

10 THINGS YOU NEED TO KNOW BEFORE ENROLLING IN MEDICAL RESEARCH

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“The successful conduct of research in a free society depends on trust between the scientific enterprise and the public, trust in the integrity of the discovery process, and especially trust in the safety of patients and healthy volunteers who participate in the process. In recent years, this essential trust has been shaken by a number of highly publicized events: tragic deaths of patients enrolled in clinical trials, high-profile allegations of financial conflicts of interest, and scientific misconduct by a few investigators.”

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INTRODUCTION

Why you need this book

So, you're thinking about becoming a research subject. You may have just been to a website advertising a clinical trial that interested you, or your doctor might have suggested one to you. You were smart enough to go in search of more information before starting in the study. You are smart enough to want to know more about the research process before committing yourself or a member of the family to it.

This book will provide you with the 10 most important things you need to know before you join a research study. You'll know what questions you need to ask your doctor and the research coordinator. You'll know how to be sure that the information collected about you is used safely and ethically.

You'll also know a lot more about the rules that doctors must follow and about the money that changes hands when you volunteer for a research study. You'll know about the concerns the government has about researchers pressuring you, and the regulations put in place to prevent it from happening. You'll also learn that no such regulations exist to protect your doctor from similar pressures.

Why participating in a study is important

Drugs and medical devices (like dialysis machines and blood testing equipment used by diabetics) are very necessary for the quality of life that we enjoy in the United States. All of us know someone or are related to someone who is alive today because of a drug or a medical device. If we want to continue to see medical advances, we have to volunteer for research.

Volunteering for research is important enough that my son, my husband, and I have all participated in different studies at one time or another in our lives. But we knew what studies were worth the risk to our health, and what studies were not, or were a waste of time.

Reasons to be careful in selecting the research you participate in

You don't want your life placed in harm's way (the worst research outcome) or your time wasted (an annoying outcome), so you need to know as much as possible before you enter a research study.

Today, there is so much profit to be made in clinical trials that you need to be very careful to protect yourself. The problem is caused by two competing issues:

- Insurance companies have been slashing what doctors get paid. Many doctors feel that they are not making the salaries that doctors made just a few years ago. Doctors have not been successful in getting insurance companies, HMOs, and the government to pay them better.
- At the same time, pharmaceutical companies are being forced by the FDA to do broader and more intricate testing of drugs and medical devices. Pharmaceutical companies cannot test patients directly; they must find doctors who are willing to follow their patients through very complicated studies.

Doctors are among the busiest people on the face of the planet. They already have to pay tens of thousands of dollars for the staff and malpractice insurance they need for their busy practices. Being involved in research requires not only a lot of a doctor's time, but requires him to hire additional staff just to manage all the

paperwork and regulations associated with doing research. So why on earth would they ever consent to do studies in their patients?

For lots and lots of money, that's why. Doctors get paid big bucks for you to participate in a study. They're paid so much that it offsets the money that they've lost from insurance companies and the government. The problem is that you're the one that assumes the risk here, and your doctor and the sponsoring company make the money.

Finally, you need to ask yourself if a pill is the best cure for everything. While swallowing a pill is certainly easier than changing your lifestyle, or using a less convenient treatment, it's not necessarily best for you. Here are some examples of what I mean.

- If you're women, should you risk damaging your liver for a yeast infection? Why ask your liver to take on the task of cleansing the pill out of your body when a topical application is more effective (even though messy).
- Should you risk your liver and kidneys for toenail fungus? That's what you may do when you take a pill for those yellowing nails rather than applying a liquid to the nails themselves.
- While we're on the subject, why would you try to lose weight by risking stroke, heart disease, or liver and kidney damage? Aren't those the very ailments you're trying to avoid by losing the weight in the first place?

So if you feel that taking a pill for these things is not worth the risk, why participate in research on the same subject?

I've worked in research for over 25 years, 20 years in clinical research, and 16 years in the industry. The vast majority of the research I've been intimately involved in was conducted ethically, carefully, and with great respect for the human beings who participated in it.

Unfortunately, I've seen a lot of questionable research. I've seen research begin in humans without strong safety data from animal studies. I've encountered research professionals who twisted information to gain the results they wanted. I've seen well-meaning individuals make serious mistakes in research design, or miss information about your safety.

My background is unusual for clinical research. My Ph.D. is in industrial and organizational psychology, as opposed to biostatistics, biology, chemistry, or medicine. My training provided me with tools for assessing the overall health of an industry (as opposed to the mental health of an individual). Additionally, my training was heavy with statistics classes and research design. All three of these areas have given me a unique perspective on clinical research.

I have thoroughly learned the regulations that govern the use of humans in research during my time working for one of the Navy's largest medical centers, as well as my subsequent employment for contract research organizations.

I ran an animal research facility for more than 8 years, and know what goes into pre-clinical trials. Pre-clinical trials are required to ensure that a new product is safe and effective in animals before any human is placed at risk. It's been my experience that it is tougher to get research approved to do in animals than it is to start research in people. This was certainly borne out by the time I've spent on animal care and use committees.

It's been my privilege to serve on several institutional review boards (IRBs). These boards were created by federal law to make sure that research is as safe as possible, and to make sure that you are not subjected to any trickery during a study.

I've written informed consent forms, the document that you should have right beside you as you read this book. Informed consents are crucial to your understanding of what you're about to get into, and they amount to a contract among you, your doctor, and whoever is paying to have the research done.

I've written new drug applications and clinical protocols, worked on many investigations of new drugs and devices, and have served on Data Safety Monitoring Boards (also known as Data Monitoring Committees). I've appeared before the Food and Drug Administration, and know what kind of questions and concerns they have.

My employment history is not completely clean. I left one job because of disagreements over the ethics (or lack thereof) behind a Data Monitoring Committee, and been fired from another for questioning the competence and ability of a doctor and his investigator. I want you to know this, not because I think I'm holier-than-thou, but because you need to know that there are some people in the pharmaceutical industry who do not think highly of me. It's important to have the whole picture before you read further.

I currently advise government, academic institutions, and commercial companies about human research protections. I serve as the Quality Assurance Officer for the National Institute of Environmental Health Sciences. I assisted in the

development of policies at the National Institutes of Health governing research in humans.

Finally, I've participated in research, and know what it's like to give over your physical health and safety to a process without any "knowns." I've been a research subject in psychological research (not too risky, but worrisome from a "messing with your mind" perspective). I've participated in radiological research so serious that I can never participate in any other radiological trials (for fear of causing cancer). It was difficult to ask questions of my doctor, and it was hard to know what the right questions were. I'm hoping that this e-book can help you in this process.

There are some terms you need to be familiar with from this point onward. While each term will be explained in greater detail in specific chapters, you'll see them discussed in every chapter. It's good if you know what they are before we get started. They are:

- **Data Monitoring Committee** (DMC, also called a data safety monitoring board or DSMB) – this is a group of individuals who are charged with reviewing safety and effectiveness information during your study. Not every study has one, but they are becoming more common. They are more or less independent, and will make recommendations about whether a study is safe to continue, or perhaps so effective that a trial should stop early. The Food and Drug Administration takes their recommendations very seriously, even when a research sponsor may not.
- **Food and Drug Administration** (FDA) – this is the government agency that decides which new drugs and medical devices are approved to be used in people. Unfortunately, it continues to be very under-funded, and as a

consequence doesn't catch all serious safety issues before approval. The FDA wields great authority in medical research, and they like to hear from subjects, not just doctors and drug companies.

- **Informed Consent Form** (also called “informed consent” or “consent form”) – I can't over-stress how important this document is. Anyone who enters a clinical trial has to sign one. It is imperative that you also understand it. This document outlines the bulk of what you need to know about the research you're thinking about. The US government requires that it be written so you understand it. If you don't understand it, don't enroll in the study.
- **Institutional Review Board** (IRB, also called independent ethics committee, research review board, scientific review, and other names) – this is a group of doctors, scientists, and community members who review research studies and informed consents to be sure that you are protected. If research is submitted to the FDA, then an IRB had to approve it. Your informed consent form should contain information on how to contact the IRB if there are any issues.

CHAPTER I THE 10 THINGS YOU NEED TO KNOW

When you are asked to participate in a research study, you are being asked to do something risky. Sometimes it's hard to see it that way, because you trust your doctor (or at least you want to). But before you allow yourself (or your child) to start the study treatment, you must know the answers to the following questions:

- 1. Will I be safe?** What steps are taken to minimize the risk I'm taking?
- 2. Will I benefit from this study?** Will this study treat my condition? Will I receive payment for my time and effort?
- 3. Did I really give informed consent?** You must completely understand the form you were given to sign. Never sign it at the office! Being completely informed is your number one responsibility
- 4. What are my odds of actually getting treated?** Are placebos used in the study, and if so, what are my chances of receiving real treatment?
- 5. Who is making money from my participation?** You'll be surprised at how many people are paid for your participation.
- 6. Who is independently watching this research and how do I contact them?** You need to know which institutional review board (IRB) approved this study, and you'll need to know if there is a Data Safety Monitoring Board, (DSMB) or a Data Monitoring Committee (DMC) reviewing the information about you and the others in the study. During the study, you need to know how to contact the head of the IRB, the chair of the DSMB or DMC, and the relevant people at the FDA. Write the numbers down and carry them with you.

- 7. What do I do if someone breaks or bends the law?** If you suspect that your doctors, or other representatives of the hospital or university, haven't followed the rules that govern research, here's what you need to do to stop them.
- 8. How important is this research?** You need to know this to determine if it's worth your time and your health to join the study.
- 9. Can I negotiate a better deal?** Some things to consider before you sign up.
- 10. How do I best protect my child?** What do I need to know in addition to the information from the previous 9 questions?

For the majority of studies, you'll receive prompt answers, and you'll know that you're being treated with respect. But if you don't feel you have gotten full and complete answers to these questions, don't get involved. It is not worth the risk!

CHAPTER II WILL I BE SAFE?

Introduction

When you consider entering a research study, the most important question you need answered is whether or not you'll be safe. This is also the most difficult question to answer. One of the main reasons for doing research is to answer this safety question. And no matter how well-designed a study is, there is always the potential for something unexpected to happen.

But there are ways to determine just how much risk you are taking on, and there are regulations and procedures you need to know about that are aimed at minimizing risk to you as much as possible. We'll explore these further in this chapter.

Before entering the study

First and foremost, ask your doctor if s/he would participate in this study, or have a family member participate. If your doctor says "yes", write it down, and proceed with your other questions. If your doctor says "no", don't enter the study!

A doctor who would participate or have a family member participate probably believes the study would be safe for you, and of benefit for you. While it's possible that a few doctors will lie about this, it is still documentation if something goes wrong later on in the study.

You need to read the informed consent form very closely. As mentioned earlier, it is a very important document, and forms the contract between you and those

conducting the study. By law, it must contain statements about the risk you're about to assume, and clear statements of the possible problems. You need to read through it carefully, and write down any questions you want to ask the doctor. Make sure the doctor is available to answer these questions the next time you go in. While the research coordinator (who is frequently a nurse) will have a lot of information, only your doctor can adequately address your concerns about safety.

By law, the informed consent form is supposed to be written so that an average person (someone without medical training) can understand it. It must discuss your safety risks in terms that you understand. For instance, if blood will be drawn as part of the study, the informed consent form must warn you that there's a chance you'll have a bruise where the blood is drawn, and that there is a very small chance you could get a blood infection from the needle puncture. It should not say that there is a risk of hematoma and sepsis (the medical terms for these risks)!

Challenge any terms that you don't understand. Sometimes informed consents do not use the easily understood term, because it could frighten you away. For instance, when a drug or device contains beef products, there is a very miniscule risk of mad cow disease. Frankly, you're more likely to get mad cow from the beef you eat at home. But the term "bovine spongiform encephalitis" is almost always allowed instead of the term "mad cow." You deserve to know what they're really warning you of, even if the risk is nearly non-existent.

There are some terms you need to learn before signing your informed consent, or going in with your concerns. These are:

- **Adverse Event**

An adverse event is any problem that shows up in you during the time you're in a study. It may or may not be related to the study treatment. Adverse events are considered minor, and can be related to everything from a mild headache to breaking your leg from slipping on an icy step. Hundreds of adverse events are reported for most studies, unless the number of people enrolled is small.

Your doctor makes the decision about whether an adverse event is related to your treatment during the study. Doctors usually are cautious about this, and will say the event is related to treatment if they are not sure. This is the right thing to do. If there is any doubt, then the new treatment should be suspected.

But that can create problems for the company making the new product. Ever wondered how “the flu” could be the side effect of a medication? It could be that the bulk of the research was done during the winter, the prime season for catching the flu. During the winter, it is to be expected that more people come down with the flu, but how to decide if your patient has the flu because it's winter, or got the flu because the new treatment lowered the immune system? It can't be done.

