

INVESTIGATIONAL NEW DRUG APPLICATION (IND) CASE STUDY

AN INVESTIGATOR-INITIATED MULTICENTER IND STUDY

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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). 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:

Dr. Yang is a world-renowned child psychiatrist working at Massachusetts General Hospital (MGH). For years within her clinical practice, she has prescribed several marketed anti-psychotic medications to children with ADHD, at varying doses. To date, all of her clinical prescriptions have been for drugs approved for use in children. Dr. Yang now wants to conduct a research study to investigate the effects of adult ADHD treatments on children. She would like to publish her findings and seek FDA marketing approval to support amending the label for Drug X to allow its use in children.

Dr. Yang drafted a research protocol to submit to her IRB and the FDA. The protocol involves conducting a phase 2 dose escalation study (in which she will evaluate both safety and efficacy) in children with ADHD and other spectrum disorders, and to determine whether using Drug X at various doses will provide treatment to this population.

Dr. Yang successfully obtained an IND for this protocol from the FDA for her intended new use of Drug X in children. She plans to enroll 25 subjects and is using internal department funding to support the conduct of this study. Dr. Yang has one dedicated research coordinator and one monitor, subcontracted through her institutional quality improvement program, to oversee the study at MGH and at nearby Brigham and Women's Hospital.

Following the initial IRB approval from MGH, Dr. Yang added additional study sites, including hospitals in Detroit, Los Angeles, and Miami, to enhance recruitment and increase the diversity of the subject population. Dr. Yang selected these sites based on her previous collaboration with colleagues at these locations and their mutual agreement to help each other when conducting future research studies. She now plans on enrolling 100 children in total.

Since these additional sites were added, communication and coordination of the project have deteriorated. For example, the various sites were conducting different iterations of the protocol, and study staff were confused about which IRB their site was relying upon to review any protocol modifications. Due to budget constraints, site training had to be conducted over the phone, and the monitor could not adhere to the quarterly onsite monitoring visits specified in the protocol. Additionally, to ensure sites received adequate quantities of the study drug, Dr. Yang shipped drug inventory to the sites in bulk, with the plan that the monitor would then confirm receipt and dispensation of the drug when he was able to make it on site, as time allowed during the monitoring visit. If this was not possible, and supply of the study drug was running low, the monitor would inform Dr. Yang, who would make sure a new bulk shipment was sent ASAP.

REGULATORY ISSUES:

- How were the additional sites selected and appropriately vetted? Were adequate measures in place to ensure co-investigators at these sites were sufficiently qualified? (21 CFR 312.53)?
- Is the sponsor-investigator aware of changes made to the protocol at the different study sites? Do any of these changes require notifying the FDA (21 CFR 312.55)? How might this situation have been avoided?
- Is the current monitoring of subject safety and data integrity adequate? If not, how should it be corrected? (21 CFR 312.56)?
- Is the recording of drug disposition and control adequate? If not, how should it be corrected (21 CFR 312.57)?

RESOLUTION & DISCUSSIONS:

A sponsor-investigator is responsible for the conduct, initiation, management, and/or financing of a clinical trial. Developing a plan to adequately manage an investigator-initiated multicenter study poses several additional challenges, from ensuring all the necessary resources are in place at the various sites to ensuring all co-investigators listed on the study are adhering to protocol, their institutional policies, and FDA regulations. Communication to and from the sponsor-investigator is vital to the

success of conducting a multicenter research study. Dr. Yang should consider implementing the following corrective actions/best practices to address the issues outlined in this case scenario:

- Consider implementing weekly/monthly meeting with co-investigators and their research teams to assess the status and conduct of the study (including dose escalation decisions).
- Develop drug accountability logs for each site that will capture/track the receipt, disposition, and destruction of the study drug.
- Establish a process for notifying the sponsor-investigator of any/all changes to the protocol prior to initiating and submitting to the local IRBs for approval.
- Apply for additional funding and/or cut back on the number of study sites to ensure appropriate monitoring can occur.

REFERENCE(S):

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

- 21 CFR 312.30 – Protocol amendments.
- 21 CFR 312.32 – IND safety reporting.
- 21 CFR 312.53 – Selecting investigators and monitors.
- 21 CFR 312.55 – Informing investigators.
- 21 CFR 312.56 – Review of ongoing investigations.
- 21 CFR 312.57 – Record keeping and record retention.
- 21 CFR 312.58 – Inspection of sponsor’s records and reports.
- 21 CFR 312.59 – Disposition of unused supply of investigational drug.
- 21 CFR 312.60 – General responsibilities of investigators.
- 21 CFR 312.61 – Control of the investigational drug.
- 21 CFR 312.62 – Investigator record keeping and record retention.
- 21 CFR 312.66 – Assurance of IRB review.