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How to improve accrual to clinical trials of symptom control 2: design issues

Andrew J. Vickers^{1,2}

¹ Department of Medicine, Memorial Sloan-Kettering Cancer Center

² Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center

Abstract

The major reason why clinical trials in integrative oncology fail is that inadequate numbers of patients are accrued. One important cause of inadequate accrual is eligibility criteria that are overly-restrictive. Investigators should critically examine every single inclusion or exclusion criterion to determine whether possible benefits to the study clearly outweigh harms in terms of reduced accrual. Accrual will also be harmed if the burdens for participation – traveling to appointments, completing questionnaires – are excessive compared to the benefits for patients. In a traditional randomized trial, half of participants do not receive treatment, reducing the benefits expected by any patient. This can be offset by guaranteeing free treatment to patients in the control group after they have completed the study. Patient burden can be reduced by limiting the number of hospital visits and avoiding excessive numbers of questionnaires.

Introduction

This is the second paper in a series of two examining the problem of inadequate accrual to clinical trials. In the first paper(1), I suggested that careful data gathering before a trial starts can help identify potential accrual problems. For example, researchers wishing to conduct a trial to prevent a complication of colectomy could query institutional databases to determine the number of patients undergoing this procedure each year. Analysis of case notes can be used to determine the prevalence of a symptom that is the focus of a trial. Alternatively, researchers can conduct “dry runs” by following rounds to see how many eligible patients they can identify or by asking doctors to refer patients for off-study treatment. I also argued that recruitment cannot merely be passive – sitting and waiting for the patients to come – it needs to be proactive, including strategies such as advertising, writing to patients at home, analyzing care pathways to identify the best time to approach patients and visiting clinics to scan appointment lists.

In this paper, I focus on recruitment issues as they pertain to trial design. This involves thinking about eligibility criteria - on the grounds that these criteria determine exactly who is able to be accrued on trial – but goes on to include a more general discussion of how studies can be designed such that the expected benefits of participation outweigh the inconvenience of taking part.

This paper is a personal perspective on recruitment issues for integrative oncology trials. It is anecdotal in nature, being based on my experience as an investigator on trials in both

complementary and conventional medicine, and both within and outside of the cancer setting. Most of the trials I have worked on have been conducted within single institutions, rather than being multi-center, and so the paper is most applicable to the single center trial. My focus will be on trials for symptom relief: trials of anti-cancer agents, whether for prevention or treatment, present an additional set of challenges that will not be covered in detail here.

Setting eligibility criteria

One of the first integrative oncology trials that I was involved in was a randomized trial of acupuncture for hot flashes in women with breast cancer. When the study was presented to the IRB, they recommended that we restrict the patient group to patients premenopausal at diagnosis. It was argued that this group constitutes a “pure” sample as they would not have had experience of hot flashes, and their treatment, before cancer diagnosis. It was also argued that including both pre- and post-menopausal patients would lead to a “heterogeneous” study sample. We pointed out including patients irrespective of menopausal status was absolutely standard practice in hot flash trials (some of which had been published in the *New England Journal of Medicine*), indeed, we were unable to find any trials that including only premenopausal or only postmenopausal women. Perhaps more importantly, there was no reason to believe that the effects of acupuncture, if any, would differ depending on menopausal status. The IRB were unmoved. What ending up happening was that we opened the trial, failed to accrue, closed the trial, rewrote the protocol for both pre- and postmenopausal patients, sent the revised protocol through the six separate IRB committees, were approved and started the second trial over year later. We had no accrual problems and recently completed the trial. Nonetheless, our research was delayed unnecessarily due to insistence on overly restrictive eligibility criteria.

A few principles: first, every single eligibility criteria you have reduces the number of patients you can accrue. For example, one of our trials examined whether music therapy could reduce mood disorder in patients undergoing high dose therapy with autologous stem cell rescue (“bone marrow transplant”). Our primary endpoint was anxiety, but we thought it would be worth measuring pain too, as reducing anxiety scores sometimes helps pain. One investigator suggested that reduced pain might lead to reduced requirements for opiates and, as opiate use would be automatically recorded in the case notes, we added this as an endpoint. Then a different investigator pointed out that if we wanted to look at opiates, it would be silly to include patients who were using opiates at baseline so we added this as an exclusion criterion. Given that the purpose of our trial was to examine symptoms caused by treatment, our guess was that few patients would be symptomatic at baseline and therefore that excluding opioid users would not have an important impact on accrual. When we started the trial, however, four of the first six patients were excluded for opiate use. So our desire to obtain supplementary information on a quite secondary endpoint reduced our eligible population by two-thirds.

Accordingly, you need to examine each and every eligibility criterion extremely carefully to determine whether the benefits for the trial in clinical or scientific terms outweigh the harms in terms of reduced accrual. We work very hard to reduce eligibility criteria to the bare minimum: as a general rule, we drop any eligibility criterion unless it is crystal clear that it will dramatically improve the trial. Typical eligibility criteria we use include:

1. Identification of the patient group: such as breast cancer patients, or patients with any form of advanced cancer.
2. Symptom severity: it is difficult to have an important effect on symptoms that are very mild to begin with, so we normally specify that patients must have, for example, at least three hot flashes per day or a pain score of 4 out of 10.