Ever wondered why a pill for indigestion can cause diarrhea and nausea? It could be caused by the pill, or it could be because the patient has some underlying problem like irritable bowel syndrome. It could be that the patient ate too much. But doctors don't have that information, and so they say the adverse event is related to treatment.

If you're a drug company, all those adverse events taken together can make your drug look unsafe, when it isn't. So companies have a habit of asking doctors to reconsider their decision. Ethical companies avoid asking directly, but have independent monitors ask the doctors. But many companies pressure doctors, citing experts or actually bringing those experts in to ask questions that put the doctors on the defensive.

You need to talk with your doctor about how he or she would handle a situation like this, and you need to be comfortable with the reply.

- **Serious Adverse Event**

A serious adverse event is a reaction to a treatment that results in:

- death
- a life-threatening situation
- an admission to a hospital
- staying in a hospital longer than if the treatment hadn't been given
- a temporary or permanent disability
- a birth defect in a study participant's child.

A serious adverse event may or may not be related to your participation in the study. Again, your doctor decides whether it's related. Doctors usually find it easier to determine if your treatment caused a serious adverse event. For instance, if someone is hit by a truck, and hospitalized as a result, it is unlikely to be related to treatment. However, if a healthy patient is suddenly admitted for anaphylactic

shock (usually caused by an allergic reaction) after receiving a new vaccine, the vaccine is most likely the cause.

Serious adverse events must be reported to the FDA and to the IRB (institutional review board). But the ones that are related to your treatment in the study must be reported within 2 weeks of occurring. While that 2 week timeline may seem generous, it isn't. The doctor and the research coordinator have a great deal of paperwork to file. Then the principle investigator of the study and whatever group is monitoring safety will want to review it. Usually the company sponsoring the study will want a representative to review it, although they must be very careful not to interfere with the doctor's decision.

Since serious adverse events that are related to treatment must be reported to outside agencies, these events can (and should) stop the study. It is likely that more intense pressure will be placed on your doctor in this situation. If your physician is receiving a large payment from a company for running the study, do you think that might influence whether he thinks it's related to the study? It could.

As with adverse events, you need to talk with your doctor about how he or she will deal with this pressure, and you need to feel comfortable with the answer.

- **Minor Complications**

A minor complication is essentially the same as an adverse event. This term is more commonly used in research using a new device, while “adverse event” is more commonly used in drug trials.

- **Major Complications**

A major complication is essentially the same as a serious adverse event. This term is more commonly used in research using a new device, while “serious adverse event” is more commonly used in drug trials.

- **Expected Complications**

In certain circumstances, the FDA allows the sponsor to list all expected safety events before the start of the trial. Anything listed as an expected complication is treated a little less rigorously than would be the usual case in research. This is usually done for studies in diseases and conditions that already pose a safety risk to the patient. For example, someone with end stage kidney disease is already pretty sick. This individual would be at higher risk for kidney failure, stroke, and heart attacks. Since this is already the case, these would be treated as expected complications.

- **Expected Adverse Events**

This is the same as an expected complication.

Finally, tell your doctor that you expect to be told about adverse events or serious adverse events that occur during the course of the trial. State specifically that you want to know about overall safety issues that are considered to be related to treatment, and that you’re not asking for information about some other patient (which is a violation of the law).

This information is vitally important to you. Sometimes very serious safety issues can crop up in a doctor’s office across the country from you. Most consent forms

say something vague about results being shared with you when new critical information is acquired. However, patients are rarely-to-never informed about what adverse events and serious adverse events occur on the trial, even when their doctors are given this information. Would you want to stay in a research study if you knew that it had provoked a heart attack in someone? How about liver failure or a stroke? My guess is that you would not stay in the study. You probably wouldn't want to stay in it if it was causing migraines, and you already suffered enough of them.

Your doctor is entitled to know about safety information that is submitted to the FDA as part of the annual safety update. While he or she has a right to the information, they may not think to ask for it unless they know that you are interested. Your doctor and the sponsoring company are required by law to provide you with this information, **BUT ONLY IF YOU ASK FOR IT.**

Make it clear that your continued cooperation in the research is dependent on getting this information.

During the study

Once you're in the study, make sure you report anything unusual that you experience to your doctor or study coordinator. It's important for them to know about even minor events that impact your health. Neither they nor the FDA can get a complete picture of the new drug or device unless you and the other research subjects report what is going on.

If you experience an adverse event, ask your doctor if it is related to treatment. It may be, and your physician may consider it minor enough not to take you out of

the study. But your opinion may be different from your doctor's, so make sure you find out.

If you experience a serious adverse event, you will likely be removed from the study, even if it's not related. You may be too sick or too injured to continue, and your doctor will want to focus on getting you well, not on the data you can provide to the study.

If a serious adverse event is NOT related to the study, you or your health insurance company will have to pay for your treatment regardless of what it may say in the informed consent form.

You will receive payment from the company sponsoring the trial only if the serious adverse event is related to the trial.

When you are better, check with your doctor to make sure your serious adverse event has been reported to the FDA and the IRB. The reason for reporting them quickly is to stop other patients from being harmed. If you haven't been told yet, ask your doctor if it is related to treatment.

Sometimes, even if your doctor has provided the information about your safety problem, the company sponsoring the trial might not have. It is very important that you follow up with the IRB and the FDA to make sure that they know about the event. Information about how to report this is in Chapter VIII.

If your doctor says your serious adverse event is unrelated and you believe otherwise, then you **MUST** contact your IRB, or other people in the study could be hurt. Ask your doctor if he believes it's related.

After the study

As your informed consent form should have indicated, you are entitled to know the results of the study. When you're done with the study, it may be several months to a year before the results are analyzed, so be prepared for a wait. But make sure you insist on getting them, particularly those listings of adverse events and serious adverse events. They will give you valuable information about risks that you might still experience due to your participation in the research.

CHAPTER III WILL I BENEFIT FROM THIS STUDY?

Before the study

As with information about safety issues, your informed consent form will tell you if you can expect to feel better as a result of being in the study. Most IRBs insist that possible benefits be downplayed, so that you don't get suckered into a study that promises you the world, and then fails to deliver. But sometimes this means that you're not told of very realistic benefits that could occur.

For instance, you may receive diagnostic tests that your insurance company would deny you because of their expense. These tests could conceivably uncover other problems that would have worsened before they were discovered. Typically, IRBs won't allow that to be said in the informed consent form since the benefits are "iffy." Because of this, it's important to talk with your doctor about any tests or procedures that are being done beyond the "standard of care." It could be that you decide to enter the study because of the information YOU could gain about your body and your health.

It is very important that you review the information about compensation that you will receive because of your participation. There are very strict guidelines about payment for joining a research study. They're aimed at making sure you don't agree to something very dangerous because you will receive a large amount of money. So you're probably not going to be offered a lot for being in the research. Here are the standard types of compensation:

- **Reimbursement in money**

You should receive money for driving to and from appointments, for parking, and time from work that isn't covered by sick leave. You should receive money for meals.

You should also receive money for any painful procedures, like having your blood drawn, mammography, and things of that nature. Usually, the greater the risk or pain, the greater the money is – to a point!

Remember that they can't offer you so much money that you agree to be in research you otherwise wouldn't agree to do.

Only you can decide if the money being offered is sufficient for your time and trouble. I urge you to compare the amount offered to you to the amount offered to your doctor, though. If you feel that the amount he receives for his time and trouble is reasonable, by all means participate in the trial.

- **Reimbursement in chits**

Instead of being given money for parking, you receive a parking pass. Instead of being compensated for lunch or breakfast, you receive a pass to the cafeteria. Personally, I don't believe this is right. Why should someone else determine where you park, or where or what you eat? However, if you're okay with it, join the study.

During the study

As was discussed in the previous chapter, you are entitled to any information that comes up that might affect your ongoing participation in the research. For instance, if you are in a drug trial, and feel that the new drug is not working as well as your previous one, you'll want to know what has been discovered about this new drug's effectiveness so far.

Getting this information is not as straightforward as getting information about safety issues. The FDA does not require an annual effectiveness report. This is because it can take a while for some types of treatment to do their jobs.

So what's an inquiring mind to do? Ask if there is a Data Monitoring Committee (DMC). These are independent groups of physicians and statisticians that review the data from a study at regular intervals. While their job is primarily to assure that a new product is safe, and to stop a trial if it isn't, sometimes they look at effectiveness, too. This happens particularly if the belief is that the new product will be extremely effective. Then the committee can stop the trial if it's found that the new treatment is much better than the alternative. If there's a DMC, contact the chair, or ask your doctor to do so.

Also, see if there is going to be an "interim analysis." Sometimes companies will examine all the data they've collected at a specific time point (such as half way through the study) to see if the results are good. This usually happens with smaller companies, since they may plan to raise more money for their product based on these results.

After the study

As mentioned before, you are entitled to know the results of the study. Again, you'll need to wait several months to a year before the results are analyzed. But you must insist on getting them. If the results indicated that the new treatment was not effective, it is very likely that the company will not want people to know about it. If it is a study that must be submitted to the FDA, then it is likely that the company will not get the treatment approved, and if they are a small company, they may disappear altogether. Since there still could be long term consequences for you from being in the study, you'll want to know about this, and to be sure to keep track of the people responsible should something go wrong for you later.

CHAPTER IV DID I REALLY GIVE INFORMED CONSENT?

Before the Study

YOU MUST UNDERSTAND YOUR INFORMED CONSENT! Before you sign it, you must feel comfortable with every word, and every section. This document is your only protection if anything goes wrong. It is your proof that the IRB, your doctor, and the sponsoring company either were careless, misrepresented the facts, or in extreme cases, lied to you.

This document provides (or should provide) all the information you need to know about the study and the risks and benefits to you. In the event that something goes wrong, or you suspect dishonesty or fraud, it is the starting point for whistle blowing activities that could bring about better research practices, and could put money in your pocket.

The following is the list of required components in an informed consent form (from the Code of Federal Regulations Title 21, Part 50.25, “The Elements of Informed Consent”):

- A statement that the study **involves research**
- An explanation of the **purposes** of the research
- The expected **length** of your participation
- A **description of the procedures** to be followed [both by you and your doctor]
- **Identification of any procedures which are experimental**
- A description of any **reasonably foreseeable risks or discomforts** to you

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- A **description of any benefits** to you or to others
- **Alternative procedures or treatment**, if any, that might be advantageous to you [rather than participating in the study]
- A statement describing the extent, if any, to which your **records will be kept confidential**
- A statement that notes that the **Food and Drug Administration may inspect the records**.
- For research involving **more than minimal risk**, an explanation of any **compensation**
- For research involving **more than minimal risk**, an explanation of any **medical treatments that are available if injury occurs**, and, if so, what they consist of, or where further information may be obtained.
- **Who to contact** for answers to questions about the research and research subjects' rights, and who to contact in the event of a research-related injury
- A statement that your participation is **voluntary**
- A statement that **refusal to participate will involve no penalty or loss of benefits** to which you are already entitled,
- A statement that **you may discontinue participation at any time without penalty or loss of benefits** to which you are already entitled

Make sure that each of these items is in that consent form! If it's not, it suggests that there are issues with how research is conducted at your doctor's office. If anything is missing, bring it to your doctor's attention.

Be particularly careful to follow up with your doctor about the confidentiality of your information. Most doctors and IRBs think about confidentiality of information. They tend not to think about the confidentiality of your person. Many safeguards are in place to make sure that information about you doesn't fall

into the wrong hands. Few doctors think twice about involving strangers in the examination of your person, though. Ask your doctor if a representative of the sponsor will be attending any of your examinations. Ask if a representative of the company will be attending your surgery or procedure, if you're having any. Do you want strangers (and non-medical strangers, at that) in on your care? If you don't mind the sponsor observing, that's fine. But if you do, you need to let your doctor know. This is completely your call, and not the doctor's. If your doctor tells you that s/he must have the sponsor's representative there, ask why. If the sponsor needs to be there to run equipment, or supervise the use of the device or drug, think twice about entering the study. If the new product is so difficult to use that it requires a company representative, it may create problems that no one anticipated.

Usually, informed consent forms include a list of inclusion and exclusion criteria, in addition to the items listed above. While not required by law, it's become common since doctors know they may not have your full medical history. Below is more detailed information on both topics.

- Read **inclusion** criteria carefully – should you be in this study?
 - Inclusion Criteria – these are the requirements you must meet to be included in the study
 - You must meet **every** requirement to be in the study.
 - These requirements exist so that doctors won't do research on patients who shouldn't be in the study.
 - If you're enrolled in a study and don't meet these requirements, all the information collected about you could be thrown out. This means it could be a complete waste of your time, at the very least!

