

The Consent Form Revisited

It has been more than a decade since the Code of Federal Regulations ¹ clearly defined the responsibility of the research investigator to obtain written consent from human subjects engaged in clinical trials. The “elements of consent” have been widely disseminated by various federal agencies concerned with the protection of human subjects engaged in research.^{2,3}

Researchers, regulatory affairs experts, and institutional review board members possess more than a basic knowledge of consent requirements. Food and Drug Administration (FDA) fact sheets are readily available for reinforcement, and most hospitals circulate consent form prototypes as templates. Why, then, is the consent form the biggest stumbling block for most investigators? Why, in the face of easy, step-by-step instructions for the investigator, do most consent forms require two and three revisions? How can principal investigators be taught to view the consent form as a useful tool in educating prospective subjects rather than a tiresome exercise devised by obstructive bureaucrats?

The solution to the dilemma of producing a readable document that reflects the procedures, risks, and benefits of the protocol and also meets regulatory requirements lies in the investigator’s ability to separate himself or herself from the investigation and view the consent document with the fresh eyes and open mind of a research subject. Each of the standard required elements of consent will be reviewed to uncover common pitfalls and problems.

EXPECTED DURATION OF PARTICIPATION

To take this phrase at face value, the investigator would simply assign a time span such as “two weeks” or “three months” and move on to the next category. This answer might satisfy regulatory requirements, but it would leave the subject uninformed. Much more useful is a disclosure such as: “one week of testing and observation followed by a week of treatment with the test medication.” OR, “an hour of surgery with a post-operative follow-up of six months.” Even better would be a breakdown inclusive of geographic factors: “a week of treatment *as an inpatient* followed by weekly outpatient visits to the doctor’s office over the next two months.”

THE PURPOSE OF THE RESEARCH

The purpose of a study is often obscured by excessive background material, causing even intelligent and sophisticated readers to read and reread the material to discern the research objective. This section may become the repository for extraneous material, the purpose of the research obscured by lists and disclaimers, with text punctuated by introductory phrases such as “I understand” or “I certify”, the sum total of which defies comprehension!

Typical of many deficient consent forms would be a listing of inclusion and exclusion criteria in the “Purpose” section, items

that surely belong in a protocol but that cause confusion in a consent form. “I understand that I must be over eighteen years of age,” I understand that I must not be taking any antibiotics,” or “I have told my physician that I do not have kidney disease,” have no place in a consent form. If the subject is not 18 years of age, he/she should be declared ineligible immediately. If the subject is taking antibiotics and the protocol excludes such medication or the subject has a pre-existing condition such as a kidney disease that precludes participation, initial screening prior to protocol-mandated activity should uncover these facts and render the subject ineligible. An ineligible subject should never *receive* a consent form.

The purpose of a research project should be expressed succinctly. Purpose might be described in the following ways: to determine if once-a-day dosage is as effective as the standard twice-a-day regimen; to test safety; to test safety and efficacy; to find out which of four dosages is most effective; to determine whether surgery followed by chemotherapy is as effective as surgery followed by radiation; to determine whether drug X, FDA approved for use in depression, is also effective in treating subjects with obsessive-compulsive disorder.

**DESCRIPTION OF
PROCEDURES TO BE
FOLLOWED AND
IDENTIFICATION OF ANY
PROCEDURES THAT ARE
EXPERIMENTAL**

If a common problem in consent forms lies in the investigator's providing too much material in the foregoing "Purpose" section, an equally common difficulty is found in the *omission* of important material in the "Procedures" section. Researchers often forget to include a medical workup, psychiatric interviews, videotaping, laboratory assessments, or a drug washout period as part of methodology.

Commonly, consent forms fail to note that subjects will be expected to record their observations in a diary or quality of life instrument. While this information might seem trivial, investigators must not make value judgments concerning which items relative to participation should be included. Everything relative to a subject's participation belongs in this section.

Subjects should be able to determine by reading this section whether some phases of research, for example, would necessitate hospitalization. They should also be appraised of the number of study visits expected during the treatment period and follow-up period.

