Evaluating a Clinical Trial

Let's say you've found some candidate clinical trials for your cancer. How do you decide which if any of these trials are for you? If you meet the inclusion criteria and the exclusion criteria don't disqualify you, take a very close look at the informed consent document and—if you can get your hands on it—the trial's protocol. Then you should make sure you get answers to all your questions from the investigators and the clinical trial staff. Finally, you should ask yourself a number of questions before deciding to proceed.

Inclusion and exclusion criteria

The first step is to examine the inclusion criteria, the list of conditions you must meet in order to be considered for participation in a certain clinical trial. It's easy to find the inclusion criteria because it's featured prominently in every clinical trial listing, even if it is very brief.

You'll learn quickly, for example, that a certain clinical trial is looking for people with stage III or stage IV non-small-cell lung cancer. If you have stage II lung cancer, or small-cell lung cancer, or a different kind of cancer entirely, it's pointless even to make a phone call to investigate the trial further, no matter how promising you believe the treatment to be. You simply won't be considered if you don't meet the inclusion criteria.

If you seem to meet the inclusion criteria, the next step is to phone (or to have a friend, relative, or your physician phone) the investigator or the clinical trial coordinator. The first thing she'll do is ask you about your diagnosis. She might have a more detailed list of inclusion criteria than that in the brief clinical trial description. If you still seem eligible, she'll go over the exclusion criteria.

This point is where most potential participants in the clinical trial fall out. In many trials, more than 90 percent of people inquiring about a clinical trial are excluded. Dr. David Jablons, a thoracic surgeon and cancer expert at the University of California, San Francisco, explains:

> *The typical clinical trial in cancer is not being done in early stage patients who have the luxury, hopefully, of a long disease-free interval. On the contrary, it's being done on patients with advanced disease who are desperate for any potential, hopeful, experimental therapy. The problem is that the studies usually (but not always) are looking at patients that are freshly diagnosed with advanced disease who haven't seen a lot of therapy to date. It helps keep the data cleaner. If you have a Substance X that you think is really going to be effective, and you start it on patients who have never seen any chemotherapy, who have never had any radiation, then it's pretty easy to say that the result is due to the trial drug. On the other hand, if they've had a bunch of chemotherapy and then you give them Substance X, the data are not as clean.*

It's really a paradox. The patients who are the most desperate, the most motivated, and the most interested in innovative therapy plans are usually the patients who have failed conventional therapy.

Some critics of the current system of clinical trials cite overly strict exclusion criteria as the primary cause of the low levels of patient participation. Moreover, they charge that the reasoning behind the desire for strict exclusion criteria might be faulty. The designers of clinical trials want a homogeneous population that has the best possible chance of responding to the experimental treatment. If they succeed in finding that population, clinical trials would take less time and would be less expensive. But that assumes that trial designers can tell in advance which subgroup of patients with a given disease would respond better. There's no evidence that that's the case, and suppose they guess wrong? There's a possibility that they're excluding the very patients who might benefit the most from the new treatment.

As Dr. Jablons notes:

> *Sometimes the rules can be bent. For example, if they've had radiation a year ago, focal radiation might not rule a patient out. But if a person has failed fourteen different drugs as of a month ago, and their disease is rapidly progressing, is that the right person to try a new*

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substance on? It could be, because if you saw a response, you'd say that not only is Substance X effective, but it's effective as a salvage treatment. The problem is that these are rapidly progressing diseases. Clinical disease doesn't always wait for careful, controlled, cautious, trial progression.

Examining the informed consent document

Many people with cancer are so desperate to try anything, or so hopeful that a certain experimental treatment will work, that they're willing to sign the informed consent document without examining it closely.

No matter how hopeful or desperate you are, no matter how anxious you are to start treatment quickly, no matter how much you trust and respect your doctor, it's always a mistake to sign the informed consent before examining it closely, making sure your questions are all answered, and then giving it careful consideration.

Both you and the investigator may terminate your participation in the trial at any time. You might want to consider what might make you leave the trial prematurely. And you should ask the investigator what would cause her to drop you from the study. How much of a deterioration in your health would be enough, for example? How closely must you follow study procedures? Would you be dropped for forgetting to take a single dose or for taking the dose an hour late?

