; an appropriate informed consent process; a valid randomization process; procedures to preserve masking; valid sample size calculation; procedures to ensure and evaluate the accuracy of administration of study therapy; and a predefined statistical plan employing an intent-to-treat analysis. The study protocol serves as a guide for study personnel and establishes the procedures to be used in the trial.

The success of any RCT is based on having qualified and experienced individuals involved in the study. Requirements for a multicenter

clinical trial include collaboration and cooperation between investigators at participating hospital centers, a data coordinating center (DCC), and the steering committee. Motivated and interactive principal investigators are necessary to supervise patient recruitment at each hospital center; the DCC develops the manual of operations and monitors data collection and management, whereas the steering committee oversees conduct of the entire trial. Ideally, the steering committee should be multidisciplinary and include at a minimum an established principal investigator, clinical trialists, co-investigators experienced with the chosen patient population, and a bio-statistician as well as a representative of the DCC. While assembling a multidisciplinary team may seem unwieldy, the heterogeneous makeup of the steering committee ensures inclusion of unique perspectives and allows diverse viewpoints to aid in the development of the study protocol and oversight of the trial.

Primary End-point

Regardless of the studied intervention (pharmaceutical or IP), selection of a clinically relevant and biologically plausible primary end-point should be required for an RCT. Ideally the choice of the end-point would be supported by the collection of preliminary data, but at very least must be validated prior to the start of the trial. The merits of choosing a single end-point are discussed below. To limit the effects of patient or investigator expectation, it is suggested that the end-point be objectively determined by review of clinical data or medical records and not based on subjective patient or investigator reports. As will be indicted in the blinding section below, all end-point data should be collected by study personnel blinded to the patient's treatment allocation.

The typical pharmaceutical RCT purports to examine the efficacy of a treatment (acting through specific mechanisms) on a 'biologically relevant' outcome in a particular patient population. One major difference between pharmaceutical and IP trials is that in the latter there is no empirical evidence identifying a precise mechanism, biologically plausible outcome, or even the

appropriate patient population. Thus, it is very difficult (some would say impossible) to select the proper outcome to measure without a known mechanism or considerable preliminary data to indicate what the specific effect may be. This lack of specificity has been especially problematic in IP research and has probably added to the inconsistency in published results.

Nevertheless, although selection of a biologically plausible end-point is currently impossible in an IP trial, it is possible to investigate the effect of IP on an outcome that is widely accepted to be clinically important in a specific study population.

Statistical Analysis

Design of any RCT requires development of a statistical analysis plan, including statement of hypothesis, projection of probable effect size, sample size calculation, choice of primary end-point, and statistical tests. Since there is limited information on mechanisms underlying the possible effects of IP, data from smaller pilot studies can assist investigators in hypothesis generation and provide expected effect size for the larger RCT. Additionally, data from either pilot studies or the published literature may be used as the basis for a realistic sample size calculation. Importantly, studies that do not enroll enough patients to detect differences between treatment arms are statistically 'underpowered'. Underpowered trials risk incorrectly accepting the null hypothesis (that there is no beneficial effect of an intervention) when a difference does exist (type II error). In addition to limiting the pursuit of an effective intervention, results from underpowered studies may hamper progress in promising areas of research.

Unless there is compelling evidence necessitating the inclusion of multiple end-points, use of a single, primary end-point is suggested for two reasons. First, the comparison of multiple end-points without correction to the overall *P* value, which has been used in previous IP trials, increases the risk of rejecting the null hypothesis (that there is no benefit of an intervention) when a difference does not exist (type I error). Second,

appropriate correction for multiple comparisons reduces the likelihood that significance would be achieved for a given end-point. For example, if an investigator were to compare outcome on 20 different end-points, use of the Bonferonni technique (O'Brien 1984) would reduce the standard *P* value of 0.05 to 0.0025 (*P* value/number of outcomes or 0.05/20). Finally, well-designed clinical trials should also include a predefined analysis plan with a contingency for patients lost to follow-up, patient withdrawal as well as those who do not undergo the studied procedure. Use of intent-to-treat analysis is standard in well-designed pharmaceutical trials and must be employed in IP trials.

