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CONSIDERATIONS THAT CONTRIBUTE TO A COMPLETE PROTOCOL

IRC is often asked to provide a "sample protocol." Because we see studies from a multitude of sources, and from companies with different standard operating procedures, we have not provided one. Instead, in 1990, we issued our first IRC Guide to Investigational Protocols and Consent Forms. A major overhaul has resulted in this web-based document that we hope will help you evaluate or construct your protocol.

The intent of this document is to assist thinking. It is NOT to provide a template or outline. We suggest printing it out and using it as a checklist to determine that each of the points relevant to the area of study is addressed in the protocol.

We have attempted to provide enough sample questions and items to be inclusive of multiple disciplines. Not all research is pharmaceutical and we hope that this document will be helpful to investigators in such diverse fields as education, psychology, drug and device testing, and epidemiology.

See Also:

Considerations that go into Informed Consent

Considerations of a Principal Investigator

- I. An Investigational protocol has many Purposes**
 - A. Why have a protocol?
 - B. Who is the audience?
- II. All IRBs use the same basic review criteria for all studies**
- III. Investigational protocols should tell a story**
 - A. The protocol should not be anonymous.
 - B. The story should be clear
 - C. The study should be well designed
 - D. The subjects recruited should be those most appropriate to yield a valid answer to the question with the least violation of their rights and welfare.
 1. Recruitment methods
 2. Equitable selection
 3. Advertising
 4. Payment compensation, reimbursement
 5. Vulnerable populations
 - E. Be clear about the procedures to be done or altered because of the study.
 1. Boundary
 2. Communication
 3. Information flow
 4. Biological specimens
 5. Study end
 - F. Study subjects are taking a risk.
 1. Physical risks and discomforts
 2. Financial risk
 3. Privacy risk
 4. Emotional or social risk
 5. Treatment and compensation for injury
 - G. The Benefits should also be considered in terms of probability.
 1. Personal benefits
 2. Societal benefits
 3. Benefit probabilities
 - H. Knowledgeable agreement should precede participation.
 - I. It is said that if it is not recorded, it didn't happen.
 1. Protocol
 2. Case Report forms
 3. Adverse event reports
 4. Protocol violations
 - J. Test articles are central to clinical and non-clinical studies.
 1. Drugs
 2. Devices
 3. Instruments

I. AN INVESTIGATIONAL PROTOCOL HAS MANY PURPOSES

1. Investigational protocols can serve multiple purposes. These may include:

- A set of rules and goals

A protocol establishes a set of measurable outcomes and written rules of conduct against which both outcomes and conduct can be judged. Protocols can assist later investigators in their attempts to replicate the results.

- Part of a Grant or Contract Application

For this purpose, rationale, objectives and efficient use of funds are important. Again, the primary readers are peers. However, grant applications make terrible protocols. They are a persuasive attempt to convince an agency to fund the activity; a protocol is the logistical road map.

- Part of an application to the Food and Drug Administration

For this purpose it must adhere to FDA regulations in section 312 or 812 that specify the sections that must be included in an investigational protocol. It is written for peers who understand the field and who often know and have reviewed similar products under review.

Most sponsors resist modifying the investigational protocol submitted to FDA. Each IRB attempts to deal with this problem appropriately through supplemental abstracts, subsequent

correspondence, or investigator attendance at an IRB meeting.

- A “Cookbook” for Investigators

For this purpose the protocol must specify exactly how to do each of the procedures in fine and technical detail. It is presumed that the investigators selected are highly involved in the problem being addressed and will understand the background and rationale. (It is also presumed they will follow the recipe!)

- Submission to an IRB

An IRB is a committee composed of people who, by regulation, are not necessarily involved in, or knowledgeable, about the field. This committee makes judgments such as weighing risks and benefits and considering the rights, safety and welfare of the individual subjects.

2. It is important to know your audience:

It is difficult for one document to address the needs of such diverse audiences. Similarly, each discipline requires coverage of different elements in a protocol. No one sample can cover all bases. In many cases protocols presume background knowledge and scientific expertise not available to all readers.

An IRB is a diverse group of people. It is intended to provide an outside

viewpoint. By definition, most of the IRB will not be experts in the field. Authors that do not anticipate this audience will eventually respond to more questions. Communication in clear language to all potential readers will

minimize miscommunication, mistakes, and length of review.

Murphy rules: If there is an expert in your field on the IRB, that person will be absent at the meeting at which the protocol is presented.

II. ALL IRBS USE THE SAME BASIC REVIEW CRITERIA FOR ALL STUDIES

Both FDA and DHHS regulations contain basic review criteria. Industry sponsors must follow the Food and Drug Administration regulations (21 CFR 50 and 56). All other clients are more likely to follow the Department of Health & Human Service regulations (45 CFR 46 – also known as The Common Rule). As there are only minor differences between these rules, *they are equally applicable to clients from all fields of interest: education, psychology, sociology and medicine.*

The baseline review criteria as set in the regulations are:

1. Risks to subjects are minimized by (i) using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the person for diagnostic or therapeutic reasons.

