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How to improve accrual to clinical trials of symptom control 1: recruitment strategies

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Abstract

Inadequate patient accrual remains the primary problem for clinical trials of integrative therapies for symptom control. Many difficulties can be predicted and avoided if a careful, evidence-based approach to trial design is taken: trialists should attempt to get as much data as possible on the study population by querying institutional databases, examining case notes, following in-patient rounds and conducting “dry runs” by asking doctors for referrals. Trials require aggressive recruitment strategies, including advertising, writing to patients at home, scanning clinic lists and identifying critical points during clinical care at which patients can be approached. The information given to patients during any initial contact should be as simple and general as possible: presenting too much information too soon can be overwhelming and off-putting.

Introduction

Trials fail for all sorts of reasons. For example, David Sackett, a key figure in the development of evidence-based medicine, describes when, as a young doctor, he had no option but to enter a very sick patient on a randomized trial of antibiotic therapy, but felt obliged to subvert the trial by administering proscribed off-study treatment(1). Sackett's view is that the trial was weakened by a failure to incorporate the “uncertainty principle”. This states that clinicians should not enter patients onto a trial if they are reasonably certain that one of the trial treatments would be inappropriate for the patient; hence only patients about whom there is uncertainty should be included.

In cancer research, however, there is almost universal agreement that the most important reason why trials fail is poor accrual. Indeed, there is a burgeoning field of what might best be described as “meta-research” on how to improve accrual to cancer trials. In perhaps the first study of its type, Charles Moertel, a famous cancer trialist, conducted a survey of oncologists and identified a number of simple practical considerations, such as travel time and the expense of non-essential trial-related tests, that had an important impact on accrual rates(2). Subsequent researchers have analyzed cohorts of patients to identify specific reasons why individual patients were not placed on trial(3,4) and have even conducted randomized trials comparing different accrual methods(5,6).

This is the first part of two didactic papers in which I will give a personal perspective on recruitment issues for integrative oncology trials. The papers are 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.

There are three key stages in accrual: identifying patients, checking that patients are eligible and consenting patients. Eligibility is clearly a design issue, and consent ends up being about design as well: whether a patient consents to go on study often depends on whether the study is designed in such a way that the expected benefits of participation outweigh the inconvenience of taking part. As such, both eligibility criteria and consent will be dealt with in the second paper, which focuses on design issues. In this paper I will focus on identifying patients, in other words, the recruitment strategies used for the trial. To start, however, one general rule: get data.

Get data before you start getting data

We were approached by a doctor who asked if anything could be done to treat hepatobiliary cancer patients with refractory pruritus. We thought of acupuncture and, given a lack of prior research on this subject, suggested a clinical trial. The doctor thought that this was an excellent idea and we met to discuss design issues. Our first question concerned patient numbers: a trial would not be feasible if only a few patients presented with pruritus each year. As I recall it, the doctor didn't actually answer the question, he made a dismissive and exasperated noise to the effect that we were silly to ask, and that he was swamped with cases. So we spent the 12–18 months designing the study, pushing the protocol through the IRB process (it was seen by six different committees) and applying for funding. The rest of the story is pretty short: we opened the trial, nothing happened, we waited around, still nothing happened, we closed the trial.

In our *post mortem* of the study we found out that pruritus is rare until patients are end-stage. Our institution focuses on active treatment and patients nearing the end of life are generally referred on to hospice care. As a result, we see few pruritus patients. When we spoke to the doctor on this point, he said that, yes, this was correct, but that he had two or three patients in a row and it seemed like “everyone was getting it”.

I don't blame the referring doctor in this case, I blame myself. Everything we found out after the study had been closed could have been found out before we started, had we focused on systematically obtaining data on trial feasibility, rather than forging ahead to trial design. Simple expedients such as pulling case notes for all hepatobiliary patients seen over the course of six months would have demonstrated that few reported significant pruritus, and that our trial was therefore unlikely to accrue.