Some informed consent documents have a separately enumerated "Experimental Subject's Bill of Rights," which is a legislative requirement that has been enacted only in certain states. In other states, some or all of such rights will be incorporated into the main body of the consent document. If you believe that any of your rights have been violated, you should contact the investigator or the Institutional Review Board immediately.

Examining the protocol document

Because the informed consent document often lacks crucial information, the savvy patient will obtain a copy of the trial's protocol. The protocol is a lengthy and highly technical document that contains every scientific detail of the clinical trial.

The protocol contains sections explaining the full scientific rationale of the study. Why do the investigators expect this compound to be active in cancer? What is its chemical makeup? What does it do in the test tube? How did it perform in animal studies? How did it perform in earlier phases of human testing?

The protocol also contains sections explaining the detailed conduct of the present study. How many patients and what kind of patients will be enrolled? What are the detailed inclusion and exclusion criteria? What drugs will be administered, and when? What tests will be administered, and when? How is the clinical staff supposed to respond to certain side effects and other contingencies? What would cause them to drop you from the study?

All of these questions—and many more—will be answered in the protocol for those patients willing to slog through language intended not for patients but for scientists and regulatory agencies.

Joyce R. Niblack speaks from experience:

Before anybody goes into a clinical trial, they should get and read a copy of the protocol. If there's something they don't understand, they need to ask questions. And if there's anything in there that's not acceptable to them, they need to negotiate. For example, in the first clinical trial I participated in, the protocol required a bone marrow biopsy once a month. Now, these are not fun. My doctor asked me, "Do you want these once a month?" and I said, "Hell no!" He said, "Well, I think it's insane." So I refused to agree to that. I negotiated through my doctor. He felt it was absolute nonsense to require it once a month. Interferon works slowly on the marrow, so he didn't think in any event you would see a big change from month to month. He told them he would be happy to monitor me through blood work, and he would give them bone marrow slides every three months, and that was it. My disease is so rare that I don't

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think there were many people falling off the tree saying, "Let me in your study," so they agreed.

Steve Dunn offers another reason to examine the protocol:

I think the most valuable thing in the protocol is to read about the prior history of this thing, and why they think it's promising, because that will tell you what the worth of the trial is. What most people hear about is the rate: "This has a 30 percent response rate in previous trials." But what you really are looking for in a Phase I or Phase II trial is that it makes the cancer go away and makes the cancer stay away. The problem is that there are an awful lot of treatments where the cancer might go away, but it'll grow back. What's really promising is if it looks like the responses are long-lasting and some of these people are getting quality time.

Steve points out that there's no way of telling what kind of valuable nuggets of information you might find in a careful perusal of the protocol. He believes that one of the things he learned might have helped him derive the maximum benefit from his trial.

When I read the protocol document for my trial, I found that they were very interested in neurological side effects and that they would withhold doses of the treatment if you had any. Knowing this helped me when I was in the treatment because they would offer me pain pills, and they would offer me compazine [a major tranquilizer that also decreases nausea], and they would offer me sleeping pills. Guess what? All of these things sedate you, and if you get into enough of a stupor with all of it, they would withhold doses. So I went really light on all of that stuff. You can't predict what little facts you might learn in the protocol that would help you get through the treatment better.

The major problem with the protocol is that it's written not at the eighth-grade level or below, as are most informed consent documents. On the contrary, it's written for people with MDs or PhDs.

In *Childhood Leukemia: A Guide for Families, Friends, & Caregivers*, Nancy Keene lists some of the reasons that parents will want to obtain protocol documents related to their children. These reasons apply equally well to adults enrolled in cancer clinical trials.

Admittedly, for some parents, the full protocol could be overwhelming or boring. There are many parents, however, who throw themselves into research to better understand their child's illness. These parents may benefit from having a copy of the study document for several reasons. First, it provides a description of all the clinical trials that preceded the present one and explains the reasons the investigators designed this particular study. Secondly, it provides detailed descriptions of drug reactions, which comforts many parents who worry that their child is the only one exhibiting extreme responses to some drugs. Thirdly, motivated parents who have only one protocol to keep track of occasionally prevent serious errors in treatment. Physicians treat scores of children on dozens of protocols and sometimes make mistakes. And finally, for parents who are adrift in the world of cancer treatment, it can return a bit of control over their child's life. It gives the parents a job to do: monitor their child's treatment.