IP as a Clinical Intervention

There are numerous challenges to the use of IP as a clinical intervention in RCTs. First, although the majority of IP studies have not included a clear description of the IP intervention, it is vital to clearly define the intervention that is being tested. Some report the number of minutes intercessors provide the intervention (e.g. 30 minutes a week for 6 weeks), whereas others provide the number of days intercessors prayed for a given patient (e.g. 30 days). Other factors to be clarified are the onset and offset of IP. Is it necessary that the IP be initiated prior to the start of a medical procedure or can IP be initiated after the procedure has started? Does the length of IP vary according to when the patient may be discharged from the hospital or is a standard 'dose' provided to all patients regardless of their particular pattern of recovery? Is there a critical mass of necessary intercessors or is one intercessor enough? Other issues include the length (10 minutes *vs.* 1 hour) and frequency of IP administration (once a day *vs.* once a week), the merits of providing follow-up dosing and contingencies for providing IP when a procedure has been delayed by several hours or days. The lack of a clearly defined intervention has limited the generalizability of previous results because of non-uniformity of the IP intervention.

Second, the ideal amount and duration ('dose') of IP that should be provided is unknown

because of the lack of biologic basis for the effect of IP. In pharmaceutical RCTs, patients are provided with a specific dose of an intervention for a specified length of time. Because the quality of the pharmaceutical is reliable (for the most part), these trials can examine whether larger doses are more efficacious or establish a dose-response curve. Is a dose of IP an accurate analogy or a reasonable assumption? It is clear that in each RCT the number of prayers (five intercessors) can provide IP for a given length of time (1 minute every day for 6 weeks). However, does the difficult (some would say impossible) task of quantifying the quality of the IP preclude the provision of IP as a dose? Perhaps not, for if the quality of the IP providers can be established by selecting experienced, committed, professional intercessors, the notion of dose may not be inconceivable.

Third, although few will disagree that RCTs of IP should use clearly defined intervention that matches the primary end-point, doing so can be challenging. As part of defining the studied IP, does the investigator allow intercessors to employ their usual methods of prayer or does she or he constrain intercessors by developing a specific prayer intervention for the study? Either choice is valid, but there are limitations to both choices. The limitation of allowing intercessors to use their usual methods of prayer is that the intervention may not be relevant to the primary end-point. For example, if the primary end-point is the patient's perception of pain after a medical procedure, prayers for 'acceptance of God's will' do not appear related to the end-point. For a typical clinical trial, patient mortality is classified as a negative event. However if the focus of IP was for 'Thy will be done,' death may be deemed 'Thy will' by some individuals, but unlikely to be defined as a success by the medical investigators.

Fourth, IP provided in a clinical trial may be different from IP usually provided by the intercessors, limiting generalizability of the results. Are there limitations to 'sterilizing' or reducing prayer to a single component, as opposed to the richness of the usual prayers employed by intercessors? Rather than limiting the intercessors to a

study-directed prayer, one solution may be for the investigators to simply add a specific intention to the usual methods of the intercessors. In so doing, the duration and content of the intervention can be clearly defined without changing the established methods of the intercessors. Even with this consideration, the question remains that there might be reduced effectiveness of IP when strangers (rather than family and friends) pray for a patient.

Fifth, since it is impossible to attempt to limit prayer provided by family, friends, and others, a study of IP could only evaluate the effects of *additional* IP, not the effects of prayer in general. Because examining the effects of all prayer is not possible, investigators must distinguish between the study intervention or additional intercessory prayer offered by intercessors with non-study prayer, which is offered by the patient, family, friends, or others. Of course it would be unthinkable, not to mention impossible, to attempt to limit these non-study prayers. Thus, although the exact extent of the non-study prayer may never be obtained, it is important to ascertain from the patient their knowledge of such non-study IP to ensure that there are no differences in the amount of non-study being provided to the groups.

Finally, there must be established methods for the investigators to conduct quality assurance checks of the IP intervention. It would be an inconceivable to attempt to quantify the quality of an individual intercessor's prayers, but ensuring that the intervention was provided as directed in the study protocol is possible. As part of the quality assurance process as well as to retain blinding of hospital centers, in a multicenter trial the DCC may serve to relay information between hospital centers and the IP groups. To ensure adequate administration of the IP intervention, a clear method of contact (fax, telephone, and e-mail) with backup procedures should be in place before the start of the trial. Regardless of the specifics chosen, an established mechanism to document the IP intervention (e.g. use of prayer logs) must be included in IP trials to clearly document the extent of the intervention.