Can the blood draw be an added tube instead of an added venipuncture? Will the child be taken from the classroom for testing or will it be done after school?

2. Risks to subjects are reasonable in relation to anticipated benefits (if any), to subjects, and the importance of the knowledge that may be expected to result.

This ratio is rarely as simple as 1:2. The subject is usually exposed to possible harm. The benefit can accrue to the subject, to science or future patients (students, clients) or to both.

In evaluating risks and benefits, the IRB should consider only those that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research).

The IRB should not consider possible long range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

In evaluating risks of participation it is critical to know the baseline risks. The risk to a subject of testing a new suture material is

greater if the subject would not otherwise need suturing!

Long term effects range from mis-application of new knowledge, to community harm from correct application leading to stigmatization.

3. Selection of subjects is equitable.

In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should also be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.

Eligibility criteria can be inclusive and exclusive but they can also be used to segregate or discriminate populations. While participation in a study is a privilege rather than a right, researchers have a duty not to unfairly discriminate.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 21 CFR Part 50. Waiver from the obligation to gain consent may be approved under 21 CFR 50.23.

Regulatory writers quite wisely separated the elements of process and documentation. Many protocols are silent on the process of gaining consent. The Common Rule refers to other 45 CFR 46 sections.

5. Informed consent will be appropriately documented, in accordance with, and to the extent required by 21 CFR 50.27, "Documentation of Informed Consent."

Documentation should be appropriate to the group. Both language and presentation are important.

6. Where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.

7. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of files.

Privacy and confidentiality have become one of the most difficult and cumbersome areas of research. An entire section below discusses it.

8. Where some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

IRBs must also consider various ethical codes including the Nuremberg Code, the Declaration of Helsinki, professional codes and the Belmont Report.

The various codes are reprinted or linked elsewhere in our web site. Reading the [Belmont Report](#) annually is highly recommended for researchers in all disciplines.

In addition, every IRB is required to apply institutional rules and State law and regulation. Although we try, IRC's IRB *cannot assure compliance* with all State or local laws.

III. INVESTIGATIONAL PROTOCOLS SHOULD TELL A COMPLETE STORY

A diverse group of people will read your document(s). Some will know about the topic and some will not. Some will know the procedures, some will not. To some it will be an interesting mystery filled with new information to learn about, to some it will be “old hat.” Your task is to communicate your story and your request use humans as subjects to all the IRB members.

Investigational protocols have many formats. Many sponsoring companies have standard formats they are reluctant to change. Regardless of the format, the points raised below should be addressed in some form within the overall application to the IRB.

These sections apply to all applications regardless of whether they are thought to be “a very simple study,” or are non-clinical.

The following is more of a checklist. It is not meant to be an outline for writing a protocol. Please do not be tempted to use it as an outline. It is a terrible outline!

A. THE PROTOCOL SHOULD NOT BE ANONYMOUS!

Every protocol should be identified. (Surprisingly, we really have received anonymous applications!) There should be at least:

- a title
- an identifying number

- a version date
- sequential page numbers on every page
- the name and address of important people: client, sponsor’s medical director, and the study monitor or the study designer

Other useful information includes:

- the names of the investigators and their performance sites
- the name/address of the reviewing IRBs
- a bird’s eye view of the players involved such as the contract research organization, schools, consultants, important vendors, and lead monitor.

B. THE STORY SHOULD BE CLEAR - INTRODUCTION, BACKGROUND AND RATIONALE

This section should usually be limited to two or three pages though it can run much longer. This prelude should answer most of the “who,” “what,” and “why” questions.

Some of the questions that might be addressed include:

Some grant applications are all rationale and plans with none of the more specific sections below. Grant applications are rarely sufficient as protocols.

- ? Why is this study being done? What is the problem for which a solution is sought? Is there a piece of knowledge to be found? Is there a problem with the current treatment? Is it important to replicate a study?

- ? What is the history of the thing or therapy or problem? Upon what do the premises rest? Are there various schools of thought? Where does this fit?
- ? What is the bigger picture? Is this a part of a larger development program (investigational plan) that is not self-evident to an outsider?
- ? What is the condition being studied? What is the natural history? How is it being treated now? How and why might this be an improvement?

The "condition" could be teen pregnancy, school drop-out rates, or cancer. The questions still need to be addressed.

- ? In what way will it change the world, science or the state of the art?

Is there value added? Might the results be published? Kept confidential in an FDA submission? Used directly to improve a program? Used in a marketing push?

1. Context

Studies are considered contextually. That is, a study might be ethical if there is no current therapy. It might not be ethical if there is effective treatment. The context might also be local; the alternatives in an urban teaching hospital may be far different from the options in a small rural hospital.

- ? What treatments are available to people meeting the eligibility criteria?
- ? Are the same alternatives available at each site?
- ? Will some students get more or less attention than others?

