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CONSIDERATIONS THAT GO INTO INFORMED CONSENT

IRBs are said to place more emphasis on the consent document than on consent itself. This is often because the IRB members are not on site for the actual process and can most easily alter the form. This guide, first issued by IRC in 1990 and most recently in 2002, directs the focus back to what informed consent really is.

The intent of this document is to assist in thinking broadly about the issues of consent.

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 device manufacturers and investigators in such diverse fields as education, psychology, and epidemiology will find inspiration.

See Also:

Considerations that go into a Protocol

Considerations of a Principal Investigator

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I. RESPECT FOR SUBJECTS MEANS ALLOWING PEOPLE TO MAKE INFORMED DECISIONS.

The Belmont Report, written by the National Commission on the Protection of Subjects of Biomedical and Behavioral Research in 1978, establishes that there are three ethical principles at play in research ethics. They titled the first principle: “Respect for Persons.” Since the Commission said it well, we just include it here.

“Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

“An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make considered judgment, when there are no compelling reasons to do so.

“However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

“Some person are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences.

The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

“In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to “volunteer” or to “protect” them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.”

RESPECT

Respect manifests itself in how people treat each other.

- ? What are you calling the person you are speaking with? If you use their first name, do you invite similar familiarity back?
- ? What are the little things that can be done to show respect?

II. INFORMED CONSENT INVOLVES KNOWLEDGE, ABILITY, AND VOLUNTARY AGREEMENT – AND FAITH.

The Nuremberg Code provides one of the more succinct definitions of informed consent.

“The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

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Informed consent is
knowledgeable agreement freely given.
It is often *documented* using a consent form.

Parsed out, another iteration would be that
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
- AND in which the agreement of the subject is *documented*.

FAITH

Faith is a rarely addressed factor. We take any number of “facts” and beliefs on faith. Our faith can help us through the darkest of tunnels. Our faith can be placed in God, people, facts, science or other places.

The more we need faith to help, the more we might misplace our trust. The desire to trust one’s caregivers to do what is right may or may not be appropriate in any given circumstance but those people charged with giving information and obtaining agreement must be cognizant of the power of faith in decision-making.

III. AUTONOMY IS NECESSARY TO MAKE AN AUTONOMOUS DECISION.

Autonomy is the ability to be independent or self-governing. Most people, when given enough information, are able to make decisions that take into account their own welfare and, perhaps, the welfare of others. Autonomy, however, can be fleeting. A bright, intelligent, capable person can be stunned by bad news, influenced by biases, or rendered helpless physically. In addition, within any group of people, there is a range of skill at, and styles of, decision-making from fast to slow, intelligent to not, fearful to assertive, dependent and independent. Any recruitment process should account for the anticipated range of autonomy.

A. THE ELIGIBILITY CRITERIA OFTEN SAY LITTLE ABOUT CAPACITY.

Although most protocols describe eligibility in physical terms, most IRBs are concerned with eligibility in terms of what it means about potential for vulnerability. Part of considering local conditions is an evaluation of the target population *of that site* and, within that target population, the range of autonomy expected.

If all of the potential subjects in the target population have graduate engineering degrees, a much more complex consent form can be approved. But if all of those subjects are employees, their vulnerability in terms of employer knowledge about their health conditions and the effects on employment produce a built-in potential for coercion either real or perceived.

Most protocols include eligibility criteria such as, “patients with diabetes,” or people responding to an ad for a survey. Such descriptions fail to reveal anything about the range of literacy expected, the familiarity with jargon, or the potential for coercion. For instance, an ad placed in *Applied Clinical Trials* would garner a

very different group from an ad in *Drag Racer’s Gazette*. In both cases, however, there would be a range of intelligence, reading and decision-making skills.

Circumstances: Capacity can also be dictated by circumstances. A consent process with two people of unequal authority, power, or knowledge can be intimidating; making the person vulnerable to influences that might not normally work.

B. THERE ARE SEVERAL WAYS TO VIEW VULNERABILITY.

- Kipnis¹ has suggested that there are six major sources of potential vulnerability. Examining the intended population with these in mind and acknowledging that each may be present to some extent in everyone will assist the person guiding the consent process to recognize issues. The potential subject may be vulnerable if:
 - they cannot deliberate about something (e.g. mentally impaired) or make

¹ Kipnis reference

individual decisions (difficulty making decisions).

- they are under the authority of others (e.g., prisoners) 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, and medical care, that their choices are limited.
- they are lacking in the resources (e.g., a phone to call the IRB) to defend themselves.