Data and Safety Monitoring

Because previous studies have not reported serious negative effects associated with IP, some might consider participation in a study of IP to be risk-free. However, by convening an independent data and safety monitoring board (DSMB) to review the clinical trial, the investigator establishes safeguards and protection for patients as well as a mechanism for independent review of the on-going trial. Typically, a DSMB is provided with results from interim analyses and makes recommendations to study investigators. For example, if study intervention were found to result in a higher event rate, a DSMB would probably recommend early termination of the study. Likewise if an intervention proved significantly more efficacious, then a DSMB may recommend early termination so that all patients would have access to the successful intervention. The advantage for the investigators is these recommendations are offered while the study is active and the investigators are still blinded. DSMB recommendations may provide valuable insight and even allow for important adjustments to the study of an IP intervention.

STUDY IMPLEMENTATION

Patient Recruitment

For any RCT it is vitally important to follow the guidelines of each participating institution's institutional review board in the identification and recruitment of patients into the study. Typically, hospitals require that each patient's primary care physician or the nurse caring for the patient provide permission before study personnel are allowed to approach a patient. Especially with the enrollment of aged patients, this process is thought to ensure that the patient is physically and mentally stable and able to provide informed consent. Additionally, the nurse caring for the patient can provide the researcher with pertinent information about the person's health concerns and support system.

When approaching eligible patients in hospital, it is necessary for the researcher to clearly explain the study as well as the requirements

expected of each participant. Although many eligible patients will be interested in participating in an IP trial, recruiting patients for any study is challenging. Reasons for not participating in an IP trial may include: no interest in participating in any research study; no interest in prayer research, anxiety about being assigned to a non-prayer group; anxious, tired, stressed out by their illness and hospitalization; or would rather spend time with family or friends. As is the case with any trial, it is important to record the number of patients who accept or refuse to participate in the study – some studies even collect demographic information about eligible individuals who refuse to participate in a patient registry. In order to generalize the study results from the study sample to the larger population, specific information of patients enrolled in the trial is necessary.

Unlike a pharmaceutical RCT, many patients may not expect to be approached for participation in a clinical trial of IP. As such, it is necessary for study personnel to separate their personal religious beliefs and convictions from their role in the trial. By checking their personal religious and spiritual beliefs at the door study personnel limit the unconscious and conscious bias of their beliefs on the design and implementation of the study as well as on the recruitment of subjects and collection of study data.

Informed Consent

Eligible patients obtain information about a clinical trial from the study investigator as well as from a written consent form. The process of obtaining informed consent for an individual to participate in any clinical trial is extremely important. Along with informing patients about the study requirements, it is necessary to notify patients of the possible benefits and risks of the intervention from participating in the trial. Individuals must be fully informed that while their medical records may be reviewed for research purposes (depending on the trial), their confidentiality will be respected. Recently, two studies of IP were conducted without informing the patients that they were participants in the

study (Cha et al 2001, Harris et al 1999). Although each investigator's IRB had reviewed the protocol and approved the study, neither written nor verbal informed consent was obtained from any of the research subjects. The lack of any informed consent raised ethical concerns in the medical community (Goldstein 2000).

Theoretically, it is possible that there is a scientific advantage to not obtaining informed consent (Cha et al 2001, Harris et al 1999). These investigators contend that by not obtaining informed consent, or even letting a subject know they are participants in a clinical trial, it is likely that all eligible patients will be involved in the study and thus limit study sample bias. The notion is that limiting study sample bias can lead to increased generalizability of the results. In addition, if subjects are not aware of their involvement in a research study of IP, they may experience less anxiety from study participation. Finally, because family and friends are unaware of the IP study, they may be less likely to pray for the subject and consequently limit the amount of non-study prayer.

