This guidance addresses:

- Eight Basic elements of informed consent
- Additional elements of informed consent
- Other information required by the IRB

EIGHT BASIC ELEMENTS OF INFORMED CONSENT

Legally Required Under: Common Rule 45 CFR 46.116(a)
and FDA Regulations 21 CFR 50.25(a).

Research Statement (Requirement #1)

Informed consent information must include the following:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. An explanation of the expected duration of participants' participation.
4. A description of what procedures will be followed.
5. Identification of any procedures that are experimental.

Research & Treatment. If the treating physician is also the research investigator, some participants may not realize that they are participating in research, but may believe they are only being treated for their condition. By specifying the purpose of the research and describing experimental procedures, it is intended that participants will be able to recognize the difference between research and treatment.

To help minimize the tendency on the part of participants to confuse research and treatment, the IRB requires that the consent document avoid using the term "treatment" to describe an investigational item or experimental procedure. It may, however, depending upon the particular protocol, be appropriate to describe a goal of the research as determining whether or not the item or procedure is an effective treatment for a particular disease or condition.

FDA Investigational Drug, Device, Biologic. If the test article is an investigational drug, device or biologic, the IRB requires that the consent document disclose that the drug or device has not been approved by the federal Food and Drug Administration. If the drug/device has been approved for certain indications or age groups but is being investigated for another indication or age group, the consent document should disclose that also.

E.g., "Drug X has been approved for the treatment of bone cancer, but not for the treatment of brain cancer. In this research, we are investigating whether or not Drug X is safe and effective for the treatment of brain cancer."

The IRB requires that all consent forms for studies of investigational drugs and devices include a statement that a purpose of the study is to evaluate the safety of the test article. In studies that also evaluate the effectiveness of a test article in addition to safety, consent documents should include both purposes, but should not contain claims that the article has been proven to be effective.

Phase 1 drug studies often have the exclusive purpose of determining the pharmacological activity of the investigational drug and how high a dosage can be administered before unacceptable toxicity is reached. The IRB does not permit the consent document for such

phase one studies to describe the evaluation of effectiveness as a study purpose. If, however, a phase 1 protocol includes the collection of data relating to possible effectiveness, the IRB may permit the consent document to list this as a secondary purpose. In such situations, the IRB requires the consent document to be explicit in describing the limited experience to date in administering the investigational drug to humans (e.g., "this is the first time use in humans of drug X" or "To date, drug X has been administered to 10 human beings"). Moreover, in such situations the benefits section should include a statement to the effect that most phase 1 drug studies do not result in benefit to the participants. (E.g., "It is possible that you will (describe potential benefits). However, you should be aware that most phase 1 studies do not result in benefit to participants.")

Reasonably Foreseeable Risks or Discomforts (Requirement #2)

The IRB requires that Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. Risks should be listed in descending order of probability and magnitude (risk of death, even if remote, before risks associated with blood draw, for example). The informed consent information must include a narrative of the types of risks that are likely to be encountered, including, for example: (i) the risk of the participant's condition worsening during a drug wash-out period, (ii) in a placebo-controlled study the risk that the participant's disease/condition may go untreated and the participant's condition may worsen if the participant is assigned to the placebo arm of the trial, (iii) the risks associated with other medications or procedures associated with the study (i.e. venipuncture, concomitant medications, exposure to radiation), and (iv) risks associated with the test article that are currently unforeseeable. This narrative should include a discussion of relevant animal data. (For a fuller description of risk, see HRPP Chapter 9.)

Reasonably Expected Benefits to Participants or Others (Requirement #3)

The IRB requires that informed consent information must describe any benefits to participants or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on participants. Payment for participation in a research project is not to be considered as a benefit of the research. If no direct benefit to the participant is anticipated, the IRB requires that this be clearly stated in the informed consent discussion and consent document.

Example – FDA Phase I Study. An example is a study of the physiological mechanisms of the induction of airway narrowing in healthy persons. Another example is a phase one drug study, whether in healthy or ill participants, directed solely at investigating the pharmacological activity or safety of the investigational drug. In such circumstances, it is not appropriate to state that it is not known whether or not the participant will benefit from participation in the study. Rather, the consent document should simply state that it is not anticipated that the participant will receive any direct benefit from the research, although there may be benefit to others.