A few of the areas of vulnerability are listed here. For each, there could be support mechanisms that could bolster the potential subject’s ability to make an autonomous decision.

Legal capacity Adults have legal capacity unless it has been removed and replaced by a guardian or conservator who may have partial or full responsibility.

Mental capacity There is a range of intelligence in every group. If there is something unique (a population only of Ph.Ds or of preschoolers) about the population, the consent form and process may be targeted to that group.

Emotional capacity A person who has been handed a terminal diagnosis is in a compromised state with jumbled emotions and major new concerns. Some studies (particularly in oncology) may need to begin immediately. The process must fit the circumstances.

Lack of choice Before there were drugs for AIDS, many HIV+ people argued passionately that they had a right to be included on experimental trials as the best chance to save their lives. They were vulnerable to any claims of effectiveness implied by anyone.

Independent decision making Despite age, education, or other variables, some individuals are unable to make independent decisions. They take guidance from a specific person or from anyone with an opinion. Such a person might consider their doctor to be God and do anything to please the doctor, or they may see all the staff and their friends as equal and hear multiple conflicting opinions - effectively pre-empting their decision making capacity.

Due and Undue Influence What is due to you may be undue to another. Compensation of \$300 may unduly influence a homeless person; it would not influence a wealthy person very much due to economic variances.

Coercion Coercion is use of a threat or an implied threat. Employees might feel coerced when asked to participate by their supervisor. Children may be afraid of taunts from their peers and feel forced to participate.

C. REGULATED CLASSES OF VULNERABLE SUBJECTS

Several classes of people have been identified in the regulations as, *de facto*, vulnerable -- any evidence to the contrary notwithstanding. Minors, prisoners, pregnant women and fetuses are included in the deemed vulnerable categories. For such classes of subjects there are additional regulations to be considered.

The regulations are those found in 45 CFR 46 in subparts B (pregnant women and fetuses), C (prisoners), and D (minors). Title 45 of the Code of Federal Regulations pertains to the Department of Health & Human Services (DHHS). This regulation applies to all studies funded by DHHS. It also applies throughout any institution voluntarily applying this regulation within that institution.

Several other Federal agencies have similar or greater regulation. The FDA has adopted regulations protecting children. The Department of Education has multiple rules about protection of students.

1. Minors

Children do not have the legal capacity to consent regardless of what they may think. The age of majority is determined by State law. Emancipated minors gain the rights of adulthood, including the right to consent subject, again, to State law.

Regardless of the legal requirements, minors should be involved in the

From age 0-7: The minors are presumed to be incapable of considering the issues.

From ages 7-14: There is no set presumption.

From age 14 to majority: The minors are presumed to be capable, although legally constrained.

2. Prisoners (45 CFR 46 Subpart C)

Prisoners are vulnerable for multiple reasons extending from the bounds of their incarceration. Although all prisoners are treated equally in the regulatory structure, the vulnerability of

D. As Autonomy decreases, the support mechanisms must increase.

decisions about their participation in research to the greatest extent possible in light of their maturational decision-making skills, their comprehension, and their reading ability.

The Rule of Sevens.: A set of presumptions

those on probation with an electronic bracelet are quite different from those in State Penitentiary.

A particularly stringent reading of this regulation by OHRP (Office of Human Research Protections) says that involvement of one prisoner among many non-prisoners requires IRB review of inclusion of that volunteer at a full board

meeting with a prisoner representative present.

3. Pregnant women (45 CFR 46, subpart B)

Any research involving pregnant women (especially if it is funded by DHHS) is subject to several additional requirements. In particular, an additional element of information – risk to the fetus – is required.

Note: This requirement does not imply that pregnant women do not continue to be able to think and function as well as they did prior to becoming pregnant. It simply requires some additional assistance.

4. Fetuses

The same regulatory section establishes requirements for that most vulnerable of groups, the fetus.

A second consideration is “What is it about “No” that you don’t understand?” Refusers should have their wishes honored. Logs of those refusing or screened out should be as meticulously protected as all other documents and identities should not be passed on to sponsors.

NOTE: It is appropriate to not include everyone. Refusal is as important as consent.

Not every potential subject needs to agree to participate. Conflict occurs between study design (which seeks to eliminate study biases) and respect for persons (which seeks to empower each individual's decision-making).

E. Who consents if the subject can't?

A Legally Authorized Representative (LAR) is allowed to consent for a person who cannot give their own consent to be a research subject. The question is who is allowed to be a LAR.