- At the worst, you could have a drug or device in you that was not designed for patients like you. You could be hurt by your participation, or you could hurt the research.
 - You need to read the inclusion criteria very carefully. If you don't understand them, ask questions until you do.
 - If you don't feel that you meet each requirement, ask your doctor why he/she thinks you would benefit from participating.
 - Ask if the company who is sponsoring the trial is giving waivers for inclusion criteria. While not considered the best practice, waivers are given for studies that are difficult to enroll. If waivers aren't being given, say "no" to being in the study.
 - If they are, ask to see the waiver, and ask why the company was willing to give it in your case. This information is required, so your doctor will have it. Sometimes waivers are given when a company realizes that the inclusion criteria are too strict.
 - Examples of inclusion criteria include the exact type of disease or condition you must have to participate. Read this very carefully, as it usually contains information about the severity of the disease or condition.
- Read **exclusion** criteria carefully – should you be in this study?
 - Exclusion Criteria – these are the reasons you cannot participate in a study. These are really important, because they're meant to prevent you from enrolling in a study that could harm you if you participate
 - **If you meet even one of these, you cannot be in the study.**
 - These requirements exist so that doctors won't do research on patients who shouldn't be in the study because they could be more easily injured by the drug or device.

- If you're enrolled in a study and meet one or more of these requirements, then all the information collected about you could be thrown out (except the safety information). Again, this means it could be a complete waste of your time.
- Participating in the research could actually hurt you. The research was designed SPECIFICALLY TO EXCLUDE YOU!
- You need to read the exclusion criteria very carefully. If you don't understand them, ask questions until you do.
- If you feel that you meet any requirement, ask your doctor why he/she thinks you would benefit from participating. Really probe here. Your health is at stake.
- Ask if the company who is sponsoring the trial is giving waivers for exclusion criteria. If they aren't, then ask your doctor why on earth you should be enrolled.
- If they are, ask to see the waiver, and ask why the company was willing to give it in your case. This is about your personal safety. You must be completely comfortable before allowing anyone to experiment on you.
- Examples of common exclusion criteria:
 - Being overweight
 - Being too young
 - Being too old
 - Being too sick (this is generally covered over several items, broken down into specifics like complete blood counts, urinalysis, x-rays, etc.)
 - Taking other medications that could interact with the new drug or device

If you don't see a list of inclusion and exclusion criteria in your consent form, ask for it. Your research coordinator has checklists for both, and should be willing to share them with you. It is not uncommon for a busy research coordinator or your doctor to make a mistake with the criteria. They see a lot of patients every day, and it's difficult to keep track of all the pertinent information. It's also possible that you know something about your health that your doctor may not, particularly if you see several doctors. For your own safety, you need to make sure that you're not enrolled in a study that you don't qualify for. For your own health, you want to be sure that you're included in a study that you qualify for.

Do not sign the informed consent until you've had every question answered. Also, make sure that the doctor is present during the discussion. Sometimes the research coordinator does not have all the answers, or doesn't have the right ones.

If you decide to enter the study, there is one last thing you need to do to protect yourself. You need to add the following language to the informed consent form, and initial it:

Under no circumstances is the commercial use of bodily fluids, tissue, bones, or discarded parts authorized. The undersigned retains all rights to cells, blood, DNA, and any other body part given during this research.

There are several reasons for this. Academic institutions and biotechnology companies are patenting specific genes, patterns of genes, and cell lines for later use. They frequently seek patents on body parts for which there is currently no known use. In the rapidly changing field of genetics, today's discarded blood,

bone marrow, organ tissue, etc. may be tomorrow's block buster cure for something.

During the Study

Sometimes, informed consent forms change. Sometimes this happens long after you've finished active participation in the study, but before the study officially ends. When that happens, you may be asked to sign a new informed consent, or an amended informed consent. While there are usually very good and harmless reasons for this, sometimes the informed consent changes because the FDA, the IRB or the DMC (if your study has one) has decided that the risks have changed significantly, and that you must be informed of it.

If you are asked to sign a new informed consent form, insist on being presented with a copy of the original you signed. This way you can review them side-by-side to see what's changed. Again, don't sign the consent form in the office, but take it home to examine. If two trips is a big strain on your time, insist that the doctor's office mail you both your original consent form and the new document.

If you have questions after your review, insist on a meeting with the doctor to discuss them. Do not sign until you're sure about it, and feel free to contact the agency or company that asked for the new consent.

After the Study

Keep all copies of informed consent forms in a secure location, like a safe deposit box, or a fire-proof safe. If you've got the resources, scan them to your computer

and back them up over the web. You'll need to keep these documents the rest of your life. You never know when something may turn up years or even decades from now. This is your only proof that you participated in research, and your only claim to compensation, should you need it years from now.

CHAPTER V WHAT ARE MY ODDS OF ACTUALLY GETTING TREATED?

Before the study

To completely understand your odds of getting the new treatment, you need to understand the concepts of randomization, blinding, and placebos. In this chapter, I'll explain the terms, and how together they determine your chances of receiving a real treatment, and the risks that you're undertaking.

- **Randomization**

Unless your study is an “open label” trial, one where you'll know exactly what you received, it is likely that your study will be randomized. Most clinical trials are. In a randomized study, each subject is assigned a treatment by a mathematical formula. The formula is set up to make sure that the right number of subjects end up in each treatment group, and may be set up to make sure that other traits of the subjects are evenly distributed. For instance, the formula may be set so that 20 people are assigned to a placebo, and 40 are assigned to actual treatment, and to make sure that men and women are equally assigned to both groups. In a randomized trial, you have no say in what treatment you receive, and neither does your doctor, or the company sponsoring the study. That formula makes all the decisions.

- **Blinding**

There are many factors that can influence the results of a study, besides the treatment itself. One of the most powerful is the human mind's

ability to be persuaded. It's called the placebo effect, and I will go into more detail about it below. What it boils down to is that your doctor or you could decide you were better after taking the treatment, when in fact you are not. To avoid that kind of contamination of the results, the concept of "blinding" was added to research.

Blinding means that you probably will not know what treatment you received until after the study, and it's very likely that your doctor won't know either.

Again, if the study is "blinded," your consent form will tell you so. It will also tell you what steps will be taken to "unblind" the doctor (weird idea, huh?) in the event of an emergency. If anything occurs that compromises your safety, then the doctor will be told immediately (24 hours a day) what group you were in so that you can receive appropriate care.

- **Placebos**

When you read your consent form, it will include specific information about treatment or the lack of it. If you are in a dose response trial (a study aimed at picking the right dose for a new medication), the consent form will list the different dosages, and likely a placebo (also known as a sugar pill). It's pretty easy to understand the various treatment options, but it is not so easy to grasp the concept of no treatment at all.

So what is a placebo? How will it affect you if you receive it? A placebo is a necessary for a lot of research, but can be risky for patients. A placebo is made to look like the real thing, so you and your doctor

won't be able to tell if you're getting the actual drug or device, or a pretend one.

Many people actually get better when taking placebos! It's believed that we respond to being taken care of even more than we respond to being treated. Our tendency to get better with placebos is called the placebo effect. The placebo effect could mean that even if you're not in the group receiving treatment, you could still improve. This is an important consideration, as all of us would rather improve on our own than by taking a pill. So there is a genuine value to a placebo-controlled trial.

It's unethical to give someone with a serious condition absolutely no treatment. If the study you're considering has a placebo, then it is unlikely that your medical condition is serious or life-threatening. If it is, ask your doctor what steps are being taken to safe-guard your health in case you receive the placebo. Also ask why an IRB decided that this study was appropriate. There can be reasonable explanations for the use of a placebo in these situations, but they are rare, and you need to understand them before considering risking yourself.

While the use of placebos in serious conditions is rare, it is far from rare in studies of "me too" drugs. "Me toos" are slight changes to a drug that allow a drug company to either extend their own patent, or perhaps move closer to someone else's. Since effective drugs already exist (which is why a "me too" is being considered), it would be more appropriate to compare the new "me too" to the drugs that are already approved. But since the new drug is so similar to the one on the market,

it's unlikely to be better. So the drug companies prefer to compare their “me too” drugs to placebos. To risk receiving no treatment in these studies is not worth your time. There is considerably more about this situation in Chapter IX.

So you need to review that consent form very carefully to determine the chance that you'll actually receive the treatment. Since you have no control over what group you're assigned to (randomization decides that), and will probably not know what group you're in (because of blinding), you need to find out if placebos are part of your study; and, if so, how many patients will receive placebo versus how many will be treated.

Finally, you need to consider the other treatments that may be part of the study. Do you want to receive the highest dose of drug, or the lowest? Both carry potential problems. A high dose will most likely be the most effective, but probably the least safe. The low dose will be safer, but less likely to help you.

This is not always an easy decision. My husband needed a knee replacement and was offered the chance to enroll in a study. It was a randomized study, with 50% of the patients receiving a knee with 120° of rotation, and 50% of the patients receiving a knee with 155° rotation. The aim of the study was to determine if the knee with the greater rotation pre-surgically would transform into greater rotation after surgery.

While my husband would not have known which knee he received, his doctor would have. Clearly, it wasn't a placebo-controlled trial, as a knee replacement is serious stuff.

My husband had more than 120° of rotation in his natural knee, so he wanted to keep more than that in the new artificial knee. A 50-50 shot didn't look too good to him. As luck would have it, both knees were already FDA-approved, so he decided NOT to be in the research, and to have the knee with 155° of rotation instead.

During the study

If your study has a DMC or DSMB, then they will regularly evaluate the safety and effectiveness of the study. If they discover that a treatment is doing very well, then the study could be stopped early to allow everyone to benefit from the advance. So even if you ended up in a placebo group, you would have a chance of beginning early treatment.

If at any time during your participation in the study, you find out what group you're in (and you shouldn't know), tell your doctor. It is very important that he or she know immediately so that the IRB, FDA, and sponsoring company can monitor whether this has any effect on the results of the research.

After the study

At the time you complete the study, or at the end of the entire trial, you will be told which group you were in.

CHAPTER VI WHO'S MAKING MONEY FROM MY PARTICIPATION?

It is an unfortunate fact of life that there are many people who will make a great deal of money from your enrollment in a research study. You will not be one of them. As discussed in Chapter III, you are the only one who is actually barred by regulations from profiting from clinical research. Since it's your body that is providing all this money, it is only fair that you know who is profiting from the use of your body.

While it's obvious that the sponsor of the study stands to make money if the new product is approved, the others who may make money are not so obvious. They include the FDA, the IRB members, the DMC members, and most importantly, your doctor.

How Much Is the Sponsor Making?

Unless this is a Phase IV study, the sponsor is not making any money. It's more likely that the people working at the sponsor are panicking about what the study is costing, and whether or not they'll still have jobs when everything is over. At this point in drug or device development, it is no fun at all to be the sponsor. But that doesn't prevent a sponsor from using this time to develop good personal relationships with the doctors actually running the trial. One of those doctors is yours!

How Much Is the FDA Making?

Depending on the size of the company sponsoring the research, they may have paid the FDA a hefty fee for the review and (hopefully) the approval of the new product. The Prescription Drug User Fee Act (PDUFA) allowed pharmaceutical and biotechnology companies to pay a hefty fee to expedite the review and decision process. Many believe that this act has actually gutted the independence of the FDA, and allowed the large companies control over it. I don't subscribe to that belief whole-heartedly. If the user fee was put into a general governmental fund then I have no problem with it. Why shouldn't people pay for the services they use? But the money from user's fees goes for the salaries of the very FDA employees who review and approve research. As it stands now, how can those FDA employees avoid thinking about job security when reviewing research from companies that pay users fees?

If you would like further information on the impact of PDUFA on drug safety, please read Marcia Angell, M.D.'s book, [The Truth about the Drug Companies: How They Deceive Us and What to Do about It](#). Her presentation of the finer points of this issue is easy to understand, accurate, and a bit frightening. The good news is PDUFA must be renewed by Congress every 5 years, and 2007 is the year it's currently up for renewal.

You need to ask if the sponsor of your research usually pays user fees to the FDA. Your physician may not know, but should be willing to find out for you. If a company normally pays the fees, think carefully about whether you want to be in trial.

This usually breaks down into a “big” company versus “little” company item. Large drug companies and device companies have the resources to pay the FDA to speed up the review process. Smaller companies, who depend on venture capital, usually don't. Since smaller companies are also more inventive, it is more likely that one of their studies will be of benefit to you.

How Much Is the IRB or DMC Making?

IRBs and DMCs are supposed to provide you with some measure of protection. In the DMC's case, its allegiance is more to the overall safety of the study than to the protection of subjects, but anyone looking out for safety is looking out for you in one way or another. In the IRB's case, the sole reason for its existence is to protect human beings. If it is doing anything else, then it is not following the regulations.

But let's get real. The people who serve on IRBs and DMCs are very busy people, and they usually are keenly aware of their value. So it's not surprising to learn that most DMC members and many members of “central” IRBs are paid for their time. And who's paying for their time is the very company who is sponsoring the research.

