

Pertinent Excerpts from the Regulations regarding Informed Consent and Subjects Unable to Provide Consent

21 CFR Part 50 – Protection of Human Subjects

Subpart B – Informed Consent of Human Subjects
§ 50.23

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legal representative.
- (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

Comment: The above indicates that IC should be obtained from the subject's legal representative if the subject is unable to provide legally effective consent.

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§ 1.37 **Legally Authorized Representative:** An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in a clinical trial.

Comment: Legally authorized representative is a term that suggests that a person has medical power of attorney for another person, generally a person who is unable to make medical decisions for a variety of reason. For an individual to gain medical power of attorney for another person, most countries require that a court or other judicial proceeding must grant this status.

FDA has stated that "the agency defers to state and local laws regarding who is a legally authorized representative. FDA recognizes that a durable power of attorney might suffice as identifying a legally authorized representative under some state and local laws." For example, a subject might have designated an individual to provide consent with regard to health care decisions through a durable power of attorney and have specified that the individual also has the power to make decisions on entry into research. FDA added that "The IRB should assure that the consent procedures comply with state and local laws, including assurance that the law applies to obtaining informed consent for subjects participating in research as well as for patients who require health care decisions.

FDA recommended that before a person with medical power of attorney (or equivalent) signs a consent form for another person, the study staff member should ask to see documentation that grants this power and should make a note in the source document and/or on the consent that this document was presented and reviewed. A second-best alternative, in a clinically emergent situation, is for the person who had medical power of attorney to present this document at a later time, at which point the staff would enter a note to the source document and/or the consent document. FDA concluded that is not good clinical practice to have a

person who is not the subject sign the consent unless the individual's legal authority to do so be clear. When there is uncertainty, it is better not to enroll a subject under these conditions.

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§ 4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of pertinent aspects of the trial.

§ 4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject, or the subject's legally authorized representative, and by the person who conducted the informed consent discussion.

Comment: For subjects unable to consent, then a legally authorized representative must provide consent on behalf of the subject.

Directive 2001/20/EC of the European Parliament and of the Council (EU Clinical Trials Directive

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

Article 3, Protection of clinical trial subjects

2. A clinical trial may be undertaken only if, in particular:

(b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;

(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation;

Comment: European law also requires use of a legal representative but also expressly requires consideration of weighing the risks against the benefits for including patients unable to provide personal informed consent.