An LAR is defined by state rules and each state is different. If an LAR is contemplated, the investigator submitting the application to participate on a study, should demonstrate knowledge of the state involved.

F. Refusal and Withdrawal are autonomous acts.

Reasonable people can disagree and can have different values, fears and hopes. People have different tolerances. What might be opportunity to one person might be dreaded by another for no apparent reason. It is appropriate for some people to refuse.

IV. THE CORE OF CONSENT IS THE PROCESS.

IRBs are often accused of nit-picking the consent form to death while ignoring the process entirely. IRBs are not alone in this distinction. Calling the form “informed consent” or saying that one will “consent a subject” when only a signature is being obtained often reveals a lack of consideration of process.

The consent process will be discussed here prior to any discussion of either the elements of information or the form itself because the process is critical.

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A THE INVESTIGATOR IS ULTIMATELY RESPONSIBLE

The final paragraph of Principle 1 of the Nuremberg Code reads,

“The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.”

Under all research regulations and under all IRB approvals, it is the principal investigator who is responsible for assuring that the subjects enrolled in his or her study are fully informed and are making a voluntary decision.

1. Delegation of responsibility:

Responsibility may be, and often is, delegated. Many investigators are not the most appropriate people for discussing the issues. First, they have spent years learning

to speak medical and upper income bracket English and may not be able to change dialects. Second, they may have a conflict of interest. Investigators often stand to make some profit from the conduct of studies or, at least, to keep their practice alive. Third, often nurses, coordinators, trained interviewers and others on staff have more time. Fourth, if a person is deferential to authority, the title of investigator may be more intimidating than the title of a staff member.

Although the investigator can delegate this task to anyone, the qualifications of that person to obtain consent should be equal to the task.

- ? Who will be informing (teaching) the potential subject about the study?
- ? Is this person specifically named or is this a task assigned by fact of their job title?
- ? Will this person be available to answer later questions?

- ? How was this person trained about the study?
- ? How was this person trained about consent for research?
- ? Is the delegation to this person clear and unambiguous?
- ? Is the role of the investigator clear?
- ? Who is giving the information and answering questions? Is this a formally delegated responsibility? What is the training of this person? If not the investigator, how integral to the study is the person? Could they refuse to enroll a subject?
- ? Is the person obtaining consent also the primary caregiver?
- ? Is the information conveyed in a language the subject can understand?

2. The Role of the Witness

A witness is necessary only when the subject or the legally acceptable representative is unable to read (ICH (4.8.9. and 21 CFR 50.27(b)(2)) and a short form is used.

A witness may be used in other circumstances but, if so, the protocol should describe the role of the witness and the document should make that role clear.

- ? Does the witness speak the primary language of the potential subject?

B. ADVERTISING AND RECRUITMENT MATERIALS PROVIDE A FIRST IMPRESSION

First impressions are important. Recruitment materials are often considered to be the first part of the consent process. Although neither the FDA nor the DHHS regulations require IRBs to review advertising, each agency has required review. They cite two ethical principles from the Belmont Report: Respect for

Persons (truthful advertising) and Equitable selection of subjects (equity in recruitment).

Definition

Although neither agency has defined advertising, the FDA has published a guidance on it and several IRBs have policies. IRC defines advertising as "*any outreach effort designed to encourage potential subjects to contact the investigator's site requesting information.*" The FDA has unofficially limited advertising to anything directed toward the potential subject; they do not include information directed to those who might refer potential subjects such as other physicians.

As competition for limited numbers of patients increases, investigators are becoming more creative in recruitment measures.

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.

These are generally reviewable:
Print, radio, or TV ads health fair materials about the study Computer bulletin boards or Internet 1-800 number ads Disease databases (PDQ)-if you have any control over the content or if the information is subjective Talk show appearance media kits Press releases Telephone voice-mail messages
These generally do not require IRB review
Ads in professional journals potential subjects are not likely to read Ads targeting referring doctors Flyers to referring agencies that are not to be seen by patients. Disease database if all data is objective Talk show dialogue Newspaper interviews.

- 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?”

Placement of materials

As advertising will attract various subsets of the desired population depending on placement, the IRB will also consider placement of any advertising.

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 subset of those eligible to participate?

If any HIV+ patient is eligible, advertising should be placed in a variety of places that targets HIV+ groups rather than those seen primarily by white gay males.