The USPHS Syphilis trial (aka "the Tuskegee Trial" took a dramatic ethical downturn when subjects were denied access to penicillin.

2. Review History

Applicants could improve their chances of a successful IRB review by generalizing from

other IRB reviews. Ideally, each IRB submission should build on prior review experience. If one IRB asked a question and was satisfied with the response, adding that correspondence to the record might forestall the question being asked again.

C. THE STUDY SHOULD BE WELL DESIGNED.

The principle of beneficence (see the Belmont Report) suggests that harm should be minimized and benefit maximized. Each study should take this criterion of beneficence into account. The Nuremberg Code, principle 2, suggests that "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature."

Questions to be considered in the design of a study include:

It is the duty of the research community as a whole to maximize benefits. An IRBs' job is to make sure benefit to the subject and the importance of the knowledge is greater than risk to the subject; a lesser requirement. Many IRBs impose a higher standard rather than approve something they don't really like.

- ? Is this a phase I study or a late phase study that seeks to commercialize the product? Is it descriptive, a field study, epidemiology, a registry, or something else?
- ? What is the objective? How will you know if it is achieved? Is there a specific hypothesis? If there is no hypothesis, what is the study about and how will the results be analyzed?
- ? Are there defined end points for the study and for subjects? Do those end points relate to the stated objectives?
- ? Are there periodic re-evaluation points?

- ? How many sites and how many subjects per site will be involved? How many total?

Statistics play a large part in research. It is just as useless to conduct an underpowered study as it is unlikely to provide the desired benefit to offset risk. On the other hand, enrolling too many subjects puts more people at risk unnecessarily (and costs more money).

Not all trials deserve the same level of statistical rigor. A feasibility study of a device is very different from a Phase III trial. Nevertheless, there should be some justification given for the number of subjects to be enrolled.

- ? Is there a statistical evaluation of the number of subjects required to yield the desired information? How many subjects should be enrolled to anticipate drop-outs?

Every few years there is a call to have a national count of participants in research. What would be counted is unknown; it is likely to be either those authorized, those enrolled, or those completing. Clinical studies usually keep excellent track of such numbers. Other studies are not well prepared for such reporting.

D. THE SUBJECTS RECRUITED SHOULD BE THOSE MOST APPROPRIATE TO YIELD A VALID ANSWER TO THE QUESTION WITH THE LEAST VIOLATION OF THEIR RIGHTS AND WELFARE.

The appropriate subject population must be selected to accomplish the goals of the study most efficiently. A very tight selection description is appropriate to answer a very tight question; but it is not likely to be speedy and can cause many violations of protocol. Very loose selection criteria can

recruit very quickly but may not yield precise answers.

The study should start with a population that is most capable of giving informed consent and should proceed with caution to involvement of those who are less capable. If any potentially vulnerable subject populations are included, additional safeguards should be considered. If any site in a multi-center study has a population at some unique risk or with a unique viewpoint, this must be mentioned.

- ? What is the target study population? Student? Cancer survivors? Patients?
- ? What are the inclusion and the exclusion factors? A 4.0 grade point average? Truancy?
- ? If not obvious, why this particular group?
- ? Will any part of the subject population potentially have a limited capacity to consider consent? Why and to what extent? Are they ill? Are they frightened of a diagnosis or of revelation as a child abuser? Are any of the subjects considered to be in "vulnerable" populations (e.g., fetuses, children, prisoners, comatose, institutionalized, incompetent, etc.)
- ? Might any subjects be at greater risk? Might a small demographic cell be easier to identify.
- ? How does the investigator have access to these individuals? Is access to be provided through a third party? If so, are incentives or rewards being offered for recruitment?

1. Recruitment Methods

It is important to know the source of subjects. Are they from the investigator's private practice or referred by another practitioner? Are they obtained through advertising, or a snowball sampling? Are they all the students taking a state test or selected students? An IRB must assure that selection of subjects is equitable. This is

difficult without knowing the constraints on subject selection or recruitment.

- ? How are subjects to be found? Is there advertising? Is there a call center using their already collected names? Are they all students in a given school?
- ? Are there finders' fees to recruiters or referring physicians?
- ? Are subjects obtained through record searches of some file and, if so, which one, and through what right is access obtained?

Ethical dilemmas are often raised if there are substantial investigator or staff incentives to enroll many subjects quickly. Equity in the sponsoring or competing companies, bonuses for rapid enrollment, and other incentives may lead to enrollment of marginally eligible subjects and to cutting corners in the consent process or protocol compliance.

2. Equitable Selection of Subjects

Equity implies that there is a fair distribution of the burdens and benefits of research. This is interpreted in both exclusive and inclusive ways.

The traditional application of equity guides an IRB toward being exclusive; being in research is a privilege rather than a right. Research should not be imposed on the poor who are unable to afford any alternative, especially if the benefits will accrue to those who can pay.