While the "Procedures" section contains the fact that subjects will receive one of the available treatment arms, it is necessary for the investigator to specify that such assignment will be based on randomization. Also necessary in this section would be information concerning crossover

features or use of placebo at some point in the study.

A subject is entitled to know whether a study is single blind or double blind. If deemed appropriate, subjects should also know that if a medical emergency arises, the study blind for that patient's therapy will be broken.

While investigators generally detail various drugs that might be administered in the "Procedures" section, they often fail to include the route of administration. It is debatable whether dosage should be included. A lay subject would not be expected to understand, for example, whether 3 mg is a large or small dose. It would be better to omit the dosage entirely or to supply some explanatory information, such as "3 mg, which is the standard dose," "4 mg which is considered investigational," or "2 mg, which is the standard pediatric prescription."

In the same vein (!), when blood is to be drawn, the investigator should provide the subject some idea of the amount needed. If the consent form reads, "2 ccs will be drawn," this, by itself, is not illuminating. The phrase, "2 Tbsp of blood will be drawn," conjures up images of Dracula! A better description would be, "Two cubic centimeters of blood will be drawn, which is the equivalent of less than half a teaspoon." The quantity of blood drawn might also be expressed to the subject as, "The amount of blood to be drawn during the study period will total about half the amount that would be taken in volunteers who routinely donate blood."

Another common problem lies in the failure of the investigator to differentiate between standard care

and investigational procedures or to note the frequency of procedures that are a requirement of participation in the research project as opposed to the expected frequency of such procedures in routine clinical practice. If, for example, routine clinical care would involve one lumbar puncture or one endoscopy, but participation in this trial involves two or three, these facts should be clearly stated in the "Procedure" section. The additional risks should also appear in the "Discomforts and Risks" section as well.

**POSSIBLE DISCOMFORTS
AND RISKS**

Investigators are usually forthright in listing the possible side effects of the test drug. A problem, however, lies in the less obvious aspects of risk. In the case of investigational drugs, a statement concerning the possibility of unknown side effects should be included.

If blood is to be drawn, the possibility of pain and swelling at the venipuncture site should be included. If there is a drug washout period, subjects should be warned that symptoms might worsen; if there is a placebo group, the same proviso should appear. If women of childbearing potential are eligible for participation in a study, in most cases the "Risks" section should include a statement that since risks to the fetus are unknown, these subjects should use a medically accepted form of birth control.

If an FDA-approved drug is to be used with an investigational drug, side effects of both drugs should be listed. Similarly, if any

drug is mentioned as a “rescue” medication, such as a medication offered to counter nausea, the risks and side effects of this medication should also be included. Simply stated, any drug, hormone, or therapeutic preparation noted in the “Procedures” or “Methodology” section of the protocol should occupy a corresponding place in the “Discomfort and Risks” section of the consent form.

Sometimes a drug, such as a monoamine oxidase inhibitor, can prove dangerous in the presence of certain foods. If this is the case, the foods to avoid should be listed in the consent form. Similarly, if a medication is rendered less effective when certain foods are ingested (as is the case with some oral antibiotics), a warning to this effect should be included in the “Risks” section. If a possible side effect is drowsiness, subjects should be warned in this section not to drive or use heavy machinery.

A common error lies in listing side effects, even in lay terms, without explaining the possible sequelae. If, for example, a side effect is “depressed white count,” should the subject expect the sniffles or pneumonia? If “elevated blood pressure” is noted, should he worry about headache or stroke? If “impaired kidney function” is involved, should he expect minor problems in urine output or imminent hook-up to a dialysis machine? Similarly, subjects should be told whether the side effects are transient and whether they are reversible.

POSSIBLE BENEFITS OF PARTICIPATION

Obvious direct benefits of participation are apparent to most investigators: eradication of infection, shrinkage of tumor, alleviation of pain, etc. This section, however, should also contain indirect benefits to be derived by the subject. If participation would result in more complete medical attention, additional monitoring for a medical condition, or tests or drugs at no charge, these facts should be included. If the only benefit to be derived is payment by the sponsor (and the institutional review board has determined that the amount is not so large as to be coercive), the investigator should state “subjects will be paid ‘\$X’ for participation.” It should be made quite clear in the consent form, however, what the conditions for payment are. If, for example, subjects will be paid only on *completion* of the trial (and not if they drop out before completion), the consent form should clearly reflect this provision.