Make sure you ask your doctor about possible IRB or DMC compensation. He or she may not know about it, but should be able to find out something for you from the company.

How Much Is Your Doctor Making?

This is the \$64,000 question. And it is likely that over the course of the study, \$64,000 is close to how much your doctor will make. According to Marcia Angell, M.D., the average amount per patient that doctors received for studies was \$7000 in 2001 (p.31, [The Truth About the Drug Companies: How They Deceive Us and What to Do About It](#)). While there is no information readily available for 2006, my experience with trials from 2002 until the end of 2006 suggests that number is now between \$10,000 - \$12,000 per patient.

If a company proposed paying **you** \$10,000 - \$12,000, the study would never be approved. That amount of money is high enough to be considered coercive. You might agree to some pretty dangerous research for that amount of money, particularly when you're weathering a bad financial patch. So why is it that no one is worried about whether that amount of money might be coercive for your physician? Remember, that's the amount he will receive per patient, and he will probably enroll 5 patients at a minimum. The total your doctor could make is \$50,000-\$60,000. Is that amount coercive?

Many doctors genuinely believe that they cannot be coerced. They genuinely believe that they are intelligent enough and educated enough to avoid being influenced by money from the drug and device companies.

Unfortunately, many investigators ARE seduced by all that money. If you talk to someone who works in Clinical Affairs at a contract research organization (CRO, an organization hired to conduct research), that person will tell you about the numbers of patients that are enrolled in violation of exclusion criteria across all the

trials they supervise. You'll be surprised by how many physicians enroll patients in trials the patients shouldn't be in. If you talk to someone who oversees safety issues at a CRO, you'll hear about how many of the SAEs that they review are for patients with waivers, or who are protocol deviations. These, too, are patients who should never have been in the studies.

While most of the errors in enrollment are unintentional or due to sloppiness, there are some doctors who actually deceive the patients they're planning to enroll in studies. Here are just two examples I've encountered in the last two months:

My husband's orthoped (a doctor who specializes in problems of the skeleton and joints) tried misleading us about the trial he wanted my husband in. The company who supplies the artificial knees the orthoped uses is trying to get their new (and already approved) knee labeled as supplying more than 120 degrees range of motion. The orthoped was trying to cherry-pick patients who already had greater than 120 degrees to be in the study. My husband, Don, had more than 120 degrees. The doctor began by telling us that the only way Don could get the knee was by being in the trial. While he was talking to Don, I used my cell phone to go online where I discovered the knee was already approved. I then asked the doctor what phase trial it was, and he said phase III. I said that was odd, as the knee was already approved. Since he didn't know me as anyone other than "Don's wife", he was clearly surprised by my comments, and said it was more of a phase IIIb. I countered that it sounded like a phase IV, and asked to see the consent. When we read it, it was clearly labeled a phase IV, and the consent clearly said that the knee was available outside the trial. The physician's response to this was that he does so many trials he didn't remember all the specifics.

At a data safety monitoring board (DSMB) meeting that I attended at the end of February, the sponsor was complaining about the difficulty of enrolling patients in the trial. A premier surgeon, well-known and well-respected in his field (and fellow member of this DSMB), laughed and said that in his opinion, doctors need to be given training in how to convince reluctant patients to enter a trial. He said that you need to trade on your relationship with the patient, and tell them "contrary to the informed consent, do you think I'd enroll you in anything dangerous? This is the best thing for you." I wrote this exchange down because it was so surprising. The other MDs in attendance laughed, and agreed. The sponsor asked this surgeon if he would be willing to train her investigators....

Physicians like these are few. Most doctors try to be ethical. But the amount that's being paid per patient is now so large that a doctor makes serious money from a single trial. It's hard for the psychologist in me to be persuaded that physicians can't be coerced by money, but patients can. Think about it. If doctor's were paid only what it cost them for a trial, plus the same amount as a patient, would they be investigators? I think most of them wouldn't.

The only hope for patients maybe the CROs. Even though CROs are paid to do the research by the sponsors, CROs represent enough additional independence from the sponsor to prevent many of the problems. CROs don't want any black marks against them with the FDA, and will send out warning letters to sponsors about investigators they believe are dangerous. The purpose of a warning letter is to demonstrate to the FDA and other government organizations that the CRO knew right from wrong, and attempted to stop an unethical or sloppy investigator from putting subjects at risk. Sponsors hate receiving those letters; they know the CRO is documenting wrong-doing to protect themselves. Almost always, a

sponsor will back off from including the offending investigator, since there is now a documentary trail showing a pattern of poor research conduct.

Why do companies pay doctors for the use of your body, instead of paying you? The first reason is because by law they can't pay you very much. But Big Pharma has a track record of getting around those kind of obstacles. They have lobbyists in Washington, D.C. who make sure that our senators and representatives listen to what the large drug and biotechnology companies want. If the large companies believed that you were the ones that should get the money, then they'd make sure the laws were changed so that you could. The major reason that the doctors get paid large amounts instead is because large companies know that the doctor is where they make their money. Currently, drug and biotechnology companies spend millions every year to gain access to our doctors. They pay for lunch for the entire office in order to pitch their products. They pay for educational workshops and expensive educational trips just for the 20 minutes that they are allowed to talk to the assembled doctors about their drugs and devices. They pay doctors to present the results of the company's research at professional meetings. So why wouldn't they prefer to pay the doctor to paying you?

The problem of money from large companies flowing to doctors is so pervasive that Vermont and Minnesota have enacted laws that demand that companies report how much they spend on interactions with physicians. These so-called "sunshine laws", so called because they're supposed to shine a light on the process, are not having the desired effect, though. According to an article published in the March 21, 2007 issue of the Journal of the American Medical Association ("Pharmaceutical Company Payments to Physicians: Early Experiences with Disclosure Laws in Vermont and Minnesota", by Joseph S. Ross, MD, MHS et al.), most payments to physicians exceeded the \$100 limit agreed to by the

industry, but most companies failed to comply with the laws, citing “trade secrets”. Tell me, what is a trade secret related to paying physicians? Are they concerned about the effect on the public of learning how much money is funneled to doctors each year?

The Journal of the American Medical Association published an editorial in the same March 21, 2007 issue, further elaborating concerns with drug company payments to physicians (“Sunshine Laws and the Pharmaceutical Industry”, by Troyen A. Brennan, MD, MPH, and Michelle M. Mello, M Phil, PhD, JD). The editorial concluded with:

“Drug companies’ attempt to evade regulation may backfire, as public resentment over non-compliance with existing laws sparks demand for additional regulations.”

Most of the rest of us non-medical people recognize that doctors are also human. All that intelligence and education doesn’t mean they are above being influenced by money. In fact, there are a growing number of voices within the medical profession itself raising alarm bells about the impact of all this research money.

For instance, the Journal of the American Medical Association (JAMA) has been tightening the standards that doctors must meet before they can publish an article in JAMA. Prior to 2001, most within the American Medical Association felt that as long as doctors reported possible financial conflicts, that was enough. In 2001, however, JAMA concluded that simply disclosing a conflict of interest was not sufficient, as it did not remove the source of the conflict. JAMA added some rules that required doctors to specify “the role of the funding organization or sponsor in the design and conduct of the study...” (see Reference 7 in Appendix 2). This

was aimed at allowing its readers a full picture of the financial conflict, and then to draw their own conclusions about the worth of the study to their practice.

But by 2005, JAMA concluded that these safeguards were not enough to prevent money (i.e., financial conflict of interest) from possibly tainting the study results reported in articles, and included significant new safeguards in its acceptance policies. In its editorial in the July 6th issue, JAMA stated that “the perception that conflicts of interest of financial concerns may have potentially detrimental effects on medical science has prompted medical journals to critically examine and more vigorously enforce policies for disclosure of potential conflicts and for reporting of relationships with industry” (see References 8 & 9, Appendix 2). Now JAMA required that “All authors of all manuscripts submitted to JAMA (including research reports, reviews, opinion pieces, letters to the editor, and book reviews) are required to report potential conflicts of interest, including specific financial interests relevant to the subject of their manuscript.” Concern at JAMA about clinical trials in particular was high enough to warrant this:

‘In addition, beginning September 13, 2005, randomized clinical trials must be registered in a publicly accessible clinical trial registry, such as clinicaltrials.gov or one that requires the minimum registration data set as determined by the World Health Organization and the International Committee of Medical Journal Editors.’

The reason for this requirement is that drug companies try very hard to avoid telling doctors about studies that show that a product **doesn't work**. They do not register information that is negative. JAMA is trying to get more of that type of information into the public arena, so that everyone, doctors and patients alike, will know about medicines that don't work, or are not safe.

Why would JAMA, and other publications like The New England Journal of Medicine have to do this? Because they are concerned that the money that doctors like yours receive is influencing how they care for patients.

In addition to the amount your doctor is paid for each patient, your doctor may be receiving even more money. If a study is slow to enroll enough subjects, your doctor may be offered a financial incentive to enroll a certain number of people in a certain period of time. That incentive can amount to thousands of dollars more for your doctor.

You must carefully consider if your doctor is suggesting you participate in research because this study is best for your condition, or whether s/he is suggesting it because the study is best for her bank account. You also need to determine if the study she is proposing to you is the best one for you, or whether she is recommending it because she wants to get the greatest possible financial reward for your participation.

Ask your doctor what he's being paid. Federal regulations don't require that you be told what your doctor gets paid for your participation in research, so you may not get an answer. If he won't tell you the exact price, quote the \$10,000 - \$12,000 average to him, and ask him if he's in that ballpark.

Your doctor will tell you that he or she is only reimbursed for expenses. In my family's experience, that is always what the doctor says. This is not completely true, though. It doesn't mean that your doctor means to lie to you. It's likely that it's what he or she prefers to believe.

For an example, your doctor will tell you that the amount the company pays him is to cover office expenses and the research coordinator's salary. First, you and your insurance company pay for office expenses. If that weren't the case then ALL doctors would do research. Second, a research coordinator is someone a doctor hires to handle MULTIPLE research studies, not just one, and no one hires the coordinator until there's already enough research money to pay for the position. So the study is not ONLY for covering office expenses and the coordinator's salary.

Your doctor will likely tell you that the money she receives includes your medical tests and procedures. You need to ask for more information about this. Most of the tests and procedures will be paid for by insurance because they're part of your normal care, and usually the others that are required by the study are paid for monthly by the company, and not on a by-the-patient basis. If you're not satisfied with your doctor's answers, call a local hospital, and ask them what they charge for the same procedure. Also, remember that many of the procedures are done in the doctor's office, or with companies that doctors own and operate, so that this is not "reimbursement" but what the doctor would usually make.

The next thing you're likely to hear is that the hospital and/or university are making a profit from the payment that your doctor receives. That's very true. And since the hospital or university's facilities, electricity, heat, and equipment are being used, that's only fair. But ask specifically what the hospital is getting. It's usually a very small percentage of the money (10-15%). And don't forget that your doctor profits from the money the hospital or university receives. The more money that your physician brings in, then the more salary and power your physician commands.

Ask your doctor very specifically what dollar amount he or she is receiving for you. Tell him or her it doesn't matter how much is for expenses. Any publicly traded company has to let its stockholders know about financial conflict of interest. And the money that your doctor receives for your participation in research absolutely impacts your care, whether your doctor believes it or not.

Currently, federal law requires that your doctor disclose if he or she has a financial stake in the company doing the research, although the law does not require that you be told. Nonetheless, you need to ask your doctor if:

- He holds stock or stock options in the company
- He is a paid consultant of the company
- If he receives educational money from the company.

However, federal law does not ask if your doctor gets a fee for each patient.

Here's the bottom line:

Compare all of this to what you're making, and what you're risking. If your doctor is making much more than you, do you believe that amount is justified? If you do, enroll in the study. If you think that the investigator is making too much money to be objective, then don't enter the study.

CHAPTER VII WHO IS INDEPENDENTLY WATCHING THIS RESEARCH, AND HOW DO I CONTACT THEM IF SOMETHING GOES WRONG?

There are three possible watch dogs tracking the research study you're in: the Food and Drug Administration, an institutional review board, and a Data Monitoring Committee. Some studies will have all three groups. Some will have only one or two. You need to know which ones are involved in your study, so that you'll know who to contact if something goes wrong, or you suspect that something has gone wrong. There is a 4th watch dog who has recently started examining whether humans are protected during research: the Office of the Inspector General of the Health and Human Services Department of the US government.

Before the study

All studies involving the use of human beings must be approved by an **institutional review board**. The exceptions to this are few, and involve tissue or data that have already been collected, studies where people's behavior is observed (no actual intervention), and a few others. For additional information on these exceptions, please see "IRB" in the Glossary of this book. Almost no research study can take place in this country without an IRB reviewing it, and determining that risk to human subjects has been minimized as much as possible

If your study is a clinical trial for a new product that a company wants approved, then the **FDA** is watching this study. It enforces a raft of regulations aimed at

lessening the chances that you will be harmed while information is gathered about whether a new product should be available for sale in the United States. Ask your doctor if the FDA is overseeing this trial.