The well-known example from the syphilis trials in which the poorest and least literate Black farmers were included is instructive.

Are drugs that will be expensive being developed using poorer clinic patients?

The principle of equity is now being interpreted more inclusively to ask if people are being unfairly excluded. Although no person has a right to be included in a study,

more questions are being asked about whether certain subject populations should be.

If a drug will be used to treat children should it be done off-label or should the drug be tested on minors?

Should women of child bearing potential be included or excluded if it is realistic to assume that women will use the product upon its release?

If an educational program is implemented, can it be limited to use in only one group?

If women have heart conditions, should not large cardiac assessment trials include a representative sample of women?

If HIV infection occurs in several populations, should an effort be made to recruit from all of those populations?

IRC's IRB tends to be proactive on this issue. Though the IRB will not generally deny approval, they will often challenge stated or implied selection criteria.

- ? Is there any group of people with the condition who are excluded?
- ? Will the recruitment methods identify people with little likelihood of later benefit?

3. Advertising

Advertising is not defined officially. Unofficially, it is any outreach effort designed to encourage potential subjects to contact the investigator's site requesting information. Examples of outreach efforts include:

- Print and radio ads
- e-mail messages,
- employee bulletin boards,
- waiting room flyers,
- planned appearances on talk shows,
- study listings on web site,
- recruitment materials for a health fair,

- flyers posted at colleges, on telephone poles, and at street fairs,
- pre-printed sponsor materials about a study,
- sponsor-answered 800 number ads,
- recorded telephone messages,
- web site information about a study or a product.

Advertising is viewed by Federal agencies and by the IRB as an extension of the consent process. If subjects are to be recruited through advertising, the IRB wishes to review the copy to assure that it is not misleading.

There are several basic rules about the content of advertisements:

- It cannot be misleading. It should not disguise investigational interventions as treatment. Avoid the “therapeutic misperception.”
- It cannot make promises of safety or efficacy.
- It should not feature or emphasize compensation including free medical care. Benefits or financial rewards must be reasonably stated.
- It must be quite clear that it is for research.
- It should give the name of a primary contact and give a method of making contact.
- It may give some brief eligibility criteria such as disease state or age limits.
- It may give some brief procedural information such as the location of the research, duration of participation, mode of administration and name of test article.

- ? Is it full of cheerleading, come-ons, and hyperbole? Is it an offer to be in “an important study?”

For each advertisement, the IRB wishes to know:

- ? Where is the ad to be placed? What kind of media?
- ? What is the targeted audience of that outlet?
- ? Is the selected media outlet available to any particular sub-set of those eligible to participate?

4. Payment, compensation, reimbursement

Payment can be the source of much misunderstanding. Subjects are generally paid for participation when there is no direct clinical benefit accruing to them.

Investigators have made proposals to give a free drug or service, to give trinkets to children, completion bonuses, returning something of value upon completion, or giving something of value to a community.

Whatever the form of the offering, and while it should be meant to merely offset expenses and inconvenience, it is realistically understood to be an incentive to participate. The IRB would like to be assured that money or other payment does not act to coerce or unduly influence any subject.

It is rarely acceptable to pay the entire amount at the end of several sessions as this could be felt to coerce a subject to finish instead of exercising his or her right to withdraw.

The amount should be enough to cover expenses of participation but not sufficient to unduly influence a person to participate.

- ? What is the incentive for subjects to participate? What motivates them?
- ? What is to be paid? What is the payment schedule?

- ? Is there a completion bonus?
- ? Is the payment mechanism clear?
- ? Is there any suggestion the amount could be an undue inducement?
- ? Is the consent form exceedingly clear about amounts and schedules and about when payment can be expected?
- ? How is payment made? If a check is involved, what confidential information will accounting need to have? Is an IRS form 1099 required?

Reimbursement should be separated from compensation. Reimbursement should be considered so that a subject is not paying out-of-pocket to participate.

- ? What are the subject's costs likely to be?
- ? Are these costs the subject would have as a client/patient or are they added because of agreeing to participate?

5. Vulnerable populations

Respect for Persons demands we treat subjects as autonomous beings. It also demands that we recognize that not everyone is equally autonomous, and to provide additional support where needed.

Additional regulations must be considered for consideration of **children** (minors), **prisoners**, and **pregnant women and fetuses**. Those regulations require greater deliberation about the risk levels and a higher benefit to risk ratio. There are also additional consent requirements.

More interesting than thinking about groups is considering the causes of vulnerability. People can be vulnerable because they cannot make decisions on their own, or they feel they have no choice but to agree. An individual can have a vulnerable personality or be at a vulnerable time.