Despite the value of the protocol document to the patient, it's not always easy to pry it loose from the investigators or their staffs. There are several reasons that they may be reluctant to show you the protocol. Sometimes it's misplaced paternalism. You have no medical training, they'll say, and the protocol is far too complicated for you to understand. You can counter that objection by pointing out that you or a trusted family member has been forced into becoming an expert in one narrow area of medicine, that you realize you might not understand every word, but that you'll ask questions if something concerns or confuses you.

Another reason the staff might be reluctant to give you the protocol is that it's a pain in the neck for them. Most protocols are 70 to 100 pages long, and some are even longer than that. They tend to reside in thick, loose-leaf notebooks, and it's not an insignificant task to photocopy something like that. They might say, hey, we're running 50 patients through this trial, and the protocol

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is 100 pages. Suppose everybody asks for a copy? You can answer this objection by pointing out that you're not 50 people, you're only one person who needs one copy. And you or a relative can offer to work the photocopier or take it to a copy shop if staff members don't have the time. You can also offer to read their copy in their offices, but if you choose that option, be sure not to let yourself be rushed. Take your time, and come with a pencil and paper so you can take notes.

A more serious obstacle to obtaining the protocol can present itself in some trials sponsored by pharmaceutical companies. Because these companies are often concerned about details of their new wonder drug leaking to their competitors, they often insist that investigators sign confidentiality agreements. This prohibits investigators from showing the protocol or even discussing certain details of the trial with others. If a member of the clinical research staff tells you that you can't have the protocol for this reason, you should immediately ask to speak to the principal investigator because people lower on the totem pole usually don't have the authority to make exceptions to the confidentiality rule.

Explain to the investigator that there simply isn't enough information in the informed consent document for you to make a fully informed decision about participating in the trial. He will likely counter with an offer to answer any questions you have. Tell him that although you appreciate his willingness to answer your questions, until you've had a chance to read the protocol, you won't even be able to formulate proper questions. The investigator may well conclude that he has an ethical obligation to release the protocol to you despite the confidentiality agreement. If he's still hesitant, offer to sign a confidentiality agreement yourself. Dr. David Jablons offers his view: "I think that patients should have complete carte blanche access to the protocol, within the bounds set by the company."

If the investigator still won't budge, ask to see just part of the protocol. The introductory sections tend to be the parts that are most valuable to clinical trial participants, and the investigator might be more willing to show you this one section than the whole thing. If even that suggestion won't move him, contact someone on the Institutional Review Board (IRB), whose telephone number will appear on the informed consent document. Explain to the IRB member why you want to see the protocol. The IRB might direct the investigator to make an exception to the confidentiality rule.

Throughout this process, be pleasant and polite but firm in your resolve to obtain the protocol. It would most likely be counterproductive to become angry or confrontational, and it would be an especially bad idea to suggest that the investigator was withholding the protocol because he had something to hide.

If you are unable to obtain the protocol even after applying your best efforts, you might want to draw up an especially long and detailed list of questions for the investigator. Be sure to ask for all the information you expect you might have learned by reading the protocol.

Getting questions answered

No matter how desperate you are to enter a clinical trial, you should make sure all your questions are answered before proceeding. Lydia Cunningham Rising tells a story that illustrates this point nicely. When Rising was searching for a clinical trial for her ex-husband, she found only two physicians doing research on his type of brain cancer. One of them was very hard to reach, and when she finally did get him on the phone:

> *He was very evasive. He would not answer my questions. When I tried to find out how many people he'd treated and how they did, he would never give me a straight answer. The other doctor told me that he'd treated nine patients and two were still alive after a few years. Joe would be number ten. He just laid it all out, so we went there. Six or seven years later, I came across a journal article written by the doctor who had been evasive. Of the sixty-five patients he treated, not one survived longer than a year. Now you know why the man didn't tell me. If anyone is being evasive, he may well have something to hide.*
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> *It's a good idea to bring a tape recorder to meetings with the investigator or trial administrators*

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in which you ask these questions. It can be difficult to take notes while listening with full concentration, and a tape will contain a full record of everything that was said. Be sure to inform everyone in the room that you intend to tape the conversation; in many states, it's illegal to record people without their knowledge. If you don't have access to a tape recorder, go with a friend or family member and ask that person to take notes so you can devote your full attention to the discussion.