Listed below are a few ideas on getting data that can be useful in trial planning stages.

1. **Analyze databases.** Institutional databases can be an excellent source of data to aid assessments of trial feasibility. As a typical example, we are currently putting together a study of complications after surgery for colorectal cancer. It was a relatively straightforward matter to query the Department of Surgery database to determine how many colorectal surgeries are conducted each year.
2. **Scan case notes.** The prevalence of specific symptoms, such as pain, nausea or hot flashes, is not generally recorded by institutional databases. A simple alternative is to use the institutional database to identify a group of eligible patients, for example, those with a particular type of cancer or those receiving a particular type of treatment. You then obtain the case notes for these patients and record the proportion of cases

in which the study symptom is recorded. There are privacy issues involved in reading case notes so it is normally necessary to obtain an IRB “waiver” first.

3. **Follow rounds.** If we expect to accrue in-patients to your study, tag along to rounds and see how often you identify patients that might be eligible. You can see this as a sort of “dry run”: following rounds is probably what you would be doing when the trial started, so give it a try and see how well it works.
4. **Ask for referrals.** This is another “dry run” tactic: ask doctors to refer to your clinic the sort of patients you hope to accrue to your trial. One idea to speed things along (although there are sometimes institutional rules against it) is to offer free treatment for these patients. A few years back we met with a doctor who claimed that he commonly saw patients with a certain problem, that he was unable to treat them effectively, and that they were “desperate” for anything that could help: how about setting up a trial? We said that this was an interesting idea but suggested that he refer some patients so that we could get some idea of how best to treat them. Six months later we had exactly zero referrals and the idea for the trial was dropped.
5. **Ignore any guesses about participation rates (alternatively, divide by ten.)** In the initial planning stages of any trial, you will inevitably hear optimistic projections of accrual rates. It is useless to express any skepticism about these estimates or even mention the general truism that researchers normally over-estimate accrual, because all you'll hear back is a list of reasons why the general rules don't apply in this particular case (believe me, I've been there).

Identifying patients: recruitment strategies

Trialists use one or more of a variety of strategies to identify potentially eligible patients. We'll start with the worst.

Strategy 1. Wait and see

Many trialists assume that all you have to do to get a trial done is to get the protocol approved, email it to a group of doctors and then sit back to watch the referrals flood in. It is not hard to see why this doesn't work.

1. Academic doctors receive enormous amounts of email each day and need to sort through it as quickly as possible. Carefully reading through a protocol takes much more time than most have available.
2. Often a very large number of trials are open at an institution and it is almost impossible for doctors to remember them all, even assuming that they opened the email and read the protocol.
3. Most doctors have extremely busy clinics and have very little time. Introducing a new protocol to a patient is particularly time consuming because most patients have numerous questions and concerns about research.
4. No doctor likes to appear incompetent, but this is exactly what can happen when they are asked to introduce a protocol the details of which they cannot reasonably be expected to understand in full. This is a particular problem for integrative oncology protocols where patients might have specific questions about therapies, such as acupuncture, of which many doctors have limited knowledge.

Doctors do have to be supportive of your research, but they will generally be too busy to drive the recruitment process. Better approaches to accrual are based on the principle that the less work a doctor is asked to do, the better.

Strategy 2. Advertising

I once saw an advert on the New York subway that stated “Depressed? Earn \$300 to take part in a study with Columbia University clinicians”. Advertising need not necessarily be so direct: one good tactic is to turn the study into a news story. Your public affairs office should be able to advise you on this, but it can involve issuing a press release or contacting a small number of sympathetic journalists. What you end up with is a story in a newspaper or magazine (“Harvard researchers to study meditation for arthritis”) that describes the study and why it is novel. At the end, of course, you slip in something like (“anyone interested in taking part in the study can call the study hotline on 1 800 ...”). Advertising for cancer studies is somewhat rare, mainly because cancer-related problems are markedly less prevalent than the chronic disease trials typically advertised (e.g. depression or arthritis). Advertising can also have unanticipated effects: we got a cancer magazine to run a story about a trial of ours and were besieged by calls, which would have been a good thing if not for the fact that the magazine had a national distribution and there wasn't much way we could help a patient, in say, South Dakota. Nonetheless, a form of local advertising can be very useful: put up flyers around the hospital and leave some in patient waiting rooms. Keep the flyers simple and non-technical and don't include too much information (see the text box)