Data Monitoring Committees are relatively new, and more and more studies have them. However, they are not a requirement, so it is very possible that your study may not have one. You need to find out if a DMC is reviewing your study. If it is, then you know there is additional safety scrutiny taking place.

IRBs and DMCs are supposed to provide you with some measure of protection. In the DMC's case, its allegiance is more to the overall safety of the study than to the protection of subjects; but anyone looking out for safety is looking out for you in one way or another. In the IRB's case, the sole reason for its existence is to protect human beings. If it is doing anything else, then it is not following the regulations.

But let's get real. The people who serve on IRBs and DMCs are very busy people, and they usually are keenly aware of the value of their time. So it's not surprising to learn that most DMC members and many members of "central" IRBs are paid for their time. And the one paying for their time is the very company who is sponsoring the research.

You need to ask your doctor whether the IRB that approved your study is central or local. If your research study was approved by a "local" institutional review board (one comprised of members of the hospital or university where the research is conducted), it is unlikely that any members are being paid. The members are generally serving on the IRB as a public service, or because they are very interested in research ethics. Local IRBs are usually very thorough and very

conservative, which means that they can drive doctors and companies crazy. It can take months to get an approval, and sometimes IRBs ask for changes to a study's design that aren't remotely feasible.

Because of these problems, “central” IRBs were created. These IRBs are not in the same community as you. They frequently aren't even in the same state. While some members may volunteer, the majority are paid for their service. While they aren't paid directly by the drug companies, they are paid by the IRB's administration which is paid by the drug companies. Central IRBs are careful to follow the same regulations as local IRBs. But their distance from the communities the research will be done in makes them much less vested in the potential problems the research could create. Don't get me wrong. These members are ethical, but they don't know the standards that your community lives by. They may approve research that a local IRB wouldn't.

They are, however, well-organized, well-trained, and fast. You can't blame sponsors for wanting to use them.

But you definitely need to be more careful in considering involvement in a study approved by a central IRB.

After all, they make money from approving research, not from disapproving it.

Once you've determined if the FDA and DMC are involved, and whether your study was approved by a central or local IRB, you'll have a better idea of who's watching this study.

During the study

If you've decided to consent to be in the study, you need to do some homework now that you're in it. First, you need to get to know your IRB. Your consent form should have the name of a contact at your IRB. Call that individual up, and either ask for a meeting, or ask if he or she has time to answer some questions for you.

Your first question should be the exact name of the IRB or independent ethics committee who approved it. Next, ask who the chairman of that Board or Committee is. It could be that you're talking to that person, but in case you're not, you'll need the names.

Next you want to know something about the IRB members. By federal law there must be:

- A minimum of 5 members
- A mix of men and women
- A mix of race and backgrounds
- Should have the experience and expertise to be able to review the research (so members will mostly be M.D.s and Ph.D.s)
- Should have individuals who know the law and regulations that govern research
- Must have a someone who doesn't work for the institution or company, and who is not related to someone who works for the institution or company
- Must have someone from a non-scientific background (can be the same person as the one not affiliated with the institution or company).

Once you're satisfied that the IRB members meet the requirements listed above, ask about how the IRB handles research that's submitted by one of its own members. They are required to have a documented policy.

Next, ask if you can see the parts of the IRB minutes that cover the approval of the study you're in. Most IRBs will share that information with you readily. They're not required to, so don't be offended if they decline. Instead, ask the IRB official what the findings were to the following issues [all IRBs must document (in writing) that it has assured these things]:

- Are the risks you're undertaking in the research as minimal as possible?
- Are the risks you're taking on reasonable when weighed against the benefits you'll receive? In other words, if you're taking on considerable risk, is it likely that you'll receive considerable benefit?
- Are all patients with your condition eligible for the study, and are the ones who actually enroll selected fairly and impartially? This means that your doctor shouldn't be cherry-picking the healthiest or the sickest patients, and shouldn't be selecting them based on how much money they make, or how important they are.
- How do they document that each patient gives truly informed consent? How do they assure that you don't agree to participate in the study until you completely understand it?
- How do they verify that each patient has given consent?
- How is safety information being monitored?
- How is the IRB ensuring that your privacy is protected as much as humanly possible, and that all your information is kept confidential?
(In addition to the federal research regulations that protect you, the

Health Insurance Portability and Privacy Act (HIPPA) gives you additional safeguards to your privacy, by law. The informed consent should tell you exactly who will see your information (usually your doctor and his staff, the company sponsoring the research and anyone they hire to watch the study and the FDA)).

- What additional steps has the IRB taken to make sure that prisoners, pregnant women, the handicapped, mentally disabled, or economically or educationally disadvantaged haven't been pressured to take part in the study?
- What was the cost/benefit ratio determined to be? If an IRB member can't explain this, then it wasn't actually considered. Many IRBs ignore this important concept. For instance, there are a large variety of medicines available to treat high blood pressure. There really isn't a need for any new ones. But companies want to make new ones because they can patent them, and while they are patented no one can make a generic version. Since there are lots of people with high blood pressure, and companies like to spend millions of dollars on direct-to-patient advertising, they can make a fortune with a new blood pressure medication. Yet any research study involves risk, particularly when they're sorting out how much of a drug needs to be given. Do you really want to put your liver, heart, and kidneys at risk to test something that **ALREADY EXISTS** and **ALREADY WORKS**? The cost/benefit ratio in that situation is slanted in the cost to you, not the benefit to you! An IRB should have considered this.

Now that you know more about the IRB membership, and the steps they took in approving your study, you'll want to dig a little deeper into the information about

the member (or members) that is “non-affiliated” (not from the hospital or university) and “non-scientific.” The intent was to make sure that someone like a person who would be in the study would review the research. This was a really good idea, since that person could say if the informed consent was not easy to read and understand. That person could ask the nuts and bolts questions about whether what was asked of the patients in the study would interfere with their work, their families, or other aspects of their lives. That person could point out when a procedure that seems routine to doctors was actually painful or scary to patients.

In the literature surrounding IRBs, this person is sometimes referred to as the “community” member, and you want to determine to what extent this person is really from the community. Unfortunately, this member is usually a Ph.D. scientist instead of an M.D., or a nurse, or someone else from a medical or technical background. Many of these people owe their continued employment to the doctors who want to perform research. This means that they are looking out for their bosses, not for patients. You’ll want to determine this.

If your study has a DMC, then this is the next area to explore. This will be more challenging. You need to ask your doctor the names of the DMC chair, and the DMC statistician. If your doctor doesn’t know, and the sponsoring company won’t tell him, ask if you can see a redacted copy of their curriculum vitae (their resumes). What you want to see is that the DMC chair is experienced in the area of medicine being researched, and has some previous experience on DMCs. With the statistician, you want to be sure that the sponsoring company doesn’t directly employ this person (either as a company employee, or as a contractor), and that the individual has the statistical background and DMC background necessary to interpret the safety data correctly.

Next, you want to understand the degree to which the DMC members are in the employ of the sponsor. When a company wants an independent DMC to review their safety data, they need experienced men and women. They need physicians experienced in the area under study. They need a biostatistician who can help them sift through the data and look for patterns. Physicians and biostatisticians are not cheap. There also aren't that many of them. So if a company wants to put together a DMC, it's going to have to pay them. The rate varies with the average being around \$250 an hour.

So how are they independent? That's a good question. First, they are not employees of the company, which helps. But that doesn't completely remove the conflict of interest. That's usually accomplished by the DMC Charter, and by conducting decision making during an Executive Session. A DMC Charter lays out all the obligations that the DMC has, and states specifics about the conduct of meetings. This allows the company some control over costs (you don't want a DMC to spend so much money on data analysis that you can't complete your trial!), while allowing the DMC members to determine at what point the company can't be involved at all. At a DMC meeting, there are usually two parts: an open session that anyone from the company can attend, and an Executive Session where ONLY board members meet.

While this is not a perfect solution to a conflict of interest, it's realistic.

The next area to explore is the FDA. You need to find out what branch of the FDA is overseeing the research, and find out who the project manager is. Ask your doctor which of the following divisions is responsible for the review of the project: 1) Center for Drug Evaluation and Research, 2) Center for Biologics Evaluation and Research, or 3) Center for Devices and Radiological Health. Once

you know that information, ask for the name of the project manager. If your doctor doesn't know, and can't find out from the company, call the division responsible for the trial. You'll find information to start you on your search in the Glossary. The FDA will be very helpful. They actually hear from very few research subjects, and are delighted to help.

Once you have the project manager's name, that's all you'll need for now. Put it with your informed consent form in a safe place, so you'll have it if you need it.

Finally, take some time to get familiar with the web site for the Office of the Inspector General of Health and Human Services. The link is provided in the Glossary. While the OIG is not directly responsible for protecting you, it is responsible for the ethical and legal behavior of federal employees at the FDA. As you'll find in the next chapter, the OIG has identified some truly powerful tools that you can employ if you believe that anything has been done illegally, or in some cases, just sloppily.

After the study

The IRB is responsible for closing out the study, and your doctor must report any safety issues to it. Check again with the IRB to find out if anything was reported that you're unaware of. Since you've asked your doctor to tell you about any adverse events or serious adverse events, there should be no surprises in what you find. If there are surprises, or if you don't see information about safety issues that should be there, report it to your doctor, the IRB, and the project manager at the FDA.

CHAPTER VIII **WHAT DO I DO IF SOMEONE BREAKS OR BENDS THE LAW?**

This chapter has been difficult to write. In spite of all the negative things I've written about how research is conducted, I genuinely believe that participating in research is one of the most important community services we can get involved in. I've spent most of my adult life involved in the design of studies, and the oversight of them, and I know what good they can do. We're now close to ending cancer, thanks to research, and the last 100 years have seen remarkable progress in treating heart disease and stroke, again thanks to research. None of us want to see achievements such as these stopped. But in this chapter I'm going to lay out tools for you that have the potential of seriously harming research in the United States. Please use them wisely.

The original outline of this chapter calls for explaining to you all the mechanisms available to you for reporting research misconduct, or to ensure that your doctor has. Essentially, that outline calls for you, the patient, to do the jobs that countless other people are actually supposed to do. As I was creating that outline, it occurred to me that there was very little incentive for you to do that reporting, other than your own sense of ethics and the desire to protect others from harm. Since you are probably a very busy person, the chances that you would take on a watch dog role are pretty slim.

Then I found an article in the Journal of the American Medical Association, entitled "Legal Issues in Scientific Research" in the January 2, 2002 issue. The authors (Paul Kalb, MD, JD, and Kristin Graham Koehler, JD) were providing cautionary tales about what could happen if the federal government decided to

come after a doctor, university, or hospital for the misuse of research funds. This article was based on recent activities in the Office of the Inspector General (OIG), Health and Human Services, and they will be covered in detail in this chapter. The rock-bottom message is that the federal government may pay subjects who step forward with information about research misconduct or just plain sloppiness.

In 1998, the OIG issued a report that strongly criticized the federal oversight of IRBs and clinical investigators (doctors like yours). The report specifically recommended the following:

- Give IRBs greater flexibility and accountability
- Insist that IRBs provide greater oversight of research, and better protection of human subjects
- Establish education requirements for IRB members
- Insulate IRBs from conflicts of interests, particularly from the increased commercialization of research and the growing importance of research money to universities and hospitals
- Decrease IRB workloads. The OIG felt that IRBs reviewed too many research studies, making a thorough review of any one of them unlikely.
- Increase the federal oversight of IRBs: this would lead to new and more specific regulations; increase the number of IRBs that are audited in any given year; and increase the audits of clinical investigators, to ensure they are conducting their studies according to the rules that protect human subjects.

In 2000, the OIG reported on the progress that the FDA had made since 1998. It found the progress disappointing. As of October, 2005, the OIG still found little progress within the FDA.

This means that while the OIG has raised awareness about potential problems in the protection of human subjects, little has occurred to address the problems. But it turns out that you have legal means to pursue sloppy research – even if you have not been directly harmed.

According to Kalb and Koehler in their JAMA article in 2002, the number of whistle-blower reports to the FDA in the years since 1998 have increased 10 fold. These reports have been about failure to assure informed consent from subjects, poor safety reporting, poor record keeping, and failure to follow the study protocol.

The authors point out that many of these reports have been followed with submissions under the False Claims Act. This act allows that up to \$11,000 per claim will be paid in straightforward penalties by an institution violating the Act. But it's the potential money damages that are staggering. Violators may be compelled to pay up to three times a damage reward per claim, in addition to the \$11,000 in penalties. This can quickly add up to hundreds of thousands of dollars for a single study, and to millions of dollars for several studies at a single institution.