The protocols for some phase 1 drug studies include the evaluation of effectiveness as a secondary purpose of the study. In such situations, the IRB may allow the consent document to describe potential benefits, together with a statement to the effect that most phase one drug studies do not result in benefit to the participants.

Example – Placebos. If the research involves a placebo-controlled trial in which some participants never receive the investigational item, the consent document should include a statement to the effect that if the participant is assigned to the placebo arm of the study, it is not anticipated that he or she will receive any direct benefit from participation in the research.

The IRB requires that in all placebo-controlled trials, the consent document disclose the chances that a participant will receive the investigational item or procedure.

Appropriate Alternatives (Requirement #4)

The IRB requires that informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the participant. Enough detail must be presented so that the participant can understand and appreciate the nature of any alternatives and must include a discussion of their relative risks and benefits. It is not sufficient simply to state, "the doctor will discuss alternatives to participating."

Extent of Confidentiality (Requirement #5)

The IRB requires that informed consent information must describe the extent to which confidentiality of records identifying the participant will be maintained (or not maintained). Research often poses the risk of loss of privacy and breach of confidentiality to participants. Many persons who would not otherwise have access to identifiable, private information about the participant may be involved in the research process. Consent information should describe any procedures that the research team will use to protect participants' private information. In some research, loss of privacy may be the greatest risk of participation. (This is discussed in greater detail in HRPP Chapter 11.)

Example – Mandatory Reporting to Others. For example, during the course of research an investigator may learn about incidents of child or elder abuse that the investigator is required by law to report to public authorities. In cases where it can be anticipated that a protocol is likely to generate such information, the IRB requires that the investigator alert potential participants through the consent process to the possibility of the particular legally required disclosure to public authorities. In that manner, participants can take account of the risk to their privacy in deciding whether to participate in the protocol. See HRPP Chapter 11 for a more detailed discussion of this example and of privacy and confidentiality.

Example – FDA & Other Agency Access Statement. The substance of the following statement is required for FDA-regulated research:

> *Because this research involves articles regulated by the Food and Drug Administration (FDA), the FDA may choose to inspect and copy medical or research records that identify individual research participants.*

A comparable statement is recommended for any research that is subject to audit or inspection by any funding agency or sponsor.

Compensation or Treatment for Injury (Requirement #6)

The IRB requires that informed consent information for research involving more than minimal risk include explanations regarding:

1. Whether any compensation is available if injury occurs;
2. Whether any medical treatments are available if injury occurs;
3. In accordance with VA policy, a statement that veteran-participants shall receive medical care and treatment for injuries suffered as a result of participating in a VA research program (see discussion in HRPP Chapter 16.2 and VA consent form template);
4. A description of any such compensation or treatments or where more information about them is available; and

5. A description of any applicable state law.

When questions arise pertaining to the clarity of consent language regarding research-related injuries at Stanford facilities, the IRB staff work closely with the Research Management Group and the Office of Sponsored Research to review and compare the contractual language in the sponsored research agreement with the language in the consent document. The VA has required language contained in the VA informed consent template.

Contact Information (Requirement #7)

Informed consent information must include opportunities for potential participants to ask questions at all times during the consent process. The information must include details, including telephone numbers, about whom to contact for four specific situations:

i. **For answers to questions about the research**—The principal investigator and other members of the research team are appropriate contacts for this information.

ii. **For answers to questions about participants' rights**—The IRB Office is the appropriate contact for this information, as well as the VA Research and Development Committee for VA protocols.

iii. **In the event a research-related injury occurs**—Depending upon the nature of the research, the research team, the emergency services department, or the risk management office may serve as appropriate contacts for this information.

iv. **For more information about an investigational drug or device**--- The sponsor, or the organization under whose general authority the research is being conducted, is the appropriate contact for this information.