Strategy 3. Retrospective accrual

The best experience I have had with accrual was a trial of acupuncture for chronic headache in which a part-time research assistant and a nurse working just one day a week randomized 400 patients in less than a year. The key was “retrospective” accrual. We searched the practice databases of primary care physicians, looking for patients who had either been diagnosed with a chronic headache disorder or (what actually worked better) who had been prescribed medication use to treat migraine. We then wrote to patients at home telling them about the trial with a telephone number to call for more information (Rob McCarney, who was in charge of recruitment, has described our experience in a paper⁽⁷⁾).

The obvious advantage to retrospective accrual is that you are directly reaching those patients most likely to be eligible for the trial: you don't have to wait for referrals or need anyone else to keep your trial in mind. Retrospective accrual appears particularly appropriate for survivorship research, where chronic symptoms are a key concern. A few hints and tips:

1. Expect to send out a very large number of letters. In the headache trial, we sent over 4,000 letters and in fact this was a relatively low ratio of letters to accruals. In many situations you are not contacting patients that you know have symptoms but those at risk. For example, we have sent letters to patients who have had operations for head and neck cancer to ask whether they have chronic shoulder or neck pain; in another study, we contacted patients who had completed adjuvant chemotherapy at least six months previously with information about a trial for fatigue that persisted after the cessation of chemotherapy. As only a small proportion of patients will experience severe post-surgery pain or chronic post-chemotherapy fatigue, and only a proportion of those will agree to take part in the trial, we expected only a 2 or 3% response rate, that is, 30–50 letters for every patient accrued.
2. Have doctors sign the letters. This can be time-consuming, although there are ways to cut down the workload, such as using a signature stamp or scanning the signature to a jpg file and inserting this on the word processed letter. Nonetheless, a doctor's signature is essential for two reasons. First, there is the ethical point that patients should always be approached by someone they know (imagine you were a cancer patient and you received a letter from a stranger starting “earlier this year you received chemotherapy for colon cancer...”). Second, patients are much more comfortable taking part in studies if they feel that this is supported by their doctor.

3. Keep things simple. I was once involved in a rather complicated trial and our letter to patients included a lengthy and detailed description of exactly what we would be doing and why. This letter clearly failed the “sniff test”: precisely zero patients responded to our first mailing. For our second mailing, our letter was only a few lines long and said, roughly, “Dear Mr Doe, we are conducting a clinical trial of pain that I thought you might be interested in. Participants in the trial are guaranteed to get all the same treatments as those normally treated at the hospital. However, they may also get a new treatment that might help lower their pain levels even more. For more information, call the study nurse, Jane Brown on.... Signed, Dr Smith”. The nurse then had an in-depth conversation with the patient explaining all the ins and outs of the trial. This much simplified letter was much more successful for patient accrual.
4. Pre-screen your patient lists. Don't just dump a list of names and addresses of potentially eligible patients into a merge file and send off letters. For example, it is not appropriate to send letters to patients who have had recurrences, and it can be upsetting for families when letters are sent to patients who have died.

Strategy 4. Critical path evaluation

Retrospective accrual is only appropriate for trials on chronic symptoms. It cannot be used for trials on emergent or transient symptoms. As an example, let's consider a treatment for pain immediately following surgery. The difficulty of conducting such a trial is redoubled by the extremely narrow window to get patients on study: you might have only a week or two between a surgery being arranged and a patient arriving in the pre-operative suite, and if a patient isn't consented in this time, you have missed your chance.