According to Kalb and Koehler, private individuals can bring suit on behalf of the United States under the False Claims Act, and may then be paid up to 30% of the money the federal government recovers as a result of the suit. This means that if you believe that the study you're involved in has not been conducted according to the rules, or if you believe that your doctor misled you to get you to participate in the study, you can sue, as long as the hospital or university where the research was done receives federal money (from research, Medicare, Medicaid, etc.). If your

suit uncovers systematic problems at the university or hospital (such as an improperly constituted IRB, or an IRB who bows to internal pressure to approve questionable research, failure to disclose financial conflicts of interest, failure to keep your data confidential, etc.), you could receive nearly a third of the money paid out for multiple claims across multiple studies!

This means that there is a real financial incentive for making sure that the IRB that approved your research followed all the rules. It means there is a real financial incentive to make sure your doctor reports any safety issues you have, no matter how minor.

But use this power wisely. I don't think any of us want to live in a world where research is rarely done, or has stopped altogether. Without our willingness to join in research, and our understanding that no one is perfect, medical discovery could be hurt.

CHAPTER IX HOW IMPORTANT IS THIS RESEARCH?

Most people believe that if they are asked to take part in a research study, they will be helping others, even if they themselves get no real benefit. They believe that most research helps humans as a whole.

Unfortunately these days, the majority of research studies are for drugs that are not new, or novel. They are called “me-too” drugs, and they involve the slight modification of drugs that already exist in the hopes that the drug company can cash in for very little effort, and the outlay of as little money as possible.

It’s one thing to risk yourself for a study that might benefit you or others. It’s another thing entirely to risk yourself to put money in the pocket of big business. To decide which of these your study is, you need to know how important the research is.

In this chapter, we’ll review the key items you’ll need to know to determine if the research is important enough to risk your time and your health. There are 5 fundamental questions that you need answered before you can make an informed decision to take part in the study

Is it a National Cooperative Group?

If you or a loved one has cancer, any one of the national cooperative groups could provide you with cutting-edge cancer treatment. These national

groups cover a range of cancers, and allow for research to be conducted all over the country, and yet be analyzed as a single study. They are usually very well-designed studies, and may offer you the best possible chance for overcoming the odds. If the study you're considering isn't actually offering you treatment, then it is gathering information on your disease that can benefit others in the long run. This kind of research is worthy of your consideration, and will not waste your time or unnecessarily put you at risk.

Some of the best known of the national oncology groups are listed in the glossary. Your doctor or research coordinator should be able to provide you with the name of the group, and you should be able to find out further information about it on the web.

Government-sponsored or Company-sponsored?

The Federal government sponsors millions of dollars worth of research each year. This research is usually in very important areas of medicine, and has been found by many levels of government to be necessary. Research of this type is usually funded by the National Institutes of Health, or one of its many divisions. On occasion, research may be funded by the Department of Defense, particularly where new vaccines are needed against possible biological weapons, or diseases that may affect our troops. Government-sponsored research is usually well-designed, cutting-edge stuff. It is usually worth your time, and the risk that you assume.

Sometimes states sponsor research. This used to be pretty unusual until the Federal government began prohibiting research in certain areas, such as stem cells. Several states have decided to fund research in areas the Federal

government will not. It's still a little early to know how well-designed and safe these types of studies will be.

Because of the financial oversight that government research receives, it's likely that a government-sponsored study is important enough for you to consider joining. It is also less likely to involve excessively large payments to your doctor. As a rule of thumb, these studies are generally worth your time and effort.

As discussed in previous chapters, the majority of clinical trials are sponsored by pharmaceutical and biotechnology companies. If the study you're considering is funded by a company, then there are several more questions you need to have answered before you'll have all the information you need to know to decide if the study is important enough to be worth the risk.

Phase IV or Phase I-III Trial?

Phase I- III trials are the research studies that are done to gain approval for a new product to enter the market place. (If you want detailed definitions of phase I, phase II, and phase III trials, please see the glossary.) All of these phases of product development are necessary before the FDA will consider a New Drug Application or the comparable applications for a device or a biologic. If you participate in a phase I, phase II, or phase III study, you can be confident that the research is really necessary (although “necessary” is not the same as “important”).

The picture is not so clear if the study is a phase IV trial. A phase IV trial may also be called a late phase development trial or a post-marketing study. It may be called a pharmacoeconomic trial (looking at various aspects of the products costs), or a registry. All of these are names for the same thing.

By definition, a phase IV trial occurs AFTER the product has been approved by the FDA. Sometimes a phase IV study is required by the FDA to gather additional information on safety, or to look at the long-term effects of using the product. Sometimes the product has been approved for use for one disease or condition, and the company now wants to see if the product is effective in treating some other disease or condition. If either of these is the case in the research you've been asked to join, then this is probably a legitimate use of your time and your body.

But there are some other reasons that companies will sponsor a phase IV trial. The chief reason for a phase IV trial is to get you and your doctor used to a brand-new product. The hope is to move you from your current treatment, which is probably working fine, and get you to start taking a more expensive “me-too” product. Pharmaceutical companies spend millions of dollars to get doctors to start prescribing the new medicines, and will frequently stretch the truth, promising that the new product is better than the ones that are already in use, when the product is actually performing at the same level.

Of course, the companies never admit that this is what they're doing. Instead, they make up reasons that sound scientific, but really aren't. Let's say that the company has new medicine to treat high blood pressure. There are already many drugs available for high blood pressure, most of which

you can get quite cheaply. So the company will claim that they believe that this new drug may be more effective in women, or in Afro-Americans, and that they want to study this more thoroughly. They don't really care if it's better in a subgroup. What they care about is that you're now taking their drug, and that you will probably prefer to stay with it, rather than go on to something different.

This kind of study is absolutely not important. Why should you waste your time, and risk your health when the only thing you'll gain from the study is a bigger bill at the pharmacy?

Your doctor or research coordinator can tell you what phase study you're about to enroll in. If it is a phase IV study, you need to ask a lot more questions about the purpose. You'll need to determine if it's gathering additional long-term safety data, establishing a new use for the product, or just trying to switch you to the company's new drug or device. Remember that newer is rarely better; just more expensive.

Device, Biologic, or Drug?

Companies sponsor research in three broad categories: devices, biologics, and drugs. Devices are not as influenced by the "me too" problem. Usually devices are too distinct in their design to allow for slight tweaking to get someone a new patent. Usually, devices are new and different solutions to a problem. Some examples of devices are: 1) stents used to keep blocked arteries open, 2) the small cameras currently in development that you swallow, and that will take the place of colonoscopies, 3)

equipment used to shorten the time of surgeries and procedures, or to make recovery easier on you. Usually device studies are important enough for you to consider participating.

Biologics are a new category. They've come about as a result of the work of the Human Genome Project, and other work aimed at understanding DNA and the cells in our bodies. Many people decline to be in studies of biologics, fearing that this is a Frankenstein-like idea, and that they could be harmed. If that kind of thing bothers you, then don't participate. However, most studies for biologics are important enough for you to consider participating in them, and offer real hope for the treatment of conditions that have no other possible hope.

Drugs, of course, have been around for a long time. It's been a long time since the largest pharmaceutical companies have actually come up with a new and different drug. Truly new drugs usually come from governmental research, or from small biotechnology companies. Large pharmaceutical companies then license these drugs, and put them into large-scale clinical trials. This category is most likely to waste your time, and put you at unnecessary risk. You need more information before you can determine if a drug study is important.

“New” Drug or a “Me-too” Drug?

In her book, The Truth about the Drug Companies: How They Deceive Us and What to Do about It, Marcia Angell, M.D., gives an excellent overview of “me-too” drugs, and a scorching indictment of how little innovation drug

companies do these days. Dr. Angell points out that very few drugs are what are called “new molecular entities” or NMEs. She reviewed FDA approvals from 1998 through 2002, and found that only 32% of the drugs approved were considered new molecular entities (page 54). That means that if you’re considering enrolling in a drug study, there’s a 2 out of 3 chance it’s a “me-too” drug.

Even worse, Dr. Angell found that only a few of the NMEs were given a priority review by the FDA. A priority review is given when a new drug is expected to be better than anything else on the market now. All other drugs receive a standard review. Dr. Angell’s review of the drug approvals from 1998 through 2002 found that only 14% of the drugs were NMEs with priority approval. **That means that there’s an 86% chance that you are wasting your time, and risking your body for drug company profits only!** So if the study you’re thinking about joining is for a drug, make sure you ask if it is a new molecular entity, and if it is receiving priority review from the FDA. If the answer is no to both, the study is not important.

Research with No Informed Consent

There are a few types of research that do not require your consent. Most are harmless, and involve observation studies in public places, or surveys with no personal information attached. In the past few years, however, there has been a trend toward allowing some very serious, emergency research to be done WITHOUT the individual’s consent.

The best known example of this type of research was a study of artificial blood conducted in 1998. This research was approved by the FDA under the “Exception from informed consent requirements for emergency research” provisions of the Code of Federal Regulations (21 CFR Part 50.24, see link provided in the Glossary under “Code of Federal Regulations”). It allowed participating hospitals to administer the artificial blood, called HemAssist, to trauma victims without the victims consent, or the consent of their families. Of the roughly 50 patients treated with HemAssist, approximately 20 died (“Blood Study Halted in Emergency Rooms”, San Antonio Express News, April 2, 1998, p. 14A). The study was stopped early because of the high rate of death.

How is it that a federal agency charged with protecting you can allow this kind of thing? First, emergencies don’t allow for much time to gather informed consent. The victim is often unconscious, and the family either unavailable or occupied with other issues. If the product under consideration actually works, then the possibility of benefit to the subject is huge. The problem is that no one knows if it will work or not at the time patients are enrolled without their consent.

The FDA believes that it has covered the consent issue by requiring that communities be notified of research of this type. Newspaper articles and public meetings are supposed to allow residents of a city or county to ask questions in advance of the research starting in their area. The problem comes in that you must **opt out** of this research **at the time you are entered!** This is difficult to do when you are either unconscious or in severe distress. To counter this, the all you have to do is:

- Contact the sponsoring company (if you know who it is)
- Tell the company that you are opting out of their public research
- Get them to send you an ID bracelet stating that you opt out of the study
- Wear that bracelet until the study is completed (and you won't be told when that is!).

In a large city, you could end up wearing several bracelets all the time. This is clearly not done for your convenience, but for the convenience of the study sponsors.

To avoid being an unwitting participant in research, make sure that you inform your family and your family doctor that you do not want to participate in any research unless you sign an informed consent form. This won't save you from every possibility, but it will limit your exposure.

Also, consider contacting your senator and congressional representative to tell them that this kind of research should be stopped.

CHAPTER X CAN I NEGOTIATE A BETTER DEAL?

I'm taking you into uncharted waters now. Remember that there are many federal laws that have been developed to keep researchers from trying to lure you into research with large payments. Those laws exist for a reason. It's easier to get people to risk their health for large sums of money, or for promises of cures. Remember, too, that institutional review boards and data monitoring committees exist to make sure that you are protected, and they take very seriously any attempt on the part of researchers to give you much more than compensation for your time.

But as you've read in this book you've seen that your doctor and eventually the company that sponsors the research are making an awful lot of money from your participation in this study. It is only fair that you should begin to see yourself as the rare and valuable commodity that you are.

There's a lot of research out there. There's so much research going on that finding a subject to participate in any given study is really tough. You'll recall that part of the reason for paying your doctor thousands of dollars per patient is to get him or her to recommend that you join this study rather than another one. In other words, pharmaceutical companies and biotechnology firms are **COMPETING** for YOU! Isn't about time that you profited from this?

Now for the bad news. Unless you start screaming to your congressman and senators about this, there is no way you are going to get paid what your doctor is

getting paid. As I've said before, there are laws that forbid it. But there are other things you can negotiate for.

If you don't have insurance, or if you don't have enough insurance, consider having the company pay for more of your medical expenses. Make them pick up any co-pays for tests or surgeries. They'll scream about it. They'll say that you needed the tests or the surgeries anyway (which is probably true). So what? It is only reasonable that they pay something for the use of your body. If they say "no" to your request, don't participate in the study.

If you have great insurance, then see what additional procedures or tests you can get. If you're having an ultrasound done of your legs for the study, negotiate to have an ultrasound of your carotid arteries. Knowing if your arteries are blocked is very important, and could lead to early treatment of possible heart disease.

If you're asked to participate in a study of toenail fungus, negotiate to have someone routinely trim your nails. Toenail fungus can make cutting your nails extremely difficult. Why shouldn't you receive some benefit for putting your body at risk?

If you're asked to participate in a drug study, and the drug is for a chronic condition (like high blood pressure or diabetes), demand to have the drug supplied to you for life for free (if it's approved, of course). This has the added benefit of making enrolling you in a phase IV study less attractive, since you can never become a "paying customer" if the company has to provide you with the drug for life.

