Chapter 11
Use of an Investigational Product Outside of the Protocol

I. Emergency Use of a Test Article without IRB Review. An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval.

A. Institutional Requirements. If at all possible, HSS’s policy requires that investigators consult the IRB Chairperson for guidance when considering the emergency use of drugs or medical devices.

B. Required Conditions. All of the following conditions must be met for this type of emergency use:

1. A human subject is in a life-threatening situation
2. No standard acceptable treatment is available
3. There is insufficient time to obtain IRB approval
4. The emergency use must be reported to the IRB within five working days (such reporting must not be construed as IRB approval for the emergency use)
5. Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below

C. Emergency Use of Drugs. Emergency use of an investigational new drug occurs when the emergency situation does not allow time for submission of an IND. Use of the drug requires a request to FDA to authorize shipment of the drug for the emergency use. Such authorization is conditioned on the sponsor making an appropriate IND submission as soon as practicable (21 CFR 312.36). The emergency use of an investigational new drug may take place without IRB review and approval, provided that the use is reported to the IRB within 5 working days. Informed consent is required unless the situation is life-threatening, the criteria at 21 CFR 50.23(a) or 50.23(b) have been met, and the IRB is notified within 5 working days.

D. Emergency Use of Devices. Emergency use of an unapproved device may occur in an emergency situation when

1. an IDE for the device does not exist,
2. a physician wants to use a device in a way not approved under an existing IDE, or
3. when a physician is not an investigator under the existing IDE.

4. The device may be used if
   a. the patient has a life-threatening condition that needs immediate treatment,
   b. there is no generally acceptable alternative treatment, and
   c. there is no time to obtain FDA approval.

5. Such uses require as many of the following patient protections as possible (FDA Center for Devices and Radiological Health Guidance on IDE Policies and Procedures, January 20, 1998):
   a. informed consent;
   b. clearance from the institution;
   c. concurrence of the IRB chairperson (this concurrence does not constitute IRB approval);
   d. an independent assessment of an uninvolved physician; and
   e. authorization from the IDE sponsor (if an IDE exists).

6. Follow-up reports should be provided to the Sponsor if an IDE exists, or to FDA if no IDE exists. Such use is limited to a few patients.

7. Emergency Use Procedure:
II. **Compassionate Use of Investigational Drugs and Devices.** “Compassionate Use” is not a term that appears in the FDA or DHHS regulations or the Common Rule.

For studies involving investigational drugs “Compassionate Use” is often meant to refer to the emergency use situations discussed above.

For studies involving investigational devices, compassionate use may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious condition who does not qualify for the trial and the physician anticipates the use. Such uses require prior FDA approval of a protocol deviation under 21 CFR 812.35(a). Prior FDA and institution IRB approval for compassionate use should be obtained before...
On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA and obtain prior institution IRB approval.

Compassionate use of an unapproved device also requires all of the following protections:

A. informed consent;
B. clearance from the institution;
C. concurrence of the IRB Chairperson;
D. an independent assessment of an uninvolved physician; and
E. authorization of the IDE sponsor.

Follow-up reports should be provided to the Sponsor. Such use may involve an individual patient or a small group of patients but the decision is made on a case-by-case basis. If any problems occur as a result of the device use, these should be discussed in the Follow Up reports to the sponsor and reported to the IRB as soon as possible.

F. Procedure for Compassionate Use:
**Compassionate Use procedure: Anticipated use of off-protocol IDE/off-label HUD**

1. Physician determines that the patient meets criteria for compassionate use of a device:

   a. Serious disease or condition; and

   b. No generally acceptable alternative treatment for the condition exists

2. The physician should ensure that the following patient protection measures are addressed:

   a. Independent assessment by uninvolved doctor;

   b. Company(Manufacturer) concurrence;

   c. IRB chairperson’s documented concurrence (which will be reported to the IRB at the next convened meeting);
d. Clearance from the institution (signed letter from HSS Surgeon in Chief); and

e. Informed consent from the patient or his/her legal representative

3. Prior authorization for the compassionate use of the investigational device is required from the sponsor supplying the device

4. The physician should request access to the investigational device through the IDE sponsor and provide necessary documents for the sponsor to request the IDE supplement approval

5. A description of the patient’s condition and the circumstances necessitating treatment with the device

   a. A discussion of why alternative therapies are unsatisfactory; and

   b. Information to address the patient protection measures

6. Prior FDA approval for compassionate use of the investigational device is required.

7. FDA approval for compassionate use should be obtained by the Investigational Device Exemption (IDE) holder before the device is used

8. The IDE sponsor should submit an IDE supplement requesting approval from the FDA for a protocol deviation in order to use the patient.

