

INVESTIGATIONAL DEVICE EXEMPTION (IDE) CASE STUDY

INVESTIGATOR-HELD IDEs

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with the IND/IDE Subcommittee of Harvard Catalyst's Regulatory Foundations, Ethics and Law Program

OVERVIEW

The investigational new drug/investigational device exemption (IND/IDE) case studies provide education and guidance on regulatory and ethical issues associated with IND/IDE research and submissions to the Food and Drug Administration (FDA). Each follows a standard format of: 1) fact pattern, 2) regulatory issues, and 3) a risk/benefit analysis and risk management options.

The case studies are intended to aid IRB Administrators, Human Research Protection Program (HRPP) staff, and investigators when reviewing or conducting IND and IDE research. They can be used as a tool for: 1) training individuals in human subjects research involving investigational drugs/devices, 2) developing reviewer checklists/worksheets, and 3) designing research projects.

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CASE STUDY

SCENARIO/FACT PATTERN:

Dr. Hernandez is a radiologist who has developed, with the hospital's engineering department, a new intraoperative imaging device to help identify malignant tumors. The device is used to inject a fluorescent dye into the tumor during a same-day surgical procedure requiring general anesthesia. This dye has been approved for other imaging uses and facilitates the radiologist's ability to see the tumor; it does not treat or remove the tumor.

Dr. Hernandez wants to conduct a pilot study assessing the safety and efficacy of the new intraoperative imaging device. He will be the "sponsor-investigator," the individual who both initiates and conducts an investigation, and under whose immediate direction the investigational device is dispensed or used. Dr. Hernandez (as the sponsor-investigator) determines that this is a not significant risk (NSR) device study, but the institutional review board (IRB) disagrees with his assessment. What should Dr. Hernandez do next?

REGULATORY ISSUES:

- **Who determines whether a device study is significant risk (SR) or non-significant risk (NSR)?**

The sponsor-investigator makes the first determination, and then submits the research proposal to the IRB. Note: the FDA offers investigators IDE consultations to help with risk determinations.

- **Once a sponsor-investigator determines a device study is NSR, what happens next?**

The sponsor-investigator must submit his research proposal to the IRB, who will either agree or disagree with the assessment. The FDA is available to help IRBs make a risk determination, if needed.

- **If, as in this case, the IRB disagrees with the sponsor-investigator's NSR assessment, what steps must be taken next?**

The sponsor-investigator must then notify the FDA, within five business days of the IRB's decision (21 CFR 812.150(9)), and submit a complete IDE application to the FDA Center for Devices and Radiological Health (CDRH). Note, the IRB must re-review and approve the proposed study before the sponsor-investigator can start any research activities.

- **If the IRB had agreed with Dr. Hernandez's assessment, what steps would he take?**

As the sponsor-investigator, Dr. Hernandez would not need to submit an IDE application to the FDA. However, he would need to make a submission to the IRB to determine whether the study required IRB review and oversight. If so, the IRB would review and confirm the NSR assessment. A sponsor-investigator cannot begin a study prior to receiving IRB approval. Note that even with a NSR determination, Dr. Hernandez (and any sponsor-investigator) would still need to comply with the abbreviated IDE requirements (21CFR812.2(b)).

- **Who makes the final significant risk (SR) or NSR determination when there is disagreement between the sponsor-investigator and IRB?**

If there is a disagreement, the FDA makes the final decision.

- **What other reviews are required?**

Other ancillary reviews, such as radiation safety, biomedical engineering or cell manufacturing, may be required in conjunction with IRB review. Additional review requirements will vary by institution.

- **Does Dr. Hernandez need to complete the FDA Form 1572?**

No, the FDA Form 1572 is only required for drug studies. For device studies, the sponsor-investigator writes an 'Investigators Agreement' (per 21 CFR 812.43(c)) that all the investigators on the study must sign prior to participation in the study.

- **After an IDE is approved, what reports must be submitted to maintain the IDE?**
The sponsor-investigator must follow 21CFR 812.150 and submit complete, accurate, and timely reports, including :
 - Annual progress reports
 - Unanticipated adverse device effects
 - Deviations from the investigational plan
 - Withdrawal of IRB approval
 - Other aspects of the investigation upon request of the IRB or FDA
 - Final report

Discussion:

Questions for the reviewing IRB:

1. What is/are the medical device(s) in this example?
2. Do you have enough information to make a significant/non-significant risk (SR/NSR) determination? If not, what additional information would you need?
3. Have you confirmed that all other drugs or devices used in the research protocol are being used in a manner that is consistent with FDA approval?

Mitigation/management of risks:

The IRB will need to have enough information to determine the overall risk/benefit ratio of the research. If they don't feel comfortable making a decision, they will need to defer the review of the research protocol. The IRB may request more information from the sponsor-investigator regarding the proposed use, oversight, and design of the device and research. The research would then need to be re-reviewed by an IRB that includes sufficient expertise to make the risk determination. Note that the FDA can also be solicited to assist with the risk determination.

IRB review of the protocol and informed consent

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether the study should be approved. In considering whether a study should be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product (21 CFR 56.111). Some NSR studies may also qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure (21 CFR 56.110). FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is required. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Other ancillary reviews, such as radiation safety, biomedical engineering or cell manufacturing, may be required in conjunction with IRB review. Additional review requirements will vary by institution.

References:

Information Sheets:

- [FDA Information Sheet : "Significant Risk and Nonsignificant Risk Medical Device Studies"](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf)
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>
- [FDA Information Sheet: "Sponsor-Investigator-IRB Interrelationship"](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126425.htm)
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126425.htm>
- [DFCI OHRS Information Sheet Research Involving Medical Devices](http://www.dfhc.harvard.edu/crs-resources/OHRS_Documents/02_-_Investigator_Resources/IS_-_Resource_-_FDA_Medical_Devices.pdf)
http://www.dfhc.harvard.edu/crs-resources/OHRS_Documents/02_-_Investigator_Resources/IS_-_Resource_-_FDA_Medical_Devices.pdf
- [21CFR part 812:](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRsearch.cfm?CFRPart=812)
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRsearch.cfm?CFRPart=812>