Review of Advertising material

Advertising is reviewed using the expedited process. Although usually faster, please plan time to allow for a 4-day turn-around. Recruitment materials must be approved before they can be used.

When ads are to be type-set or professionally recorded, the text should be reviewed first with the final product sent in to confirm that the product is congruent with the text.

Concomitant information

Few subjects are limited to the information the site provides. Between check-out stand magazines, stories from friends, and the web, a potential subject may learn considerable other information which might or might not be correct.

- ? What other sources of information might the subject review?
- ? What other sources of information will be provided?
- ? Will conflicting or competing information be assessed?

C THE PROCESS FOR GAINING CONSENT SHOULD BE “UNDERSTOOD.”

Excellent research sites have standard operating procedures for the consent process. Excellent protocols include the consent process in the screening and

enrollment process. Most often, however, there is silence about the methods used.

Many Americans are unsure what it means to become a research subject.

- TIME (xx/xx/00) had a cover showing a human guinea pig.
- 60 Minutes shows a life-saving experimental drug one week and research fraud another.
- Multiple novels are based on mal-intentioned investigators.

A starting place in the consent process is ascertaining what the person believes about research and subjects. There are several brochures – mostly clinical – that explain the role of a subject and the questions that should be asked.

Medium

There are many ways to transmit information. The consent form, discussed in the next few sections, is the most popular way. There are others that may be superior depending upon the population and the study.

- Video tape can show procedures.
- Calendars can show timing.
- Group meetings can encourage discussion.
- Letters are often used to parents.
- Surveys and questionnaires can have cover pages with information.
- The internet is becoming more popular as a source of information.

Each of these offers advantages not available using only a consent form.

Timing and Sequence

Many protocols read as if the routine was a simple recruit, consent, start. In fact, time should be allowed for consent to the extent possible.

A segment on ER centered on getting consent. Following an accident, a child required surgery. The unharmed mother generally deferred to her physician

husband for all medical decisions. The husband was minimally alert. Despite the physician efforts to have the mother sign, she refused to decide. They ended up putting the clipboard in front of the husband and saying, "sign here." The formalities were completed.

- ? Will subjects have adequate time to consider participation and to seek any advice they wish? Are they encouraged to take the time?
- ? If eligibility requires a trigger event (e.g., prescribing a drug before being eligible to enter a registry) is the consent form (and are all staff members) clear about the separation between clinical events and research events?
- ? Is some eligibility data collected prior to consent to determine if the patient or client should even be approached? How is that data obtained?

Personnel:

- ? Who is designated to obtain consent? Does the investigator become involved? At what point?
- ? What is the minimal training needed to serve as the person informing the subject and gaining consent?

Privacy

- ? Where will the discussion take place?
- ? Is any phone available so the person can consult with a trusted advisor?
- ? What eligibility information makes a person a potential subject and what information becomes necessary after a person is identified? Is this "protected health information" for which authorization is needed?

Putting a name on the line: Consent, being ideally a two-way negotiation, should ideally have two signatures. The person giving the information should be asked to take as much responsibility as the person receiving it.

D. THE CONSENT PROCESS DOES NOT END AT THE START.

Consent shows an intent to proceed through the entire study. Studies of consent show that the information from the consent process may be understood at the moment of consent but is not retained.

Continued interaction

Every interaction with a subject is an opportunity to discuss pertinent information. At the start of a new questionnaire or a clinical visit, a few sentences of introduction and a probing question can elicit information about continued comprehension.

Significant new information

The agreement the subject is making is reciprocal; investigators have the responsibility of bringing the subject up to date about new information that might alter the decision to participate. This information may or may not require use of a consent document; it certainly requires informing the subject!

Modifications

Subjects who have consented have agreed to a particular set of facts, procedures, tests, or events. If the protocol is modified, the validity of that consent could be challenged. Although total re-consent is not required, the changes should be described and the subject

should be asked about continuing in the study given the new circumstances.

E THE INFORMATION SHOULD BE AVAILABLE IN A LANGUAGE UNDERSTANDABLE TO THE POTENTIAL SUBJECT

If the investigator, the staff and the intended subjects all speak English at the same literacy level, one communication issue is made much easier. This is rarely the case.

The information leading to informed agreement should be between two people speaking the same language. In addition, once a person gives consent in a particular language they should be able to expect that someone speaking that language will be available to answer questions and in emergencies.

Translating the initial information is not sufficient. A commitment is required.

Idioms: Formal language and local language differ. IRC suggests that sites back-translate – at least orally – all the translated forms to be used.