Kipnis argues there are six major sources of potential vulnerability. The potential subject may be vulnerable if:

- ❑ they cannot deliberate about something (e.g. mentally impaired) or make individual decisions (difficulty making decisions).
- ❑ they are under the authority of others (e.g., prisoners, children) who have other interests.
- ❑ they will automatically defer to persons in authority ("the doctor as god" syndrome).
- ❑ they feel that with their condition, there is no other choice.
- ❑ they are so lacking in housing, food, medical care, that their choices are limited.
- ❑ they are lacking in the resources (e.g., a phone to call the IRB) to defend themselves.

- ? What is known about the community from which subjects are to be drawn? Are they sick? Frightened? Too poor to afford non-study care?
- ? What can be done to change what is making them vulnerable? How might a coordinator obtain a more voluntary consent from a deferential person?
- ? As few people are totally autonomous, what supports will be offered to help potential subjects give fully informed consent? Do they have sufficient time?
- ? Will safety be compromised if directions are not followed?
- ? Could there be a change in autonomy levels during the course of the study?

E. THE PROCEDURES THAT WILL BE DONE OR ALTERED BECAUSE THE STUDY IS HAPPENING SHOULD BE CLEAR.

All procedures should be listed in the protocol, be they physical procedures, or accession of data from a secondary source, or sending data out.

Only one study should be included. Occasionally, generally with grant involvement, several like projects are included, although often they are melded together such that the IRB cannot parse them out. Strive for clarity and remember your audience.

1. The Boundary Problem:

Research and experimentation must be clearly distinguished from standard practice. Study procedures may include tests done for patient care with the data to be used secondarily for the study, or they may involve additional tests performed solely for study purposes. Students may be taking a state mandated test already and have the results used within a study. The test is not experimental; the use of the results is. The protocol must indicate what is involved for subjects as a consequence of becoming involved in research.

The boundary is critical as it determines much of the information to follow. What procedures contribute to the risk calculus? From what is the subject (as opposed to the patient or client) to be protected?

There are two sets of risks to a venipuncture; that from the needle such as fear and bruising, and that from the information. If the venipuncture was to be done for standard care and the study is using the results, the physical risks are derived from treatment and study risks are limited to the risks from

misuse of information (i.e., loss of confidentiality).

Boundaries change with the setting. The gold standard in one setting may not be viable in another without a crucial resource. What is done in-house in one setting may be done by referral at another. Thus, boundaries may be site-dependent.

- A site without an MRI will have different transportation, appointment, and consent requirements from the site with its own MRI.
- Use of test results will vary from a state that treats them as public information and a state that requires them to be private.

If there is no stated boundary, an IRB is likely to review all of the activities including the baseline procedures. Educators do not want IRBs to comment on the comment of state mandated tests. Do not make IRB-creep faster than it is.

2. Communication

Although the procedure section is often complete, it may be quite cryptic and not totally decipherable to the IRB members in a different field. Those tests or treatments that would be done outside the research context should be identified. Often a chart or schema of procedures, distinguishing the normal from the investigational or additional procedures, is useful. If this is well done, it becomes easier to translate to lay language on the consent document.

- ? Is there randomization? At what point in the schema? What are the arms? Is there a placebo arm? Why? Is there a no-treatment arm?
- ? Are there added screening or monitoring tests? Added visits? What is their frequency and duration?

- ? Are there self-report, diary, or questionnaire requirements?
- ? Is there any deception at all? How is it warranted? Is there a placebo? If so, is there any debriefing?
- ? Is there an alternative available? Is it innovative treatment?
- ? Is an investigational drug or device involved? What is the number, if any, assigned by the FDA?
- ? Will anything be withheld? Will there be a washout period? An alternative?
- ? When is the consent information to be discussed? Who does it? What are the circumstances? What must be done to identify the potential subject?

3. Information flow

Research depends upon complete and accurate information. Sponsors, the IRB, and FDA must be able to monitor studies and the information documented. Subjects are likely to have some exaggerated faith about the protection of their privacy. IRBs tend to work diligently to protect subject privacy. Into this melee Congress has imposed the requirements of HIPAA – the Health Information Portability and Accountability Act.

HIPAA takes effect in April 2003. It will affect all studies in progress at that time.

HIPAA pertains to¹ health information gained in a healthcare setting. That is, the information that the average person would believe is private health information is likely to be covered by the rule. Information that is traceable (e.g., coded) is likely covered;

¹ This document is not intended to be an explanation of HIPAA. Compliance with HIPAA requires an understanding of the rule.

anonymous, totally de-linked information is likely not covered.

Information gained from elsewhere: For each piece of information gained from other than direct contact, there must be a clear understanding of how the right to have that information was gained. Is it shared between “business associates?” Was there specific authorization? Did a privacy board waive the authorization requirement?

Information sent to others: Subjects should be asked for authorization to use information if any identifiable or traceable information is to be reviewed by unauthorized people.

The flow of information into and out of a study site should be clear wither it is by paper, e-mail, fax, CRFs, or over the internet.

4. Biological specimens

As with information, the acquisition, rights of procurement, transfer and disposition of biological samples should be dealt with explicitly.

