

INVESTIGATIONAL NEW DRUG APPLICATION (IND) CASE STUDY

WHEN A SPONSOR-INVESTIGATOR SHARES AN IND

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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). These case studies may be used by IRB administrators and Human Research Protection Program (HRPP) staff as well as investigators when reviewing and conducting IND and IDE research.

Case studies follow a standard format that includes: 1) a fact pattern 2) regulatory issues, and 3) a risk/benefit analysis and risk management options. This format was created to allow for flexibility in applying the case studies.

By identifying common challenges, linking them directly to federal regulations and guidance, and outlining risk mitigation options, the case studies can be used in a variety of ways, which include: 1) as an educational tool for training individuals in research involving the use of investigational drugs/devices, 2) as a basis for developing reviewer checklists/worksheets, and 3) as a tool in designing research projects.

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CASE STUDY

SCENARIO/FACT PATTERN #1:

Dr. Johnson is a sponsor-investigator based at a hospital in Boston who holds an IND from the FDA to test the use of Drug X to treat depression in adults. Drug X is already FDA-approved for the treatment of migraines in adults. Dr. Johnson is conducting a depression study with 60 patients, and stores the study drug in the locked research refrigerator.

Dr. Smith has been departmental colleagues and friends with Dr. Johnson for years. Dr. Smith is planning to conduct a research study looking at the use of Drug X to treat depression in minors. He feels that the FDA process for obtaining an IND is very time-consuming and

burdensome, and so asks Dr. Johnson for permission to use the IND for his own research as well. Dr. Johnson agrees, telling Dr. Smith that his study can take place as part of his existing IND. However, Dr. Johnson, who is already busy as the principal investigator of four studies, will not be a co-investigator on Dr. Smith's study. Given his many responsibilities, Dr. Johnson forgets to inform the FDA about adding Dr. Smith's study to his IND.

In preparation for subject 3's study visit, Dr. Smith's study coordinator retrieves the study drug from the research refrigerator, takes it to the exam room, and leaves it on the counter for the nurse. Subject 3, however, does not show up for her appointment. When the study coordinator goes back to the exam room to pick up the drug and return it to the locked research refrigerator, the study drug is nowhere to be found. Neither Dr. Smith, nor the study coordinator, document this incident in the drug accountability log or subject files.

REGULATORY ISSUES:

What issues does scenario 1 raise regarding Dr. Johnson's responsibilities as a sponsor-investigator?

1. Notifying the FDA

- a. See 21 CFR 312.30(a). The FDA was not notified about Dr. Smith's protocol; if Dr. Johnson wants to add Dr. Smith's study as an additional protocol under his IND, he must notify the FDA through an IND Amendment.
- b. See 21 CFR 312.2(b)(iii). Dr. Johnson holds an IND to treat adults with depression. However, Dr. Smith is looking at depression in a different population (minors). Given this different population, the FDA may determine that Dr. Smith needs to apply for his own separate IND, especially if there is a significant increase in the risks of using the drug in the pediatric population.

2. Drug Accountability

- a. See 21 CFR 312.50. As the IND sponsor, Dr. Johnson is ultimately responsible for ensuring that all investigations under his IND are conducted in accordance with the general investigational plan and protocols within the IND.
- b. See 21 CFR 312.57(a). As an IND sponsor, Dr. Johnson is responsible for maintaining adequate records showing the receipt, shipment, or other disposition of the investigational drug. He should maintain master logs of all drug disposition in the protocols under his IND. Even though Dr. Johnson was not an investigator in Dr. Smith's study, as the IND Sponsor of the drug used in the study, Dr. Johnson is ultimately responsible for drug accountability with the FDA.
- c. See 21 CFR 312.61, 312.62. Dr. Johnson allowed Dr. Smith to use the supply of Drug X that he obtained for research purposes as part of his IND with the FDA. Dr. Smith, as an IND clinical investigator, is responsible for maintaining control of the investigational drug and not supplying it to any unauthorized person. Dr. Smith should also be maintaining drug accountability records for quantities of Drug X used in his study.

- d. See 21 CFR 312.33, 312.64 and institutional policy. Dr. Smith must also report the incident of the missing drug in accordance with federal and institutional requirements and implement a corrective action.
- e. See 21 CFR 312.56. Dr. Johnson as the IND sponsor is responsible for monitoring the progress of all clinical investigations under the IND. If the IND sponsor discovers that an investigator (Dr. Smith) is not complying with his investigator responsibilities, such as drug accountability, he must promptly secure compliance or discontinue shipment of the drug to the investigator.

RESOLUTION & DISCUSSION:

What steps should Dr. Johnson and Dr. Smith have taken to ensure that Dr. Smith's study was appropriately being conducted in accordance with the FDA IND regulations (21 CFR 312)?