The simplest example is the car, the Nova, that was advertised in Mexico where No va means no go. Sales were poor.

Some questions on surveys have translated to mean very different things.

V THE CONSENT DOCUMENT IS SIMPLY A DOCUMENT.

Consent occurs in an exchange of information and an ensuing agreement.

A consent form is primarily evidence of the basic information transmitted to a subject.

The form should be viewed and used as a tool to aid subject's understanding of the information. To this end, IRC encourages succinct consent forms that are easy to read. Forms should be written in language such as that to be found in the daily tabloids.

No investigator may involve a human being as a subject in regulated research unless legally effective informed consent has been obtained from the subject or the subject's legally authorized representative.

A. WHAT ARE THE PURPOSES OF A FORM?

1. *The document serves as evidence*

Aside from its main function – transmitting information – a consent form serves to protect. Were its function solely to protect the subject, the form would be signed by the investigator and given to the subject to keep in case he or she should later need proof that something was not revealed. Instead, of course, the subject signs and lets the investigator retain the original. This, then, can be used in defense of the investigator. To mitigate this, it is suggested that both parties to the discussion must be given a copy of the signed form.

2. *The consent document is an informational tool*

The basic information is reduced to a document to be used as a departure point in discussion and to be given to the person so that he or she retains reference information.

Many learners are auditory rather than visual. Reading the consent form with the subject helps those people as well as those with hidden illiteracy.

? As all learners are not the same, what visual, auditory or other supports are available? Are there web sites, videos, or comic books?

? Is there any reason to suspect any limitations (other than the lack of a medical education) on the subject's ability to comprehend the information?

? Will more than one consent form be used? Will more than one version of each consent form be used? Why?

? Are there other materials to supplement the consent form?

? Are all forms and versions of forms written at a language level appropriate for the population?

? Are translations required?

? Are the subjects likely to be literate or must arrangements for reading or oral translation be included?

3. *The consent form is a memory tool that can assist with compliance.*

Multiple studies have made clear that few patients or subjects retain much information for very long. It is important to reiterate the facts at intervals. The consent form is one good tool.

? Is there a plan to review the information at intervals?

? Can a reason to review the form at home such as a calendar be integrated?

4 *The signature on the form is proof – of something.*

Can you hear the plaintiff's attorney saying, "Ladies and gentlemen of the jury, yes, my client signed this form. But during this trial I shall demonstrate to you just what that signature meant. My client may have signed. But it did *not* mean she understood. Had she but known what she knows now...."

5. *Supplements and alternatives to forms*

An IRB must determine that: "Informed consent will be appropriately documented, in accordance with and to the extent required by" 21 CFR 50.27 or 45 CFR 46.117. The subsequent section says that, except when all or some of the consent is waived, "informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject ..." The next section (b)(1) says that the written consent document is one that "embodies the elements of informed consent required by 50.25."

Traditionally, the only alternative to the long form was the short form. Not used very often, the short form certifies that the consent elements were presented orally and the document is signed and witnessed. The IRB may require an information sheet to be given.

Often used without IRB knowledge, many people explaining consent have used pictures or models available within the immediate setting, and have drawn diagrams.

Today there are multiple other methods of transmitting the information. There are web-based programs that provide a sensory experience. There are videos that offer visuals and oral presentations. These media serve to make the presentation consistent across subjects and sites. Some can measure time spent on a module.

The media should fit the audience. Some might find a comic book format more understandable than prose.

6. *Translations and Languages*

It is impossible to plan for every language. It is sometimes best not to include a person who cannot be informed sufficiently and who cannot discuss their concerns and questions or report their problems easily.

IRC does not require translated documents to be certified.

- a. Translated documents should be back translated into English by a speaker of the language from that geographic area so that local idiom and words are appropriate.
- b. The site should have a staff member who speaks the language, or have plans to assist a subject during their study participation.

B. WHO AUTHORS A CONSENT DOCUMENT AND WHO HAS MODIFICATION RIGHTS?

Consent forms are often written by clinical or regulatory people within the sponsoring company as templates for multiple investigators to use. These initial templates often have input from company attorneys. The templates are then modified by each investigator for presentation to their various IRBs with their own templates. The IRB members often edit freely. In the end, the text is written by committee – and often reads like it.

The FDA does NOT approve consent forms. It may review them within a submission packet and it may note the absence of a required element. The FDA has rarely objected to too much information. The FDA's regulations leave approval of the consent document to the IRB.