5. The End of the Study

An oft forgotten aspect is the end of the study. Consideration should be given to the care of subjects. In a therapeutic setting there may be an ongoing relationship with a physician but in many cases subjects are simply excused to go home without thanks or a plan. Please do not forget to thank the subjects.

One proposal was to do a cosmetic procedure on the right side of the face, using the left as the control. No plan was made to make sure the sides were made equal at the end!

A sponsor gave a luncheon for the subjects and presented the results and the future plans. Luckily, as it was outside and cold that day, they also gave each person a sweatshirt!

F. STUDY SUBJECTS ARE TAKING A RISK.

Risk is a statement of the possibilities of some thing -- generally a harm -- happening. These possible harms are not only physical, but are psychological, social, economic and legal.

The harm and its source should be identified. Potential harm from routine care (see boundaries above) should be differentiated from potential harm resulting from giving consent and participating.

For each potential harm there should be some description of its possible frequency and magnitude, as well as discussion of the consequences or impact of the harm, plans to minimize the risk and the possible treatments. This is closely related to subject selection, as appropriate selection may reduce risks of harm.

It is commonly accepted that risk can be greater or less depending upon the skill of the investigator (and his or her staff) and upon the backup equipment available. Therefore, the IRC IRB will also determine that the investigator attests to the fact that he or she has the minimal qualifications necessary to conduct the study.

1. Physical risks and discomforts

This is the only area most studies discuss. The physical risks attributable to participation should be discussed in terms of what is known and what is theoretical.

- ? What are the known and theoretical physical harms from this test article? From similar drugs or devices?
- ? What are the known and theoretical harms from the various procedures?
- ? Are the risks being minimized through selection of appropriate personnel - both at

the level of the principal investigators and the staff?

- ? Are there procedures that require special training?
- ? If contraception is an eligibility issue, is there any pre-clinical work available on the fetus?
- ? Are there harms from taking commonly used drugs?
- ? Are there any procedures that might cause physical discomforts or fears such as from claustrophobia or isolation?

2. Inflicted knowledge

The newest of risks considered, the question is what to do with knowledge that was not anticipated. Gaining knowledge has consequences. The knowledge may be correct or may be a false positive. The knowledge may lead one to more diagnostic tests with more expense and worry.

Inflicted knowledge is generally a result of a healthy volunteer being asked to take a test; be it a questionnaire about a learning disability or an MRI.

- ? Does the volunteer expect the test to be diagnostic?
- ? Is there a procedure in the protocol for handling alarming results?
- ? Is any counseling involved?
- ? Could there be costs related to follow-up of test results? Could insurability be affected?
- ? What is the likely consequence of having the information on the life of the recipient?

Examples: A normal blood donor is informed of an HIV status. A parent allows a child to take a test so that the test can be validated with normal children and is later told that the child performed outside the limits thought to be normal. An employee agrees to be a healthy volunteer to have an MRI which is not diagnostic and is told that there is "something here you should take to your doctor." A family pedigree reveals that the next generation is

likely to carry a gene for some disasterous disease.

3. Financial risks

Subjects should not be paying out-of-pocket for the benefit of the sponsor. Subject costs may be direct, as in being expected to pay for added follow-up visits, or may be hidden, as in covering the time off work or the baby-sitter. Third-party insurers often reject claims for procedures that are experimental. Protocols should include discussion of financial risks.

- ? What costs are involved for the subjects or their third-party payer? For additional visits? For transportation? For payment for tests or the test article? How much time off work (or need for baby-sitting) might be involved?
- ? Will the insurer be involved? Ahead of time?
- ? What is the maximum amount a subject might be asked to assume?
- ? Is there any way to minimize costs, such as by providing child care or lab tests?
- ? Are there arrangements to provide free or low-cost care if the experimental arm is not effective?

3. Privacy risks

Loss of privacy is a risk of participation in almost every study. Despite the best safeguards and best training, briefcases have been lost and gossip has occurred in elevators. If data is to be submitted in a marketing permit, FDA has the right to audit all subject files and to review source documentation. Sponsor monitors also have the right to see such documents to complete their job.

Although confidentiality cannot be promised, many safeguards are available.

- ? Might telephone calls or mail be intercepted? Could a call center with a database reveal a condition in a message?
- ? Might answers on questionnaires reveal child abuse or an infectious which must be reported under the state law?
- ? Is there any possibility of stigma if participation or any of the results become known? Does entering the building create a stigma? That is, how important might subjects consider their privacy?
- ? How will confidentiality issues be handled? Will any records of the investigator contain individual subject identifiers? What information will the sponsor (or call center) have? Is it possible to code the information so that identities are not transmitted beyond the investigator?
- ? Where will the individual subject records and consent forms be stored? Will such records be identifiable or coded? How long will they be retained? Will they be together with medical (or other records) or separate?
- ? What will happen to the records at the end of the retention period? How will they be disposed?