Nevertheless, there are many ethical limitations for failing to obtain informed consent. First, although no studies have reported adverse events associated with IP, there still may be risks associated with the intervention. Second, it is a common occurrence in clinical trials for study personnel to review medical records for adverse events or when determining the incidence of the primary end-point (such as complications after a medical procedure). Clinical review of the patient's medical record does not compromise confidentiality, whereas unauthorized reviews for research purposes may. Third, in accordance with ever-increasing scientific standards, obtaining written informed consent may be necessary for IRB approval, for obtaining Federal funding and for publication in most medical journals (Belmont Report 1979). Fourth, by providing informed consent and actively participating in the study process, the patient has the satisfaction of knowing she or he has made a contribution to scientific knowledge about the effects of IP on

health outcomes. Finally, the process of obtaining informed consent ensures that each patient's autonomy is fully protected throughout the process of his or her study involvement.

Randomization/Masking

Issues of randomization and masking are critical to all RCTs. Correct and appropriate use of randomization techniques removes potential bias in allocation of subjects to study groups. Specifically, use of a random number generator when developing a randomization table makes it virtually impossible for any patient, investigator, or statistician accurately to predict to which group a given subject has been randomized. Use of unsophisticated randomization techniques may seriously limit the scientific acceptance of study results and potentially unmask study personnel as to the assignment of specific patients.

The double blind study is the gold standard of clinical trials (Friedman et al 1998). In a double blind clinical trial examining efficacy of pharmaceutical medication both the patient and the investigator following the patient's outcome are blinded to the patient's group assignment (Friedman et al 1998). Thus even though the investigator (or hospital pharmacy) provides the active intervention or placebo pill, the patient's treatment is unknown to patient and investigator. In addition, individuals collecting data from medical records and statisticians conducting the analyses remain blinded to a patient's treatment condition.

Although not uniform, it is common in many clinical trials of IP for the patient, study investigator, data collector, and statistician to be blinded to treatment, but for the intercessors providing IP to be informed of the names of patients randomized to receiving IP. In terms of definition, this type of trial still qualifies as a double blind RCT. However, because the intercessors are unblinded to patients' group assignment, it is vital for intercessors to have no contact with the hospital center personnel who are blinded to assignment. To retain masking, in a multicenter trial the DCC may serve as an intermediary between IP groups and hospital centers.

Another difference between a study of pharmaceuticals and a study of IP is that an IP intervention may be provided without the patient's awareness. As opposed to physically taking an active or placebo pill, participants in IP studies are provided with an unseen intervention. Although patient compliance in the trial is established, the disbursement of the intervention by the prayer groups must be monitored. Another important difference is that in the IP trial non-study intervention may be provided (by friends, family, church members) without the investigators' or subjects' awareness. Thus, as it would be impossible to test the effects of 'all' aspirin that a patient may take as part of their participation in a pharmaceutical trial, it is virtually impossible to test the efficacy of a consistent 'dose' of all IP (that which is provided as part of the study and that which is not) in the IP RCT. Rather, investigators are testing the efficacy of a dose of *additional* IP from study intercessors. Assessing patient awareness of non-study prayer during the trial (e.g. before and after the procedure) can provide the patients' perception of awareness of presence or absence of non-study IP.

CONCLUSIONS

As described in this chapter, there are numerous challenges to the design and conduct of a study of IP, as well as limitations to study conclusions. First, since there is no accepted scientific basis for the effect of IP, it is difficult to select a biologically plausible end-point for use in a clinical trial. Second, the timing, amount, and duration that IP should be provided are unknown because of the lack of biologic basis for the effect of IP. Third, since it is impossible to attempt to limit prayer provided by family, friends, and others, a study of IP can only evaluate the effects of additional IP, not the effects of prayer in general. Similarly, the intervention can only be described as the prayer provided by the intercessors, not as an effect or result of communicating with God. Fourth, the need to precisely document how and when the study IP is administered may result in changes from the intercessors' usual practice. IP provided in a clinical trial may be different from

IP usually provided by the intercessors, limiting generalizability of the results. Finally, IP trials are not designed to determine whether God exists, whether God does or does not respond to IP, whether it is possible to evaluate the presence of God in a controlled clinical trial, whether God would withhold treatment from any study group, or to put God to the test. IP trials focus only on the effects of additional IP on outcomes

after a medical procedure or illness, not on the effects of any type of prayer. Based on these challenges to study design and implementation, it is not surprising that previous studies of IP are controversial. Additional well-designed and appropriately implemented clinical trials of IP are needed and may serve to limit the current controversy.

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