If the research study is bringing you in for visits you wouldn't normally have to make, insist on reimbursement for your time. Reimbursement for gas, parking, and a meal is nice, but your time is worth even more. Pick an hourly rate, and explain to your doctor that you will charge it for your time traveling from your home to the office, for the time you spend in the waiting room, or waiting in the examining room, for the time you spend with the doctor or the research coordinator, the time you spend for procedures and tests, and the time it takes you to get home. This is only fair. Your doctor charges for these same things when he meets with the company sponsoring the research (only he or she charges a lot more for each hour!).

If a company is not willing to negotiate with you, don't participate in the study. The more potential subjects who refuse to participate in a study because their requests were not met, the more likely it is that eventually you'll be compensated for your time. Companies should need to negotiate with you the same way they negotiate with your doctor!

If you participate in a drug study, and the drug is approved, you should receive a lifetime supply. After all, you risked yourself and your health for the drug company's profits.

- Drugs cost so much these days that it seems only fair that patients in clinical trials should be able to receive ongoing treatment at the drug company's expense.
- Usually, less than a thousand patients participate in the research leading to FDA approval of drugs, and frequently that number is less than 500. Supplying treatment to those who were in the studies will not break the back of pharmaceutical companies.

This kind of “payment” for your participation cannot be seen as “coercive.” Since no one knows if the drug will be successful and safe, you can’t realistically be motivated to participate based on the possibility of “payment.”

In his excellent and informative book, “What the Doctor Didn’t Say: The Hidden Truth About Medical Research” (see Reference 19, Appendix II), Jerry Menikoff makes a telling argument for subjects in research studies being paid appropriately. Mr. Menikoff points out that money is not coercive unless it is being used to force you to do something you don’t want to do. He demonstrates that it is more coercive to give you access to an unapproved product ONLY if you participate in a research study.

Mr. Menikoff argues that paying subjects an appropriate amount of money to participate in research actually tells them how truly dangerous a study is. If you give a tube of blood for a study, then you’d receive a small amount, say \$10.00. That would demonstrate that there is nothing too risky about donating blood (provided you remember to tell them they can’t grow new cell lines, or patent your genes). But if the study actually carries considerable risk (say a phase I study where the impact in humans is not yet known), then offering you \$10,000 would be a way of judging the degree to which your safety might be compromised.

CHAPTER XI HOW DO I BEST PROTECT MY CHILD?

Research regulations recognize that children are not just small adults. They recognize that they are our most vulnerable citizens, and that the parents of sick children are under intense stress. Because neither you nor your child are at your best in this situation, the federal government has determined that special safeguards are needed.

The first thing that is different is that children can't give informed consent. They don't have the capacity to. **At least one parent or the child's guardian must give informed consent.** No child can be enrolled in research without it.

Sometimes IRBs conclude that only one parent needs to give consent, if that's allowed by the laws of your state. Usually they require that both must sign, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

If you give your consent to the research, then your child will be asked to give his or her assent. The law requires the IRB to determine that adequate provisions are made for getting the assent of your son or daughter, when in the judgment of the IRB the child is capable of providing that assent. To make that determination the IRB must consider:

- Age of the child
- Maturity of the child
- Psychological state of the child.

The IRB can either determine this for the group of children to be involved in a particular study, or they can decide that each child must be evaluated on a case-by-case basis. Don't be surprised if the IRB wants someone to interview your son or daughter to determine if they're capable of giving assent.

What happens if you sign the informed consent, and your child refuses to give his assent? That depends on the IRB, and what it decided when it approved the research. The IRB can decide that the assent is not a necessary condition for going forward with the research, if it determines:

- That the capability of some or all of the children is so limited that they cannot reasonably be consulted
- That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation
- The clinical investigation involves no more than minimal risk to the child
- A waiver of the assent will not adversely affect the rights and welfare of the child
- The clinical investigation could not practicably be carried out without the waiver, and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Unless you are completely convinced that your child will benefit from a study, I urge you to accept your child's decision. There's a good reason why your child should have a say in whether he or she participates in research – it's his body!

Children can have a “sixth sense” about what is and isn’t right for their bodies. Also, kids have a good internal compass for what risks are worth the pain and discomfort.

The second thing that is different about research in children is that **the research cannot involve more than minimal risk to the child, unless the child may directly benefit from the study.** To make sure this is the case, the IRB must find and document that:

- The risk is justified by the anticipated benefit to the subjects
- The relation of the anticipated benefit to the risk is at least as favorable to the child as that presented by available alternative approaches, and
- Adequate provisions are made for obtaining the assent of the child and the permission of his parents/guardian.

On rare occasions, IRBs can approve research of greater than minimal risk, with no direct benefit provided, but **I strongly recommend that you keep your child out of any study that will not directly benefit her.**

The government has posted the following table (see next page) to guide IRBs in deciding what level of informed consent/assent of the child is suggested for what level of risk:

Category of Research Involving Children	Requirements
No greater than minimal risk	Assent of child and permission of at least one parent
Greater than minimal risk and prospect of direct benefit	Assent of child and permission of at least one parent
	Anticipated benefit justifies the risk
	Anticipated benefit is at least as favorable as that of alternative approaches
Greater than minimal risk and no prospect of direct benefit	Assent of child and permission of both parents
	Only a minor increase over minimal risk
	Likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition
	The intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child's actual or expected medical, dental, or expected medical, dental, psychological, social, or educational situations
Any other research	Assent of child and permission of both parents
	IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
	The HHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines (e.g. science, medicine, education, ethics, law) and following publication in the Federal Register and public comment

There are some specific things that **you** need to consider, too. Drug companies don't like to test their products in kids, because their liability is huge. They usually avoid having kids in studies. This doesn't stop a company from telling doctors they can use the drug in children, though, so many drugs and devices that are approved only for use in adults are in use in children. This worried the FDA, since there are obvious safety issues associated with this. To try to get companies to do adequate testing in children, they offer a 6-month patent extension to any company that examines the impact of their product in minors.

This did not have the intended effect, unfortunately. Companies still don't study drugs and devices in children UNLESS the patent on a specific drug is about to run out. Then they set up research studies that are aimed at protecting their profits, not at benefiting your child. Think long and hard about studies for conditions you usually think of as "adult", such as heartburn, or high cholesterol. Ask your pediatrician if the drug or device is already approved for adult use. If it is, ask how long the product has been on the market. If it's been available for more than 5 or 6 years, don't involve your child in the research.

If you believe that a study is really legitimate, check to see if it has a placebo group. What are the implications if your son or daughter receive no treatment at all? While you might be willing to participate in a study you might not benefit from, do you really think that's the right thing for your child?

There are some additional dimensions to the question of whether the research is important that you need to add to your consideration. You need to carefully consider if the disease or condition that's being studied is important enough to risk your child. Below are a few of the diseases/conditions that use children as subjects.

- Cancer – If your child has cancer, it is understandable that you want to do everything in your power to get to a cure. There are very few pharmaceutical companies that do research in cancer in children, so it is likely that the study proposed to you is a national oncology group protocol. These oncology groups are highly ethical, and provide innovative cancer therapies.

Unfortunately, the informed consents for these studies are usually very technical. This makes it challenging to understand what is proposed. Make sure that your doctor explains everything to you, and that you feel you have a complete grasp of what's involved.

From personal experience, I know how frightening it can be to be faced with this type of informed consent. When our son was 4 years old, he was diagnosed with a condition called *pseudotumor cerebri*. His brain was incredibly swollen as a result, and his head became adult size. While they were still trying to find what was wrong, they asked me for permission to do a lumbar puncture (insert a needle into his spine) to remove some spinal fluid for tests. The informed consent process involved explaining to me that this test that my son needed could actually kill him, or make him a vegetable. Apparently, the change in the pressure in the spinal fluid could cause his swollen brain to collapse down the spine! My husband and I talked about this at length, and concluded that the test was needed. We sat in absolute panic as the test was done. Luckily, nothing bad occurred during the testing, and our son is fully recovered.

- HIV/AIDS - If your son or daughter suffers from this disorder, of course you must do what is necessary to save his or her life.
- Attention Deficit Hyperactivity Disorder (ADHD)

There is a great deal of controversy, as you well know, about whether this disorder actually exists, or whether a disease has been made up to cover kids with high energy levels and difficulty sitting still. Whether or not the condition is real, the drugs for treating are!

ADHD is a gold mine for pharmaceutical companies. As long as there are children in the world, then there will be a steady supply of customers for their products.

It is unlikely that there will be any new drugs that represent a quantum leap forward in the treatment of this condition. Instead, drug companies are tweaking the formulas of older drugs in hopes of coming up with a new one that they can patent.

Do you really want to put your child at risk so that drug companies can make more money? Do you really think it's a good idea to risk your child's liver or kidneys for a drug that is essentially the same as the ones already out there?

- Autism – The incidence of autism has sky-rocketed in recent years. As with cancer research, it is usually national organizations that sponsor this type of research. If you're fine with the answers to the other nine questions

for an autism study, it is likely to be a study that will benefit your child, or broaden the knowledge of the condition.

Whatever you decide, I wish you the best for your child. This is a difficult time for you both, and I hope that things turn out well.

CHAPTER XII CONCLUSION AND BILL OF RIGHTS

By now you know that you must fully understand your informed consent document, and that you must safeguard your copy of it. It is the closest thing you'll get to a written contract specifying what risks you're taking on, what benefits you're likely to obtain, and who to contact if something goes wrong.

You should have a better understanding of the large sums of money that change hands when you enroll in company-sponsored research, and should be better equipped to decide if the research is worth your time and effort.

One of the free bonuses associated with the purchase of this ebook is a list of questions to take with you to the doctor. Make sure you download it so that you don't have to lug the entire book with you!

Research Subject's Bill of Rights

- You have the right to completely understand the research you are participating in
- You have the right to receive fair reimbursement for the use of your body in the furtherance of medicine
- You have the right to know how much money is being paid to your doctor for your participation in the study, so that you can decide if that amount of money is coercive

- You have the right to current information about the safety and effectiveness of the drug or device being studied.
- You have the right to be sure information gathered about you is reported properly, particularly safety issues
- You have the right to negotiate for better compensation for being in research, such as a lifetime supply of drug, or for replacing a device when a replacement is needed.
- You have a right to know how many other people are taking part in the research
- You have a right to know of any FDA concerns about the study
- You have a right to know what Institutional Review Board approved the study, and who the members of the committee are.
- You have a right to talk to the chairman of the Institutional Review Board
- You have a right to ask for every technical term to be explained to you in plain English!
- You have the right to take legal action on the government's behalf if you believe a hospital or institution is not following the law.

Remember these rights, and good luck in your research pursuits!

APPENDIX I. GLOSSARY

ADHD

Attention deficit hyperactivity disorder. This disorder was first diagnosed in school children. It is now believed that adults, too, suffer from this condition. This is somewhat controversial, as many experts believe that no such condition exists, and that this is turning minor behavior problems into a disease requiring treatment with sometimes dangerous drugs.

Adverse Event

(AE) Any safety concern occurring in a patient in a research study. These are usually minor, and the most common are headaches, nausea, colds, and flu. All adverse events must be reported to the FDA in the annual safety report, so they can determine if there are any patterns that indicate that a drug or device is unsafe.

Blinding

Process that keeps individuals from knowing what treatment group they're assigned to. Patients, doctors, and sponsors may be blinded to avoid bias from entering the results of the study.

CBER

Center for Biologics Evaluation and Research. This branch of the Food and Drug Administration oversees research into devices and drugs made from living organisms. As scientific knowledge of genes and DNA progresses, more and more drugs and devices are based on human and animal tissue.

There are new and important safety issues associated with this type of research, such as:

- Increased ability to catch diseases that currently affect animals other than humans. This is of particular importance, as new diseases in human beings are things our immune systems have a hard time avoiding. Bird flu is an example of a disease that can cross from birds to humans with disastrous consequences.
- Transfer of diseases usually obtained by other routes. An example of this is mad cow disease. Usually we get mad cow disease by eating contaminated meat. However, it is possible that if you had a drug or medical device that was made from cow serum, and that cow was infected, you could be, too.
- While genetically modified cells are generally regarded as safe, any drug or device that involves messing with DNA needs to be looked at very carefully.

For more information on CBER and its important missions, visit the CBER website:

<http://www.fda.gov/cber/index.html>

CDER

Center for Drug Evaluation and Research. This branch of the Food and Drug Administration oversees research into all drugs, except those made or derived from living organisms. For more information about the history of CDER, and about its responsibilities, visit:

<http://www.fda.gov/cder/index.html>

CDRH

Center for Devices and Radiological Health. This branch of the Food and Drug Administration oversees research into all medical devices, except those made or derived from living organisms. Examples of medical devices are pacemakers, stents, artificial valves, and many types of surgical closures. It also regulates research into anything that might irradiate human beings. For instance, MRI machines were approved by this branch of the FDA. New types of mammogram machines are regulated by this group. You can read more about CDRH and the work it does at:

<http://www.fda.gov/cdrh/index.html>

Clinical Coordinator

Individual who oversees research studies for doctors. This individual is frequently a nurse, but doesn't have to be. The clinical coordinator ensures that all data collected during the study is correct, and that subjects in the study are informed of appointments, procedures, and activities that they need to complete for the purposes of the study. The clinical coordinator is usually employed by your doctor.