9. If the FDA request is approved, a letter, including the following, should be submitted to the HSS IRB:

   a. The authorization from the sponsor of the investigational device (IDE holder)

   b. The approval from the FDA; and

   c. The following patient protection measure details:

      i. The patient’s name and age

      ii. Physical condition

      iii. Justification for use of the experimental device (e.g. documentation that no available alternative therapy exists)

      iv. Therapeutic plan (e.g. dose, mode of administration, duration of planned therapy).
v. IDE/HDE and the name of the sponsor that is providing the device and authorization

vi. A letter from a physician uninvolved in the patients’ care who concurs that the device is needed for the situation

vii. The patient or the patients’ legal representative consent document

viii. An appropriate schedule for monitoring the patient

vix. A description of clinical procedures, laboratory tests, or other measures to be used to monitor the effects of the device and to minimize risk

Note: The compassionate use of an investigational device may take place only where the FDA has specifically approved such use. IRB concurrence (by the IRB Chairperson) and the informed consent of the patient-subject must be obtained prior to use, unless the criteria for emergency use of devices have been satisfied.

### III. From the FDA Guidance on IDE Policies and Procedures:

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<th>Expanded Access Mechanism</th>
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<td>Emergency Use</td>
<td>&quot;Guidance for the Emergency Use of Unapproved Medical Devices&quot; 50 FR 42866 21 CFR 812.35(a)</td>
<td>1. Life-threatening condition; 2. No alternative; and 3. No time to obtain FDA approval.</td>
<td>Before or after initiation of clinical trial</td>
<td>Limited to few patients</td>
<td>No; submit report to FDA following device use</td>
<td>Not applicable</td>
<td>1. Independent assessment by uninvolved doctor; 2. IRB chairperson's concurrence; 3. Institutional clearance; and 4. Informed consent</td>
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<tr>
<td>Compassionate Use</td>
<td>21 CFR 812.35(a)</td>
<td>1. Serious disease or condition and 2. No alternative.</td>
<td>During clinical trial</td>
<td>Individual patient or small groups of patients</td>
<td>Yes</td>
<td>IDE supplement with: 1. Explanation of circumstances constituting need for the device; 2. Reasons alternatives not</td>
<td>1. Independent assessment by uninvolved doctor; 2. IRB Chairperson's concurrence;</td>
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<td><strong>Treatment IDE</strong></td>
<td><strong>21 CFR 812.36</strong></td>
<td><strong>1. Life-threatening or serious disease; 2. No alternative; 3. Controlled clinical trial; and 4. Sponsor pursuing marketing approval.</strong></td>
<td><strong>During clinical trial</strong></td>
<td><strong>Wide access; depends on patient/physician need</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Trt IDE supplement with: 1. Intended Use, protocol, and patient selection criteria; 2. Rationale for trt use 3. Methods used to evaluate device use and minimize risks; 4. Monitoring plan; 5. Summary of S&amp;E data 6. Instructions for use and device labeling; 7. Commitment to patient protection; 8. Investigator agreement; and 9. Price, if will be sold.</strong></td>
<td><strong>1. IRB approval and 2. Informed consent.</strong></td>
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<td><strong>Continued Access</strong></td>
<td>&quot;Continued Access to Investigational Devices During PMA Preparation and Review&quot; ODE Blue Book IDE Memorandum #D96-1</td>
<td><strong>1. Public health need; or 2. Preliminary evidence that device will be effective and no significant safety concerns.</strong></td>
<td><strong>After completion of clinical trial</strong></td>
<td><strong>Same rate of enrollment as study</strong></td>
<td><strong>Yes</strong></td>
<td><strong>IDE supplement with: 1. Justification for extended study; 2. Summary of S &amp; E data and risks posed by the device; 3. Proposed enrollment rate; 4. Clinical protocol; and 5. Progress towards marketing approval.</strong></td>
<td><strong>1. IRB approval and 2. Informed consent.</strong></td>
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‡As a matter of practice, FDA has expanded the criteria of "life-threatening condition" to include serious conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity.

IV. Planned Emergency Research. An exception under FDA regulations at 21 CFR 50.24 permits planned research in an emergency setting without the informed consent of the subjects (see Appendix IV).

Planned emergency research that is not FDA-regulated is also permitted by DHHS and the Common Rule when specific Department or Agency action is taken to exercise the waiver provision at 45 CFR 46.101(i). However, planned emergency research is usually subject to FDA regulations because it usually involves use of an FDA-regulated test article. When this is the case, the FDA requirements govern, and no notification of OHRP is required.

The requirements for planned emergency are extremely complex and require much consultation within this Institution, within the community in which the research will be conducted, and within FDA, DHHS, or other Common Rule Agency. Investigators should contact the IRB chairperson well in advance if they wish to conduct planned emergency research.

It is the responsibility of the IRB Chairperson to provide prompt written notification to the Institution’s Human Subject Signatory Official, Legal Counsel, and Compliance Officer should the IRB receive a proposal for planned emergency research.