Database information poses special problems since there is a wealth of data available to anyone with access. Similarly, pharmaco-economic studies are of concern since a wealth of additional, non-study related data illustrating other forms of treatment will be available. Protocols should address the means used to protect data.

- ? Are there passwords for the computer? How often are they changed? Who has access to restricted areas of the database?
- ? What identifiers will be used on case report forms, and on the database?
- ? If outside reports are gained (bills, insurance statements, etc.) how are identifiers hidden?

- ? What information must the investigator obtain from others? What access must others have to identifiable information?

A Certificate of Confidentiality protects an investigator from forced release of information. It is available for some studies involving subjects who might be at legal risk should it become known that they even participated, such as studies of child abuse, or illegal activities. Call IRC for more information.

The **HIPAA (Health Information Privacy Accountability Act)** provides many safeguards for medical information. Compliance with it must be incorporated into the protocol. Similarly, there are student and prisoner rights with regard to confidentiality.

4. Emotional or social risk

Subjects who feel they have been treated as a means to an end, or whose concerns have not been adequately addressed, are not only unhappy, they also sue more often and they tell others of their experiences.

Intrusive questions about sensitive, traumatic or taboo subjects can be emotionally upsetting, especially for victims of traumatic experiences or who have concealed illicit behavior.

- ? Early termination of a patient/subject from a protocol providing care can cause substantial distress unless there is orderly transition to other care.
- ? Failure to pay compensation on time causes anger, more work for coordinators and calls to the IRB.
- ? Being identified in a group may cause social stigma. Gene identification and pedigree studies have particular stigmatization risks.
- ? Interviews or questionnaires occasionally raise traumatic memories. What precautions have been taken to assist a

person who is, for instance, latently suicidal?

5 Treatment and compensation for injury

Occasionally, despite the best planning and excellent procedures, a subject is injured during the course of research. An element of informed consent requires a statement regarding the policy for treatment of injury and compensation for costs IF there is more than a minimal risk of harm. (If not, presumably the statement may be omitted, although the policy should still be in the protocol or site policy.)

A complete application reflects arrangements made to attend to anticipated injuries and financial arrangements made to cover their costs. The costs of treatment, later ancillary care, and, perhaps, time off work, child care, etc. should be considered. Simply indicating that the sponsor will not pay or has no program is to ignore the possibility and to wait for a possible lawsuit.

- ? Is there a clear policy available to investigators and the IRB on how injuries are to be handled, and who will pay for such injuries?
- ? Is the policy clear and acceptable to the investigators?
- ? Does the policy identify the responsibilities of sponsors, investigators and performance sites?

The way these policies are expressed on the consent document is left for IRC's guide on informed consent. (3.3.9)

The IRB does not need to know all financial arrangements between sponsor and investigator; it does need to know that those arrangements will result in appropriate arrangements to treat injuries and to compensate subjects.

G. THE BENEFITS SHOULD ALSO BE CONSIDERED IN TERMS OF PROBABILITY.

“Risks to subjects must be reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may be expected to result.”

There is an unresolved question whether the benefit to subjects (or to science and society) should be maximized through IRB action, beyond what is necessary to balance the risk.

Although an IRB may not be seeking to maximize the benefits from a study, it must assure itself that the risks are reasonable in relation to the benefits that the study is likely to yield.

If a study is poorly designed, then little benefit can be found to be likely; therefore, to approve it, the risks must be found to be negligible.

The more distant the benefit from the subject, the more altruism or incentive must be presumed; the more personal the benefit, the more undue influence is possible. Naturally, the nature of the benefits must be well understood by all participating.

Benefits are not a given. The drug might not work. The study intervention might be worse than the control. The web site education may not achieve integrated learning. Some individual subjects may benefit even if the study fails and some individuals may not benefit even if the study is a wild success.

Many IRBs consider payment to be a benefit. This IRB does not. Risks and

benefits should be in reasonable relation without consideration of money or other forms of compensation.

1. Personal benefits

Therapeutic misperception is a concern. Often the aim of a study is to determine if something is effective. Subjects who believe that their doctor has only their best treatment in mind may have an inappropriately inflated understanding of the potential benefits.

- ? What are the realistic physical benefits?
- ? How likely are they to occur to each participant?
- ? How likely is it that benefits will be deferred? Will the placebo group be offered the experimental regimen only after the double blind is broken?
- ? Are there non-tangible benefits (altruism or personal knowledge)?
- ? Is the family likely to benefit?

At IRC we attempt to stay away from the notion of therapeutic or non-therapeutic research. Even with studies intended to yield direct therapeutic benefit, the goal of the trial is to answer a question; not to provide therapy. Although it may be therapeutic, there is an experimental aspect either in the regimen or the selection of the regimen. To call a study a therapeutic or a “treatment” study is to support the therapeutic misperception.

2. Societal benefits

Social benefits are rarely immediate and may never be enjoyed by the individual. In fact, the benefit may be that another competitor can introduce yet another drug into the market. Rarely are societal benefits or expected benefits to anyone other than the subject expressed realistically.