3. Contraindications: exclude any patients who might be harmed by the experimental intervention.
4. Patients unlikely to respond: as an example, in a trial on acupuncture for shortness of breath, we excluded patients whose symptoms were related to obesity or deconditioning as these would not respond to acupuncture in the course of a one-week study.
5. Contamination: we normally exclude patients who have recently received the experimental treatment or whose symptoms might be expected to change for other reasons, such as recent change of medication, scheduled surgery or chemotherapy. This does not normally have an important effect on accrual: if patients have recently changed medication, for example, we just wait a few weeks, call them back to see if they remain symptomatic despite stable medication and, if so, enter them on study.

We tend to avoid any criteria aimed at making the patient group “homogenous” unless we have good data that either only a few patients will be excluded or that response to treatment really will be different. An example of the former was the exclusion of a few rare cancer types in our bone marrow transplant trial: we knew from analysis of institutional data that only one or two patients with these cancers were treated each year. Examples of the latter are extremely rare: unlike the use of targeted agents in oncology, it is difficult to find examples of symptoms or conditions that respond differently to an integrative intervention depending on identifiable patient characteristics.

The issue of eligibility criteria also illustrates the principle of “get data before you get data”, which was described in the first paper in this series on accrual(1). In the case of our bone marrow transplant trial, there was no reason to take on trust the investigator's claim that “hardly any” patients took opiates, we could have pulled some case notes to check.

Patient consent

Getting as many patients as possible to consent to take part in a trial is a design issue: in our experience, if the potential benefits of participation don't outweigh the hassle and inconvenience of being a trial subject, patients simply won't take part. This is probably a greater issue in oncology than in other areas of medical research as cancer patients face exceptional burdens on their time and energy. To ensure adequate accrual, it is essential to maximize benefits to patients and minimize hassle and inconvenience.

With respect to maximizing benefits for patients, cancer patients have been through a lot, and it is unlikely that they will go through more in return for, well, nothing. Yet nothing is exactly what 50% of patients do indeed get in the classic randomized trial comparing a treatment to control. Accordingly, we always guarantee patients that, if they are randomized to control, they will receive a course of free treatment at the end of the study. This leads to a design dilemma: from a methodological point-of-view, the end of the study should be as late as possible, as the longer a trial continues, the more information we get, particularly with respect to long-term outcomes; from the patient's point of view, conversely, the end of the study is as soon as possible so that, if they are randomized to control, they don't have to wait too long for true treatment.

Our compromise is to set the primary endpoint of the study shortly after treatment but to measure long-term outcome on a non-randomized basis. As an example, in our trial of acupuncture for hot flashes, treatment lasted about four weeks and so the principal endpoint was at six weeks. After patients in the placebo group completed their hot flash diaries at the six week time point, they were told of their allocation and offered a course of true acupuncture treatment. All patients that received true acupuncture, either because they were allocated to acupuncture or because they opted for acupuncture after original assignment to placebo,

completed diaries at six months after their first true acupuncture treatment. This allowed us to offer true acupuncture treatment as soon as possible but to obtain data on the long-term effects of acupuncture, albeit on a non-randomized basis. Figure 1 illustrates our study design.

Our design has important implications for how trials are initially presented to patients. We try to avoid saying: “This is a trial comparing acupuncture to placebo: half the patients get acupuncture and half get placebo”. Instead we first emphasize that all patients will get true acupuncture, but that some will get it immediately and some will have to wait.

With respect to minimizing hassle and inconvenience, the two things that patients don't like having to do as part of the typical integrative oncology trial is visit the hospital and fill in questionnaires. So try to minimize both. Some ideas on reducing reporting burden were outlined in a previous paper(2) in which I pointed out that most trials involve far too many questionnaires and that in most cases, “more is less”. Reducing trips to the hospital is, unfortunately, a compromise between therapeutic effectiveness and patient acceptability. For example, my guess is that patients would probably do better receiving acupuncture treatment three times a week to manage cancer pain, but few patients with the sort of late-stage cancer associated with pain would be able to travel to the hospital for acupuncture treatment three times a week. So it is likely that some less intense form of treatment will have to be offered.

Conclusions

Although integrative oncology trials fail for all sorts of reasons, inadequate accrual remains perhaps the most important cause of failure. In this series of two papers, I have argued that the reasons for inadequate accrual can often be predicted and addressed by basing trial design on carefully collected data and by applying a few simple principles for recruitment strategies, eligibility criteria and patient-friendly trial designs. It is only by completing trials with adequate numbers of patients that we will be able to fulfill the promise of clinical trials to give a sound basis for clinical decision-making.

References

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Figure 1. Structure of a trial designed to maximize accrual whilst also providing data on long-term outcome.