Voluntary Participation Statement (Requirement #8)

The IRB places particular importance that prospective participants understand the research in the context of their medical care and have complete confidence that failure to participate will not jeopardize their care or treatment. Where participants may be vulnerable to coercion or undue influence, for example when research is conducted within the prison system or in the classroom, the IRB ensures that the informed consent information explain to participants that they are free to decline participation or to withdraw at any time without negative consequences. (This is also covered as part of recruitment in Chapter 10.) Informed consent information must contain clear statements of the following:

1. Participation in the research is voluntary.
2. Refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled.
3. The participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

ADDITIONAL ELEMENTS OF INFORMED CONSENT

As appropriate, the following additional elements must be included in the informed consent information. Legally Required Under: 45 CFR 46.116(b; FDA 21 CRF 50.25(b).

Unforeseeable Risks to Participants, Embryos, or Fetuses (Possible Requirement #9):

Some research involves particular procedures or interventions that may result in unforeseeable risks to participants, to the embryo, or the fetus (if the participant is or may become pregnant). For research of such a nature, the informed consent information must warn participants that some risks are currently not known or not foreseeable.

Investigator-Initiated Termination of Participation (Possible Requirement #10):

There may be instances that would require investigators to terminate the participation of particular participants (e.g., participant non-compliance with research, participant not benefiting from research). The informed consent information must specify these circumstances.

Additional Costs (Possible Requirement #11):

If participants must bear any additional costs as a result of participation in the research study (i.e. additional tests, procedures not required under standard treatment, additional hospitalization, costs of investigational drugs or devices, etc.), these must be disclosed in the informed consent information.

If veteran participants are involved, any such costs must be consistent with VA policy concerning veterans' eligibility for medical care and treatment. Those policies are discussed in HRPP Chapter 16.2 and explained in the VA informed consent template.

Early Withdrawal/Procedures for Termination (Possible Requirement #12):

Participants have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for participants to discontinue abruptly. For studies of this nature, the informed consent information must provide participants with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that are not designed to protect the safety of participants who have decided to withdraw.

Significant New Findings (Possible Requirement #13):

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. The informed consent information must detail the procedures for contacting participants if new knowledge or findings are developed that affect the risks or benefits to participants or participants' willingness to continue in the research, and for affirming their continued participation.

Approximate Number of Participants (Possible Requirement #14):

For certain types of research, the informed consent information should disclose the approximate number of participants to be enrolled. For example, the number of anticipated participants might be relevant to an individual enrolling in a clinical trial for an investigational drug or devices.

ClinicalTrials.gov Registration (Possible Requirement #15 – for FDA if applicable):
Statement in the ICF: "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

OTHER INFORMATION REQUIRED BY THE IRB

Common Rule 45 CFR 46.109(b) and FDA Regulations 21 CFR 56.109(b)

The IRB may also require that information, in addition to these additional elements, be given to the participants when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of participants.

Other Additions/ Deletions—Conflict of Interest Language. The IRB requires additional language relating to any potential conflict of interest by the investigators involved with the protocol or the institution. After the relevant conflict of interest review process, the IRB requires a clear statement in the consent document concerning any conflict of interest that has not been eliminated when such investigator is allowed to continue. Potential conflicts of interest and the review process are addressed in detail in HRPP Chapters 3 and 14.

Other Additions/ Deletion—Exculpatory Language. The IRB requires that the consent document be free of exculpatory language where the participant waives or appears to waive any of his or her legal rights, or releases or appears to release the protocol director, the sponsor, the institution or its agents from liability for negligence. The IRB prescribes consent form language that explicitly states that the participant does not waive any liability rights (e.g., for personal injury) by signing the consent document. The IRB requires that this language appear in the consent document. See the informed consent templates.

The following are examples of language that the IRB considers exculpatory:

> By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances.
>
> I voluntarily and freely donate any and all blood, urine and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.
>
> By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
>
> I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.

If examples of the above language are found in the consent document, the IRB would consider the following to be acceptable replacements:

> Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.
>
> By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.
>
> Stanford is not able to offer financial compensation nor to absorb the costs of medical treatment should you be injured as a result of participating in this research.
>
> Stanford makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge.

(Examples of exculpatory language and acceptable language are taken from a document on exculpatory language issued November 15, 1996 by the Cooperative Oncology Group Chairpersons Meeting, and included on the OHRP website.)