The solution is to analyze the steps that a patient goes through in order to identify the best point at which to approach them with information about the trial. For example, in one study we noted that all patients scheduled for surgery came to the hospital for a special pre-operative visit with a nurse. At this meeting the nurse explained more about the surgery, did a number of tests and obtained patient consent to surgery. This was obviously the perfect opportunity to reach patients, especially as almost all of these pre-operative visits were with a single nurse. We invited the nurse to become a member of the study team and she incorporated information about the trial into the pre-operative meeting of every single patient. This approach was so successful that we occasionally had to ask the nurse to *stop* accruing for a week or two on the grounds that we were inundated with patients and couldn't keep up.

Another trial was a little bit more difficult. In this case, patients met with surgeons and then, typically, made a decision to go ahead with surgery by calling from home after a few days' thought. The next time they returned to the hospital was literally a few hours before their operation. What we set up is to have a research nurse check the surgery schedule each week to find patients that had been recently added. She then telephones patients at home saying something like, “Mr Doe, I am Jane Brown, a nurse at Memorial Sloan-Kettering Cancer Center. This is about the surgery scheduled with Dr Smith in two weeks time. Dr Smith asked me to call you to tell you about a study she thought you might be interested in ...” Interested patients are then sent further information about the trial, including a consent form that they bring when they arrived on the day of surgery.

Strategy 5. Clinic visits

Our research assistants spend most of their time visiting various clinics. Often, they are able to look at clinic lists online beforehand and then scan case notes to identify whether any patients would be eligible for one of our trials. Alternatively, they go directly to the clinic, approach a clinic nurse, ask for the list of patient appointments and then go through the list with the nurse. Whichever way that patients are identified, the research assistants go to clinic, wait to catch

the doctor and check the suitability of any patients they have identified (it is normally only one or two). If they get the okay from the doctor, they approach the patient saying, “Mr Doe, hello, I am Jane Brown. Dr Smith asked me to tell you about a trial he is working on. I am the research assistant for the trial ...”.

Conclusions

Inadequate accrual remains the primary reason why all too many integrative oncology trials fail. In this paper, I have described how careful gathering of data before a trial starts can help identify potential accrual problems. I have also outlined a number of simple recruitment strategies. In the second paper of this series, I will examine how accrual to clinical trials of integrative therapies for symptom control is affected by both trial eligibility criteria and the degree to which the trial design meets patient needs in terms of minimizing inconvenience and maximizing expected benefit.

Flyer text A

Hot Flashes?

Patients with breast cancer who experience hot flashes from treatment may be eligible to participate in a study.

MSKCC is conducting a trial to determine whether acupuncture works against hot flashes. It doesn't hurt, and eligible patients will receive acupuncture at no cost.

To learn if you are eligible or for more information, please call Jane Doe, Research Study Assistant, at (212) 639-XXX or speak with your physician or nurse.

Flyer text B

Randomized, placebo-controlled trial of acupuncture for Tamoxifen-induced climacteric symptoms

Eligibility criteria:

Age over 18

Pathological confirmation of breast cancer

Baseline hot flash frequency of 3 or more per week

No use of selective serotonin reuptake inhibitors at baseline

To learn if you are eligible or for more information, please call Jane Doe, Research Study Assistant, at (212) 639-XXX or speak with your physician or nurse.

Comment

Flyer A gives the very minimum of detail and encourages patients to call to find out more. There is an eye-catching title that will immediately grab the attention of any woman experiencing hot flashes. Moreover, one key benefit of the trial, free treatment, is mentioned clearly. Flyer B contains technical language and far too much information on trivial aspects of the trial: patients can easily be overwhelmed and put off. It is better to hear all details of the trial once a personal contact has been made with the research team. Eligibility information can

be checked quickly by the research assistant, and doesn't need to be included in informational materials

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