- ? Is it possible to have an outsider read the text to determine if it is

understandable to a person without insider knowledge?

- ? If there is a group in the company that writes “messages” for the public, (e.g., marketing or patient education) can that group be involved?

C. EDITING AND FORMATTING THE CONSENT DOCUMENT.

Which would you rather read; a lease or mortgage papers or TIME or PEOPLE? There is no reason for consent forms to be difficult to read. There is no reason not to include pictures or diagrams, a calendar or schema or a side-bar box with definitions.

The best consent form will:

- look inviting to read,
- have language that those in the expected population can probably read,
- be organized in a reasonable, clear fashion,
- contain all the required elements of consent,
- contain other information one might expect the subjects to desire, and
- be objective, not misleading, and not contain extraneous or diversionary information.

A consent form that is not visually appealing is not likely to be read.

You are standing in the check-out line and you have a long wait. Would you rather read the eye-catching materials found there or the legal document in your briefcase?

WRITING IDEAS

- Look at an 8th grade social studies book for language level. Check its format for type face and layout ideas.
- Learn to use a readability checker. They are not perfect but are helpful.

WRITING RULES

1. Use consistent personal pronouns throughout. IRC prefers use of second person. “We” are giving “you” information “you” can use to decide.
2. Write at the grade level appropriate to the intended subject population. Have several non-medical people of that literacy level read it for understanding. Talk to a 7th grade English teacher.
3. Eliminate the witness line. Add a line for the signature of the person gaining consent. Provide separate lines for all who are to sign.
4. Have a line for the printed name for everyone signing. They might need to be read later!
5. Do not imply that signing the form signifies understanding. Certifying to understanding does not assure it. Taking out “I understand that ...” will usually leave a nice declarative statement.
6. Use small paragraphs. Large, dense paragraphs are more difficult to scan. Consider that two narrow columns are easier to track across than one wide column.
7. Outline it first. The risks should be grouped together. The required elements are a list and not an outline.
8. Number every page and label each with the date that version was generated. Use the header/footer function.

Put the protocol identifying number in the footer; it means little in the title.
9. If there are supplements such as timelines, lists of symptoms or contraindicated drugs, charts or the Bill of Rights, the consent form should clearly refer to them.
10. It should look like something you would like to read. It should have large print with small paragraphs like

the newspaper instead of looking like

mortgage papers.

Dated: 3/24/03

VI. THE ELEMENTS OF INFORMATION REQUIRED OR MENTIONED IN THE REGULATIONS

A legal opinion in the 1960's* said that it was not necessary for subjects to have a medical education; they had to have sufficient information available upon which to make a decision.

The FDA regulation (21 CFR 50) describes eight required and six additional elements of consent and the situations in which exceptions from the general requirements may be made. NIH rules are almost identical.

Nothing in the FDA regulations preempts state law. Several states have more restrictive rules. California law specifies ten elements of consent. In addition, California requires use of an Experimental Subjects Bill of Rights.

Consent forms should include the eight basic elements and, when appropriate, the additional elements organized so that they will best make sense to the least sophisticated segment of the proposed subject population. This may require reordering the elements. It may also require additional tools such as pictures, a graphic display, or a schedule of events. No consent document may waive or appear to waive any legal rights or release or appear to release the investigator, the sponsor, or its agents from liability for negligence..

* Cobbs v Grant

1. EXCULPATION

21 CFR 50.20: "No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Exculpate: (ex+culpa) to clear from alleged fault or guilt. Syn Absolve, Exonerate.

Some consent forms are written to protect the investigator and sponsor from the possibility of later suits. This is not the purpose of a consent form. It is inappropriate and it is illegal.

Exculpatory language may creep in unexpectedly. It may surface after review by counsel or an insurer. Many consent forms retain this point of view when there language is peremptory or when (forbidden) exculpatory clauses are included.

B. EIGHT ELEMENTS OF INFORMATION ARE NECESSARY.

Although there are eight elements, these can be sub-divided as we have here. They need not (should not) be in this order in every instance.