* 45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2)

- ? What will be the impact of the answer to the study?
- ? Is there any economic impact?
- ? Who is likely to be able to use the results?

Benefits to the sponsor such as a marketable product resulting from a successful study might be the most realistic than any direct benefit to an individual subject.

3. Benefit Probabilities

Scientific benefits are impossible if the trial is not conducted well and if data is not collected. The calculus for benefits is different from that for risks. Rather than a risk to an individual; benefit is measured more in terms of an overall answer. What is the likelihood of answering the question? What is the importance of the answer?

H. KNOWLEDGEABLE AGREEMENT SHOULD PRECEDE PARTICIPATION.

The principle of respect for persons requires that the subject be considered an autonomous individual capable of making an informed choice about whether to participate. This requires consideration of multiple factors that should be clear to readers of the study.

Informed Consent is a process in which

- full disclosure is made to the potential subject,
- who is legally able to give consent,
- and mentally able to process the information,
- and emotionally and socially able to made a decision,
- in terms likely to be understood, and
- in circumstances free from undue influence and coercion.

Informed consent is often documented through use of a consent form.

The application form should address timing, means, staff, privacy and limitations.

Another IRC Guide discusses the consent process and document in more detail.

I. IT IS SAID THAT IF IT IS NOT DOCUMENTED, IT DIDN'T HAPPEN.

Many events occur daily that are not documented. Conversations take place between subjects and investigators that are not catalogued. The problem, of course, is that there is no proof – and of course, even documentation may not be proof.

Scientific observations are impossible if documentation is incomplete. Records are important from the beginning to the data analysis.

1. Protocol

- Each iteration of the protocol that is accepted should be distinguishable from previous versions
- Whenever possible, changes to the protocol should be inserted into the text and highlighted.

2. Case Report Forms

FDA regulated studies often differentiate between source documents – the first place a result is recorded – and report forms and to whom (including the IRB) a report is sent. Many studies make no mention of how data is gained or reported.

- ? What documents prove the point? What are source documents? (Access to these documents is covered in the privacy sections.)

- ? How is the data to be recorded? Are there case report forms? (include them) How are interviews documented?
- ? What identifiers are on the report forms? How are identities on source documents protected?
- ? Is all the information collected related to the study end points?

Every protocol should be specific about what documents are due, to whom, and when. All case report forms, diaries, screening forms, adverse event reports, questionnaires, and any other forms should be discussed in the protocol and included in the appendices.

Proper protection of subject confidentiality dictates that names appear on no document other than the consent form. Source documents with names (e.g., lab slips) should be maintained in a manner to minimize identification. No documents with identifying information should leave the premises unless the consent form discussed the transfer of identifying information.

2. Adverse Event Reports

The protocol should discuss definition of and grading of adverse events. It should be specific about which must be reported and in what time frame. The IRB should receive a copy of each adverse event report for any serious or unexpected adverse event. *All* adverse events should be reported during continuing review.

2. Violations of Protocol

The general rule is that a protocol must be slavishly followed. No violations are allowed. This does not account for human behavior. Violations will occur. The protocol should set ranges of acceptable practice and should instruct investigators

what to do if violation is necessary, or is discovered to have occurred.

Violations are breaches of protocol. Breaches that are anticipated and for which permission was obtained are exceptions; those that were unanticipated are deviations.

IRC requires 5 day reporting for all violations that are serious; that is, that will have a negative impact on either subject safety or the ability to complete the trial successfully.

A sponsor decided to allow exceptions to shorten a wash-out period rather than to modify the protocol at multiple sites. That sponsor saved substantial time by avoiding IRB review of the modification but they spent that time redoing the study after FDA rejected the data.

J. TEST ARTICLES

Drugs, devices, procedures, and paper & pencil instruments are all subject to study. The test article should be described, and if needed, illustrated. Its background and history should be discussed.

1. Drugs

The Investigator's Brochure (or package insert for post-market studies) must be submitted. The IND number should be included.

2. Devices

A Report of Prior Investigations is required for devices requiring a full IDE.

For Abbreviated IDEs* (NSR) information on prior testing and use is needed.

* 21 CFR 812.2(b)

Devices often evolve during testing. The protocol should include change parameters to avoid needing to re-submit each little device change.

3. Instruments

Validation of questionnaires or survey tools involve “test instruments” which should be included. If the instrument is derived from prior work, the genesis of the instrument should be described.

-----IV. End -----

It is our hope that your wonderfully written protocol will be approved the first time each IRB sees it, that there are few, if any protocol deviations, all investigators understand it to mean the same thing, the funding agency accepts the results, and that the study can be replicated.

Of course, even the best written protocol is no guarantee against harm, and cannot assure a positive outcome.

We hope that this has helped. Please call us with questions. Remember IRC, we provide this information because we hope that you will use our IRB.

Erica Heath