Dr. Johnson could have contacted his FDA project manager regarding the appropriateness of adding Dr. Smith's study under his IND, given that Dr. Smith was looking at a different study population. If determined to be appropriate, Dr. Johnson should have submitted an amendment to add Dr. Smith's protocol to his IND. Alternatively, Dr. Smith could have submitted his own IND application to the FDA for "Drug X to treat depression minors".

How should Dr. Smith have responded to notification of the missing drug?

Dr. Smith should have reported the missing drug to the IND Sponsor, Dr. Johnson, so that he could include this incident in his IND annual report to the FDA. Dr. Smith should have also followed institutional policy for reporting to the Institutional Review Board (IRB), including his corrective action plan.

A possible corrective action includes revising the standard operating procedure for investigational drug storage and retrieval. A designated staff member should never leave a IND drug unsupervised in the exam room. In addition, the PI and study team should receive education on drug accountability, and designate an appropriate staff member to regularly review the drug accountability records for completeness and accuracy.

SCENARIO/FACT PATTERN #2:

At a local conference, Dr. Johnson meets Dr. Campos, who is based in California. Dr. Campos' research also focuses on finding treatments for depression. Dr. Campos is starting a small study, "study #1," similar to Dr. Johnson's research, looking at depression in 50 adults. Dr. Johnson offers to amend his IND and add Dr. Campos's study. Dr. Campos accepts this offer and Dr. Johnson submits an amendment to the FDA to add the protocol to his IND. Dr. Campos begins his study. Dr. Johnson is not listed as a co-investigator on Dr. Campos' study.

Dr. Campos' study goes so well that two years later, he decides to conduct an additional study, "study # 2," with additional outcome measures of effectiveness of the same IND drug in a larger population of adults. In total, Dr. Campos enrolls 200 adults in this second study. He begins enrollment for "study #2" and dispenses the IND drug to subjects without notifying Dr. Johnson.

REGULATORY ISSUES:

What issues does scenario 2 raise regarding Dr. Johnson's responsibilities as a sponsor-investigator?

1. Selecting Qualified Investigators

- a. See 21 CFR 312.53. As an IND sponsor-investigator, Dr. Johnson is responsible for selecting qualified PIs on studies under his IND. Dr. Johnson offered to add Dr. Campos's study to his IND without first determining his credentials.

2. Maintaining an Effective IND and Reporting to the FDA as Required

- a. See 21 CFR 312.30. Dr. Johnson appropriately added Dr. Campo's study, "study #1," to his IND via an IND amendment to the FDA ("New Protocol").
- b. See 21 CFR 312.33. As an IND sponsor-investigator, Dr. Johnson must also include updates on every protocol under the IND to the FDA each year in the required annual report.
- c. See 21 CFR 312.64. Dr. Johnson is responsible for notifying the FDA about all protocols that are occurring under his IND. However, here Dr. Campos ignored his responsibility to notify Dr. Johnson, the IND sponsor, about the additional study using his IND drug, "study #2."
- d. See 21 CFR 312.56. As an IND sponsor-investigator, Dr. Johnson shall monitor the progress of all clinical investigations being conducted under his IND. Dr. Johnson is the one ultimately responsible for reporting to the FDA any serious and/or continuing non-compliance that occurs under his IND.

RESOLUTION & DISCUSSION:

How might Dr. Johnson have better vetted Dr. Campos?

Before offering to add Dr. Campos' study to his IND, Dr. Johnson should have first made sure he was confident in Dr. Campos' abilities and training, and ensured the appropriate documentation was in place confirming Dr. Campos qualifications (by virtue of his training and experience) to be a PI under Dr. Johnson's IND.

Also Dr. Johnson, as the IND Sponsor, could have made sure that Dr. Campos knew of his responsibility to notify Dr. Johnson of any additional studies he hoped to conduct under the IND. Also if Dr. Johnson was in more regular contact with Dr. Campos, he may have quickly discovered that the additional study "study #2" was being conducted and then taken steps to rectify the situation as soon as possible.

REFERENCES:

[Title 21: Food and Drugs; Part 312—Investigational New Drug Application](#)

- 21 CFR 312.2 – Applicability.
- 21 CFR 312.30 - Protocol amendments.
- 21 CFR 312.33 - Annual Reports.
- 21 CFR 312.50 - General responsibilities of sponsors.
- 21 CFR 312.53 - Selecting investigators and monitors.
- 21 CFR 312.56 - Review of ongoing investigations.
- 21 CFR 312.57 - Recordkeeping and record retention.
- 21 CFR 312.61 - Control of the investigational drug.
- 21 CFR 312.62 - Investigator record keeping and record retention.
- 21 CFR 312.64 – Investigator reports.