Many research projects are not treatment protocols, and subjects are not expected to derive any benefit. Dose-ranging studies, for example, would not provide benefit to the subject. This is permissible as long as the subject is aware that he or she will derive no direct benefit from participation. The wording in this case may be stated as, “I will derive no direct benefit, but others with my condition may be benefited by knowledge gained through my participation.” In the case of studies in which children or the mentally ill are involved, specific federal laws preclude participation when no direct

benefit will be derived or no knowledge about the subject’s specific condition will be gained, in the face of greater than minimal risk.^{4,5}

ALTERNATIVE TREATMENT

Investigators are generally forthright in stating alternative treatment, drugs, procedures, etc. Often, alternative treatment is expressed in terms of “an FDA-approved antibiotic prescribed for this indication” or “counseling and behavior modification instead of drug therapy,” etc. Sometimes, however, for some conditions, there is no clearly effective therapy and no accepted effective medical alternative to administration of an investigational drug. If this is the case, the investigator should not hesitate to express alternative treatment in this manner. Difficulties arise in describing alternative therapy in a study whose purpose is to test metabolism of one agent vs. another or a study to determine whether one formulation of a drug is more palatable to subjects than another—studies that are not treatment or efficacy studies. The correct way to express alternative treatment in these instances is to state, “not to participate” or “to receive the test medication off study.” Many investigators simply sidestep this element of consent, not realizing that it must be addressed and that not to participate is a perfectly permissible alternative.

Most investigators generally find little difficulty in addressing the remaining elements of consent: describing the extent to which confidentiality will be maintained; explaining the availability of compensation and/or medical

treatment should injury occur; identifying the source for further information concerning compensation and treatment; noting that participation is voluntary and that refusal to participate involves no penalty, loss of benefits, or care to which the subject is otherwise entitled; listing whom to contact with questions concerning the research, subjects' rights, and research-related injury.³ Institutions and some sponsors generally distribute consent forms that contain these statements, written by in-house counsel.

Problems do arise, however, in a few remaining areas. Not infrequently, the single most important and legally binding statement will be missing: "I hereby agree to participate," or "My signature below indicates my willingness to participate in this research project."

Also missing occasionally, but very useful to include, is a directive concerning the "Witness" on the consent form. A study nurse, project coordinator, or co-investigator should not be recruited as witnesses on a consent form since this might be construed as coercive. A relative who accompanies the subject, a receptionist, or some other office worker would be an acceptable alternative.

It is required that the investigator provide the subject with a copy of the consent form. To assure compliance, it is useful to include a statement to the effect that "A copy of this consent form has been offered to me." Some organizations have seen fit to print the consent form on carbonless, multiple pages, with the top copy going to the investigator and the

second copy designated for the subject.⁶ This is an excellent idea.

A consent form is not synonymous with informed consent.⁷ Informed consent implies an interaction between the investigator and the subject. Obtaining informed consent is a *process* whereby the subject (or his legally authorized representative) is given information and provided with a choice consistent with the best of ethical principles-without undue inducement, constraint, or coercion.

A consent form, on the other hand, is simply documentation that the process of informed consent has taken place; it is a written adjunct to both the experimental design and the face-to-face interaction between investigator and subject.⁶ It is never intended to replace the dialogue which is the fundamental presumption behind informed consent. It must stand alone, however, in the sense that it must be comprehensible, informative, and forthright in the absence of the responsible investigator for explanation of wording or intent.

A readable consent form that accurately reflects the research protocol and conforms to federal standards is within the reach of any investigator. If the investigator understands that subjects are best served by taking care to address the points raised in the foregoing sections, and if he/she recognizes that the best subject is an *informed* subject, then the investigator will appreciate a carefully written consent form as a very effective means in achieving this goal. The time spent in writing the consent form will be well spent.

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