1. A statement that the study involves research,

The word "research" is generally important. "Study" is used in multiple ways and can be familiar and softening. People have blood studies and study for exams. The primary goal to communicate is that this is not necessarily intended to be the best choice for the person; it is research and, as such, has a broader purpose.

an explanation of the purposes of the research, and

The purpose is to answer some question; it is not to "treat" or to "help you" or to accomplish anything for an individual. The study outcome cannot be presumed.

the expected duration of the subject's participation,

Some subjects are expected to donate considerable time for very little personal return. Unless they are very altruistic or unless they recognize the donation from the start, compliance will drop rapidly. A subject should be able to determine if it will be necessary to take time from work, to hire a baby-sitter, or to get the car on that day. This element is often taken care of in a good procedures description.

a description of the procedures to be followed, and

Often a boundary issue, this section should make clear what is to be done **as a result of agreeing** to be a participant. What is different from normal practice? What is out of the ordinary? Is this simply a pre- and post-test after introduction of a program, is it an additional tube of blood, or is it a totally experimental form of surgery or a brand new drug never given to a human before? Are there usually 2 follow-up appointments and there are now 3?

identification of any procedures which are experimental.

The background section (with the purpose) should make clear the experimental variable and procedures. There should be no reason to misunderstand that something is brand new, experimental and not previously done on humans. On the other hand, the absence of anything experimental need not be noted.

2. *A description of any reasonably foreseeable risks or discomforts to the subject.*

Subjects should be told about any problems that are reasonably foreseeable and those rare problems -- perhaps only theoretical -- that could be serious. A 99% chance of getting a headache should be mentioned as should a .5% chance of losing all circulation to the hand. A 5% chance of something discomforting or temporary need not be mentioned unless it is symptomatic of something else.

Risks may be other than physical. Compromised privacy, being identified as a slow learner in school, or receiving back some unwanted or unexpected information are all forms of harm.

3. *A description of any benefits to the subject or*

The benefits to subjects are often as problematic as the risks. There might be only a 50% chance of having the active drug and there might be an expectation it will be effective only half the time. There might be no personal benefit. Sometimes only altruism is involved as a benefit.

to others which may reasonably be expected from the research.

There should be a reasonable expectation that the study will result in some answer which might benefit someone or something in the future. Basic research may be development of a fact useful in developing knowledge. It may be that the sponsor will be the major beneficiary or that the study might allow consideration of another competitive drug or device.

4. *A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.*

In order to decide to participate, one needs to know the available options. It may be the only alternative is to say no. The option might be to refuse and to get

the same treatment off study. There might be other forms of administration or other complementary treatments. Participation in a competing study might be more appropriate. The choices, the available options -- need to be clear.

5. *A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and ...*

that notes the possibility that the Food and Drug Administration may inspect the records.

Confidentiality procedures are rarely absolute. Privacy cannot be promised.

A breach of privacy is a harm. The possibility of a breach is a risk. In many instances this risk should be incorporated into the risk section.

This section is often written without adequate concern about how well it will be understood. What are "other regulatory bodies?" (Homeland Security could be another such body.)

FDA regulated: The Food and Drug Administration, the sponsor (by name) and the IRB should be mentioned.

ICH: If the data may be used in other countries it might say, "regulatory agencies like the FDA in other countries."

HIPAA: Private information sent to a researcher should only be sent with an authorization on file with the sender. To send private information or allow others to see it, an investigator must follow the rules in 45 CFR 164.512(i)

6. *For research involving more than minimal risk,*

If there is less than minimal risk, this element may be omitted. Remember that not all harm is physical.

an explanation as to whether any compensation and

What might a subject want to know? A subject might wonder if anyone else will cover the costs or if he or she will be left holding the bill. The subject might not need to know exactly who will pay; only that the bill will be covered.

Note: Any haggling in the backroom should be invisible to the subject. The subject needs the result.

an explanation as to whether any medical treatment are available if injury occurs and,

From some harms there is little possibility of recovery (e.g., if the artificial heart stops) and from some there is a good possibility with rapid care. Subjects should have some idea about proper action to take in the event of harm.

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

Often the investigator is listed but - although he or she should have - has little information about the policies. The title of a person with information should be listed.

7. *An explanation of whom to contact for answers to pertinent questions about the research and*

Generally the research team is the contact although occasionally others may have better information.

research subject's rights and

Q. When should subjects be told they have rights and what they are? A. During the consent process. If so, then it stands to reason that the person to talk to about subject rights is the investigator.

whom to contact in the event of a research-related injury to the subject.

When injured, a person needs to have information about treatment and billing. This is the person who is most likely to have such information. It is not likely to be the IRB.

