From: Hommel, Carolyn - OC
Sent: Friday, May 09, 2003 10:27 AM
To: [Redacted]
Subject: RE: GCP Request

Dear Dr. [Redacted],

Stan Woollen forwarded your question to me for a response.

I reviewed the document that you provided, but I find that it does not correctly describe the criteria for conducting a study using the exception from informed consent as provided by 21 CFR 50.24. In particular, your document omits specific requirements for these studies, and incorrectly suggests that the "emergency exemption from prospective IRB approval", as set forth in 21 CFR 56.104(c), can be used. To the contrary, ALL studies conducted under 21 CFR 50.24 MUST be prospectively reviewed and approved by an IRB. The exemption in 21 CFR 56.104(c) applies to emergency use of an investigational article as described in 21 CFR 50.23, not 21 CFR 50.24.

In addition, 21 CFR 50.24 contains numerous additional requirements that sponsors, clinical investigators, and IRBs must carry out (e.g., community consultation and public disclosure activities), before a study involving an exception from informed consent in emergency research may proceed.

I think part of your confusion may result from the Information Sheet that you reviewed before drafting your document. That Information Sheet, "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," was replaced by a draft Guidance document, issued in March 2000. You may view the guidance document at the following URL:

http://www.fda.gov/ora/compliance_ref/bimo/err_guide.htm

FDA has received comments on this draft guidance and has re-convened an agency working group which is actively working to issue a final guidance in the near future.

I cannot tell from your e-mail whether you are a sponsor, a CRO, or a clinical investigator site, but I would recommend generally, that you make the draft guidance widely available to your staff, to help answer any questions they may have about this type of research. If you have additional questions after reviewing the draft guidance document, please do not hesitate to contact this office. Our e-mail address is 'gcpquestions@oc.fda.gov'

I hope this is helpful.

Sincerely,

Carolyn Hommel
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Good Clinical Practice Program
Office of Science and Health Coordination
Office of the Commissioner
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This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

-----Original Message-----
From: [Redacted]
Sent: Thursday, April 17, 2003 12:59 PM
To: swoollen@oc.fda.gov
Subject: GCP Request

Dear Stan,
Could you take a quick look at this Q&A and see if there are any flaws in our understanding of FDA GCP policy on this issue.
Best wishes,

[Redacted]

7.7 Q. If a sponsor is considering a study for administering a drug under emergency conditions, what steps must be taken to initiate a protocol and protect subjects?

A. This question addresses very specific situations that can occur at the scene of an accident, on an ambulance, in the OR, or in an emergency room: administration of an investigational drug that is used to treat a clinical condition that is life threatening and requires immediate intervention. In its 1998 Information Sheet entitled "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," the FDA provides specific guidance regarding this situation. This information sheet clarifies 21 CFR 50.24, which addresses exception from informed consent requirements for emergency research.

Persons with life-threatening conditions who can neither give consent nor refuse enrollment are a vulnerable population. Clinical intervention must be given before consent is feasible in order to be successful. As such, they require additional protections. These protections include, but are not limited to:

s There must be a licensed physician on the IRB or a consultant to the IRB who is also not participating in the research who independently reviews the protocol and concurs with its contents.

s The IRB must conclude that there must be no way of prospectively identifying the individuals likely to become eligible for participation in the clinical investigation and the IRB must also determine that consent from the subject’s legally authorized representative is also not feasible.

s The IRB must provide an opportunity to the community from which research subjects are drawn to discuss the research. A public meeting may be appropriate; the IRB may decide that certain groups within the community may be excluded from being enrolled.

s Available treatments for the life-threatening condition must be either unproven or unsatisfactory.

s In virtually all cases when a placebo is used, standard care, if any, would be given to all subjects, with subjects randomized to receive, in addition, the test article or placebo; an exception to this approach would be a study to determine whether standard treatment is in fact useful. In this case, there must be a group who does not receive standard care.

s There must be an independent data and safety monitoring committee established to oversee the study; this committee has the power to halt the study.

s Before the treatment or intervention is begun, if a subject’s family member is present, this individual must be provided an opportunity to object to the potential subject’s participation.

s At the earliest feasible opportunity, either the subject, his or her legally authorized representative, or a family member must give consent; these individuals can also discontinue the subject’s participation at any time.

s If an IRB rejects a study of this type, it must notify the PI and sponsor in writing with its reasons; the sponsor must notify the FDA and other investigators and their IRBs about this rejection.

Given this guidance, the situation is clouded when an approved standard drug therapy exists and a drug firm wishes to test a new drug for a life-threatening condition. Should the new drug be tested against the standard drug or against a placebo? What does it mean to say the existing standard drug is either "unproven" or "unsatisfactory?" Difficult decisions must be made by the FDA regarding the IND for emergency research and by the IRB when they review a protocol for a study for which there already exists a relatively effective and safe drug intervention.

There is also an emergency exemption from prospective IRB approval. The emergency use provision in the FDA regulations [21CFR 56.104(c)] is an exemption from prior review and approval by an IRB. The exemption, which may not be used unless the situation is life threatening, there is no standard acceptable treatment, and a timely IRB review is not possible, allows for one emergency use of an investigational product at the institution. However, subsequent use requires IRB approval.

CDER’s Manual of Policies and Procedures (MAPP) 6030.8, effective 2/04/03, describes procedures for processing an IND for emergency research for which a request, pursuant to 21 CFR 50.24, is made for an exception from the requirement to obtain informed consent from all study subjects. INDs for this type of research must be approved in writing by the FDA prior to subject enrollment. Each clinical site must develop an informed consent document and procedure for attempting to find and obtain informed consent from a subject’s legally authorized representative.

The regulations require the clinical investigator to (1) inform the subject or the subject’s legally authorized representative, at the earliest opportunity, about the subject’s inclusion in the study and (2) provide an opportunity for the subject or the legally authorized representative to withdraw the subject from the study or sign a consent form agreeing to the

subject’s continued participation in the study. Thus the informed consent document and procedures need to be developed and available so that they can be used where feasible.

All such INDs will be reviewed by DSI for inclusion of procedures for obtaining informed consent, the informed consent document, and plans for community consultation, among other components described in MAPP 6030.8.