Clinical Trial

Term referring to research done in furtherance of the approval of a new drug, new biologic, or new device. This term usually applies to a study that will be submitted to the FDA.

Code of Federal Regulations

(CFR) The government regulations that protect you when you participate in research. The specific parts that apply are:

- Title 21 – Food & Drugs Good Clinical Practice
 - Part 11 – Electronic Records; Electronic Signatures
 - Part 50 – Protection of Human Subjects
 - To read the “Exception from informed consent requirements for emergency research, 21 CFR 50.24,” go to:

http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html

- Part 54 – Financial Disclosure by Clinical Investigators
- Part 56 – Institutional Review Boards
- Part 58 – Good Laboratory Practices for NonClinical Laboratory Studies
- Part 312 – Investigational New Drug Application
- Part 314 – Applications for FDA Approval to Market a New Drug

Here is a link to the CRF for Food and Drugs:

http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfrv1_06.html

Coercion

Unacceptable subject recruitment methods which involve duress, undue monetary compensation or indirect pressure.

Consent Form

See Informed Consent Form

Cost/benefit ratio

IRBs must weigh the amount of risk that you assume in the study (the cost) against the benefits to be had either by you directly, or society as a whole. High costs can be offset by high benefits. For example, Louis Pasteur (who invented the process used to kill bacteria in milk – pasteurization) created the original vaccine against rabies. He tested his vaccine by giving it to a young boy who had been bitten by a rabid dog. Rabies was a death sentence at that time. The risks to the boy of receiving an untested vaccine were huge: he might die. However, the potential benefit of the vaccine was also huge: he might live. So the cost/benefit ratio was very reasonable and perfectly balanced.

CRO

Contract Research Organization. Clinical research is extremely expensive, and requires a large number of individuals with highly specialized knowledge to complete successfully. Many companies keep the costs of their drugs and devices down by using a contract research organization instead of hiring their own staff. CROs are extremely efficient at the conduct and analysis of research, and it is very likely that one is involved in your study. You can rely on a CRO to keep your information confidential, and to assure that the research is conducted in an ethical and legal manner.

Data Monitoring Committee

(DMC) Independent group of experts (medical and biostatistical) who evaluate primarily the safety data from a research study, and determine whether a new product is safe enough for the research to continue. DMCs may assess effectiveness data, as well.

Data Safety Monitoring Board

(DSMB) See Data Monitoring Committee

DOD

Department of Defense, branch of government consisting of the US Army, US Navy, US Air Force, and US Marine Corps.

ECOG

Eastern Cooperative Oncology Group. This is a group of universities and medical centers aimed at finding the most effective treatments for different types of cancers. There are over 6000 members of ECOG, meaning that even rare forms of cancer can be studied, because of the wide area of the country that ECOG serves. ECOG only conducts studies in adult cancer patients. For information on current cancer trials, visit their web site:

<http://ecog.dfci.harvard.edu/general/intro.html>

Exclusion Criteria

These criteria lay out the conditions that prevent you from being in a research study. If you meet even one exclusion criterion, then you should not be included in the trial.

Expected Adverse Event

In certain circumstances, the FDA allows the sponsor to list all expected safety events before the start of the trial. Anything listed as an expected adverse event is treated a little less rigorously than would be the usual case in research. This is usually done for studies in diseases and conditions that

already pose a safety risk to the patient. For example, someone with end stage kidney disease is already pretty sick. This individual would be at higher risk for kidney failure, stroke, and heart attacks. Since this is already the case, these would be treated as expected adverse events.

Expected Complications

These are the same as an expected adverse event.

FDA

Food and Drug Administration. This government agency is responsible for assuring that all drugs and devices that are approved for use have been thoroughly tested to be sure they are safe and effective. The FDA has a comprehensive website with loads of information at:

<http://www.fda.gov/>

GOG

Gynecological Oncology Group. This national cooperative group specializes in cancers of the female reproductive system, and their treatment. Information about breast cancer, cervical cancer, ovarian cancer and other diseases can be found at their website:

<http://www.gog.org/>

HIPPA

Health Insurance Portability and Privacy Act

HIV/AIDS

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

HMO

Health Management Organization, also known as health insurance and managed care

ICH Guidelines

The International Conference on Harmonization was established to try to make sense of the conflicting regulations governing research between countries. When you consider how many countries there are in Europe, and yet what a small amount of territory each country covers, you can understand that different regulations could really make a large clinical study difficult to do. The Food and Drug Administration has adopted the ICH Guidelines. Here are the ones that are applicable to your participation in a study:

- Guideline E6 – Good Clinical Practice
- Guideline E2A – Clinical Safety Data Management

Inclusion Criteria

These criteria lay out the conditions that must be present for you to participate in the study. If you fail to meet even one inclusion criterion, then you should not be included in the trial.

IND

Investigational New Drug. Before a sponsoring company can begin research in people, it must submit an IND application. If the application is considered safe and complete, the Food and Drug Administration assigns

an IND number. In order to get an IND number, the company has to supply information in the application on the following:

- An introductory statement and a general investigational plan
- An investigators' brochure
- Research protocols and informed consent forms
- Chemistry, manufacturing, and control information
- Pharmacology and toxicology information
- Previous human experience with the investigational drug
- Additional information
- Relevant information

Once the information has been reviewed, and the IND number given, the company must provide information on an ongoing basis. This information includes:

- Changes to the previously submitted research protocols
- New research protocols
- The addition of a new doctor serving as an investigator
- Information amendments, such as new toxicology or chemistry information
- IND safety reports (see below for more details)
- Annual reports (see below for more details)

IND Safety Report

Every investigational drug or device is given an IND or IDE (Investigational Device) number so the FDA can track it. The sponsoring company cannot begin research in people until they receive one. One of the

requirements for an IND or IDE is that the sponsoring company submit an annual report to the Food and Drug Administration

Independent Ethics Committee

See Institutional Review Board

Informed Consent Form

This document is several pages long, and should tell you everything you need to know about the research. Required parts include:

- A statement that the study involves research
- An explanation of the purposes of the research
- The expected length of your participation
- A description of the procedures to be followed [both by you and your doctor]
- Identification of any procedures which are experimental
- A description of any reasonably foreseeable risks or discomforts to you
- A description of any benefits to you or to others
- Alternative procedures or treatment, if any, that might be advantageous to you [rather than participating in the study]
- A statement describing the extent, if any, to which your records will be kept confidential
- A statement that notes that the Food and Drug Administration may inspect the records.
- For research involving more than minimal risk, an explanation of any compensation
- For research involving more than minimal risk, an explanation of any medical treatments that are available if

injury occurs, and, if so, what they consist of, or where further information may be obtained.

- Who to contact for answers to questions about the research and research subjects' rights, and who to contact in the event of a research-related injury
- A statement that your participation is voluntary
- A statement that refusal to participate will involve no penalty or loss of benefits to which you are already entitled,
- A statement that you may discontinue participation at any time without penalty or loss of benefits to which you are already entitled

Institutional Review Board

(IRB) This is a group of doctors, scientists, and community members who review research studies and informed consents to be sure that you are protected. If research is submitted to the FDA, then an IRB had to approve it. Your informed consent form should contain information on how to contact the IRB if there are any issues.

Investigator

This is your doctor.

Major Complications

A major complication is essentially the same as a serious adverse event. This term is more commonly used in research using a new device, while “serious adverse event” is more commonly used in drug trials.

Minor Complications

A minor complication is essentially the same as an adverse event. This term is more commonly used in research using a new device, while “adverse event” is more commonly used in drug trials.

National cooperative groups

These are non-profit groups dedicated to multi-medical center clinical trials. When the same study is done at many different medical centers, then the patients that can be treated are more varied, and many more of them get access to cutting edge treatment. For more information on these groups, along with information on the benefits of being in their studies, visit:

<http://www.cancertrials-help.org/patientsCaregivers/patientsCaregivers.jsp>

NCI

National Cancer Institute. This branch of the National Institutes of Health researches the causes and treatments for cancer. NCI has the major responsibility for coordinating the studies done by the national cooperative groups like ECOG and SWOG. Additional information on oncology studies, past, present, and future, can be obtained at the following web site:

<http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group>

NIH

National Institutes of Health. This is a series of government research facilities covering cancer research, research in heart disease and stroke, research in mental illness and nervous disorders (such as attention deficit

hyperactivity disorder), and many others. NIH and its various facilities conduct their own research, but also give research awards to colleges and universities. Most NIH-sponsored research is conducted to the highest ethical standards, and the direct financial benefits to doctors are fewer than with company-sponsored research. To find out more about the studies currently being conducted by the government, visit the NIH website at:

<http://www.nih.gov/>

Office of Human Research Protection

(OHRP) The human subjects protection regulations 45 CFR Part 46 define research as “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge” [45 CFR 46.102(d)]. A human subject is “a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information” [45 CFR 46.102(f)].

<http://www.hhs.gov/ohrp/>

OIG

Office of the Inspector General, Health and Human Services. This is the office that has paved the way for the use of the False Claims Act if you suspect that research is not being conducted according to the regulations. The link to their web site is:

<http://oig.hhs.gov/>

ORI

This is the Office of Research Integrity (that created OHRP) (<http://ori.dhhs.gov/>). Here are links to the congressional interactions with ORI related to “PHS Policy on Instruction in the Responsible Conduct of Research”:

<http://ori.dhhs.gov/html/programs/congressionalconcerns.asp>

Orphan Drug

A drug being developed for a rare disease or condition. It is difficult for a drug company to make money on the development of a drug that will be taken by only a few hundred people. But people with rare problems still need treatment. To help solve this issue, the FDA has a different set of rules that govern research in orphan drugs.

Phase I Clinical Trial

This phase can be the most dangerous. Establishing whether it's safe in humans (Parexel), what the pharmacokinetics and pharmacodynamics are

Phase II Clinical Trial

This phase frequently establishes the dose level of a drug. You could get too little or too much during this phase.

Phase III Clinical Trial

This phase is considered the gold standard. The drug/device is tested as it would actually be used if approved.

Phase IV/Late Phase Development

This type of study may be done to gather additional safety data, but it could be a marketing ploy. Your doctor's financial conflict of interest is key here – Vioxx stayed on the market despite its lethal effects because doctors were reluctant to step forward and discuss them – they could be sued (Merck threatened them), they could lose the opportunity to participate in future trials (loss of potential income), they could lose trips to conferences, and the ability to present and publish.

Placebo

A sugar pill, a pill or device made to look like the real thing, but providing you with no treatment. If your condition isn't serious, it's fine to receive a placebo.

Placebo effect

Named by researchers, since patients get better even when they're not receiving a real treatment. It's believed that people have an inner ability to heal themselves, and that they are more able to do so when they believe that someone is looking out for them. The placebo effect suggests that you might get better, even if you're not getting the real drug or device

PDUFA

Prescription Drug User Fee Act. This act allows drug companies and biotechnology companies to pay the FDA for the speedy review of a new product. Many believe that it has created a conflict of interest for the FDA in which it receives money from the very companies it is charged with policing.

Randomization

Statistical process that assigns research subjects to treatment groups, assuring that neither patients nor doctors have a hand in determining who gets what treatment. Randomization also assists in keeping patients, doctors, and sponsors blinded (see Blinding).

Reimbursement

The compensation you receive for participating in research. It can be in the form of services, chits, or money. Whatever the reimbursement, by law it cannot be so high as to be coercive.

Research Coordinator

See Clinical Coordinator

Site Coordinator

See Clinical Coordinator

Serious Adverse Event

(SAE) These are major safety concerns, and include any hospitalization, any prolongation of a hospitalization, any life-threatening event, or death.

Sponsoring Company

The company that is paying for research into a new product it wants approved by the FDA. The sponsoring company is not only paying you, but your doctor, and possibly the FDA and IRB.

SWOG

Southwest Oncology Group. Like ECOG, this is a national cooperative group of universities and medical centers dedicated to discovering the best

treatments for a variety of different cancers. SWOG covers a 24 state region of the United States, and provides a web site with information about their current research, and results of completed studies. This web site is available at:

<http://www.swog.org/Visitors/Studies.asp>

Vulnerable population

A vulnerable population is a group of people who cannot protect themselves from coercion when it comes to research participation. The following groups are the ones that must be given additional protection by IRBs:

- Children
- Prisoners
- Pregnant women
- Handicapped people
- Persons with mental disabilities
- Poor people
- People with less education

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