8. *A statement that participation is voluntary,*

This is akin to putting words into another person's mouth or volunteering in the old military. "Thank you, soldier, for volunteering." If this is truly telling the person something, it should be telling them that participation should be voluntary and that the person should not feel pressured by anyone.

that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and

It is common to simply quote this language which, in many cases, does not make sense. In a pre-post test of a new curriculum, what benefits might be involved?

that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

As above, the subject should be aware of what would happen if he or she wishes to drop out. Is there any safety issue if the drug must be tapered? Can data or specimens be withdrawn? Subjects should not be required to return for exit visits but should be very aware of safety issues.

C. THE ADDITIONAL ELEMENTS OF CONSENT

There are six "additional" elements of consent. These are required if they are applicable to the study and are optional if they are not applicable.

As these elements may add length without meaning, carefully consider whether the information is applicable to the study and proposed subject population.

1. *A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become*

pregnant) which are currently unforeseeable.

If there is any foreseeable risks, those should be in the risk section and the precautions (e.g., contraception) that are in the procedures section should be clearly linked to the risk.

If there is no foreseeable risk – no women are involved, there has been no report of harm in the class of drug, the device is for monitoring only – then this element is not required.

2. *Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.*

This is generally a safety or compliance issue and, as such, is often cast as rules of conduct, which, if broken, could result in participation being stopped.

3. *Any additional costs to the subject that may result from participation in the research.*

As a general rule, subjects should not be out-of-pocket any money as a result of volunteering to help in the conduct of a study. They should be advised of things that will be an expense to them: babysitters, transportation, and any items that insurers might not cover.

4. *The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.*

This is very similar to the discussion of withdrawal. Even though withdrawal is a right, there might be consequences and trepidation.

5. *A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.*

Learning about an important -- but immediate -side effect could be interesting but will certainly not alter the decision made by subjects who already stopped using the active study drug.

Telling subjects they will be told about new information when the only procedure is a venipuncture misses the point.

This element should be in forms where there is a foreseeable chance of finding new information during the duration of the subjects participation.

6. *The approximate number of subjects involved in the study.*

When might it be interesting for a potential subject to know how many people are to be involved? If ten are sought and they are the first to use the thing, this might be very relevant. If thousands are being sought, could the information be falsely comforting?

D. CALIFORNIA'S ADDITIONAL REQUIRED ELEMENTS

These are the California elements that are not represented among the FDA's required elements. Again, we caution that they must be included and explained when relevant.

1. *If a placebo is to be administered or dispensed to a portion of the subjects involved in a medical experiment, all subjects of such experiment shall be informed of that fact.*

2. *An estimate of the expected recovery time of the subject after the experiment.*

3. *The name, institutional affiliation, if any, and address of the person or persons actually performing and primarily*

responsible for the conduct of the experiment,

Most consent forms include the name of the investigator and his or her site and address; this makes it required.

4. *The name of the sponsor or funding source, if any, or manufacturer if the experiment involves a drug or device, and the organization, if any, under whose general aegis the experiment is being conducted.*

In California, for an FDA regulated study, the sponsor must be named.

5. *The name, address, and phone number of an impartial third party, not associated with the experiment, to whom the subject may address complaints about the experiment.*

This is usually the IRB. IRC acknowledges that people have lives, get sick and are sometimes not at work so we prefer to have subjects call the office on the subject line.

6. *Subjects must be given a copy of the Experimental Subject's Bill of Rights.*

There are two versions of the Bill of Rights that are commonly used. One uses the words directly out of the law; the other uses lay language. Not unexpectedly, IRC prefers the lay language version which can be found on our web site.

VII. Consent may occasionally be waived in part or in whole

A. Source of rules

B. Levels

1. Waiver of consent document

3. Waiver of consent

VIII. Some Sample Language

INTRODUCTION

Being in a study is different from being a patient. As a patient, the doctor's focus is on you. As a subject, the investigator must also follow the rules of the study. Those rules and your individual needs may come into conflict. In the event of a conflict, the

study doctor's first responsibility is for your safety and welfare.

This consent form describes the research study and your role as a participant. Please read this form carefully. Do not hesitate to ask anything about the information provided; it should stimulate your questions.

Dated: 3/24/03

The doctor or nurse will describe the study and answer your questions.

TREATMENT AND COMPENSATION FOR INJURY (when there is more than minimal risk)

1.

In life and in research there are risks of some harm occurring. Although we don't expect any harm, we have planned for the possibility.

The likely injury is ... The treatment would be given in an emergency room. Call 911 immediately. All costs associated with this injury will be covered.

2.

There is no program in place in the event a subject is injured. If it happens, we will attempt to work it out.

3.