Questions to ask your doctor and the trial's principal investigator

- What is the purpose of the study?
- What is the theory behind this new treatment?
- How many people have received this experimental treatment?
- How did their cancers respond? Did they have complete or partial remissions? How long did these remissions last?
- What would my prognosis be without any treatment at all?
- What would my prognosis be with the standard treatment?
- What kind of side effects have you noticed with the experimental treatment? How severe were those side effects? How many patients experienced them?
- Can you put me in touch with other patients participating in this study?
- If I experience side effects, will you give me medication to alleviate them?
- How many patients have dropped out of the study?
- Why did they drop out?
- What would cause you to drop me from this study?
- Suppose I decide to pursue alternative treatments, such as herbal remedies or massage, in addition to the experimental treatment. Will that disqualify me?
- Suppose I seem to be responding to the treatment when the study ends. Will I be able to continue receiving the treatment?
- What are my chances of receiving a placebo?
- Will I be randomized into one of the treatment arms? Please describe in detail all of the arms of the study.
- Who is reviewing this trial? How often is it being reviewed? Who will be monitoring patient safety?
- How will I know if the treatment is working?
- Suppose patients in one of the arms seem to be doing significantly better than the others. Will we all get a chance to switch into that arm?
- Will I know which arm I'm in, or will the trial be blinded?
- Is this a multicenter trial? If so, where else is it being conducted? What is the total number of patients in this trial, and how many of them are being seen at this institution? Are any of the other institutions closer to my home or easier to get to, and if so, can I be seen there?
- What other clinical trials on my kind of cancer are being conducted at this institution or elsewhere? Are any of them especially promising? Do you think this one is better than those? If so, why?
- How long will the study last? Is this longer or shorter than the standard treatment?
- Who will be in charge of my care? Will I be able to see my own doctor?
- Will I receive long-term follow-up care?
- What happens if I suffer serious harm as a result of this trial? Who would pay for the care I might need?

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- If a member of your family had the same kind of cancer I do, would you recommend this trial?
- In your opinion, am I better off enrolling in this trial now or waiting a while for something more promising to come along?

Questions to ask those administering the trial

- When will the trial start?
- How often will I have to come to the clinic?
- Can a local laboratory or my personal physician perform any of these tests so I don't have to come all the way down here every time?
- What medical records do you need my personal physician or my HMO to provide?
- Have insurance companies and HMOs been willing to pay for treatment under this study? Will you help me deal with my insurance company? Will you clearly explain to them which parts of this study involve standard treatment—which they should pay for—and which parts are experimental?
- Will I have to pay anything for the experimental parts of the clinical trial?
- Who is sponsoring the clinical trial?
- Whom can I contact if I have any difficulty with this trial? What are their phone numbers, fax numbers, email addresses, and mailing addresses?

Questions to ask yourself

- Given my prognosis, how much of a risk am I willing to take on an experimental treatment?
- Am I sure I fully understand all of my alternatives? What would happen if I did nothing? What would happen if I went with the standard treatment? What would happen if I decided to go with alternative therapies?
- What is the best-case scenario if I participate in this trial? What is the worst-case scenario?
- What would I consider a successful outcome?
- Is the treatment likely to improve my quality of life, the length of my life, or both?
- What level of side effects would cause me to drop out of the trial?
- Is there anything else that might cause me to leave the trial prematurely?
- Suppose I were randomized to the standard-treatment arm of the study. Would that cause me to drop out and search for another trial?
- Have I had all my questions answered? If not, was anybody being evasive? Do I trust the investigator?
- Do I trust the trial's sponsor?
- Do I trust my insurance company/HMO to pay its fair share of the trial's costs?
- How difficult will it be for me to get to the hospital or clinic for my treatment?
- Am I better off enrolling in this trial now or waiting a while for something more promising to come along?

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