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Investigational Device Exemption (IDE) Applications and Pre-Submissions

Context

Planning a clinical study is a major undertaking for innovators. In addition to complying with National Institutes of Health (NIH) policy, developing a statistically powerful protocol, and gaining approval from an Institutional Review Board (IRB), some medical device development clinical research requires U.S. Food and Drug Administration (FDA) oversight. When applicable, FDA oversight for medical device development requires submitting an Investigational Device Exemption (IDE) application to the Center for Devices and Radiological Health (CDRH).

Because of the short timeline (i.e., 30 days) for review of an IDE application, if you have questions about the design of your clinical study, it is advisable to request a pre-submission meeting (one type of Q-Submission) to identify potential FDA concerns ahead of time. Doing so can allow you to address these concerns in the full IDE application, rather than possibly have your clinical studies delayed due to concerns raised within your IDE application.

Which clinical studies require CDRH oversight through an IDE application?
Clinical studies involving a Significant Risk (SR) device.

An SR device meets one or more of the following criteria:

- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
- Purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a patient
- For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a patient
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a patient

The regulatory path for clinical research of SR devices follows these steps:

1. Initiate conversation with IRB, if applicable
2. Prepare and submit a pre-submission meeting request to FDA
3. Hold the pre-submission meeting, if necessary
4. Incorporate feedback and submit the IDE application to FDA
5. Receive a response from FDA (within 30 days) and modify the plan (if required)
6. Complete approval process with your IRB based on FDA feedback, if applicable
7. Perform research, then apply for Market Authorization (commonly a Premarket Approval (PMA) application)

In many cases, where the risk is clearly non-significant risk (NSR), the study can be carried out in coordination with the IRB without consulting FDA. If you believe the study should be considered NSR, provide supporting evidence outlining how the study does not fit in any of the categories outlined above in your submission to the IRB or request FDA's review in a study risk determination submission. If you believe your device is SR, but this specific study should be exempted from IDE you can request an evaluation form FDA. Your request must include evidence supporting why the device would be exempt from an IDE.

The requirements for exemption from IDE are outlined in 21 CFR part 812.
If there is disagreement about the risk assessment, a formal study risk determination (another type of Q-Submission) can be requested from FDA. FDA has the final authority on whether a device study is SR or NSR. Once FDA makes a risk determination, the device development must proceed in alignment with that decision.

How to Prepare

Develop a Preliminary Study Plan Aligned with Your Market Authorization Plans

The pre-submission meeting is an opportunity to ask direct questions and receive direct feedback regarding the planned clinical research. FDA will provide complete and detailed comments on the submitted plans. You can include hypothesized clinical end points of the study if you want to request direct feedback on whether the validation plans will be sufficient to support a marketing application. When FDA reviews the eventual IDE, they assess the risks and anticipated benefits involved with the proposed clinical study to ensure the safety of study subjects.

When the objective of a study is to support a marketing submission, FDA may provide study design considerations to support developing data to support a marketing authorization. Plan ahead as much as possible when seeking an IDE so you can obtain the necessary data within the framework of the authorized clinical study. It would be problematic if at the end of the IDE study the data is insufficient to support a marketing submission. In addition to including safety considerations in the IDE, information describing the manufacturing and quality management systems is required.

Start with the IRB

FDA has *final* authority in determining whether a device is NSR or SR, but the IRB has the *first authority*. Whether the device is NSR or SR, the IRB will always be involved in monitoring the safety and ethics of human subject research. In the pre-submission meeting request package, include a summary of any existing communication with the IRB. If the IRB has any concerns or questions, let FDA know beforehand. NIH has a single IRB policy for multi-site studies—ensure the sites where you plan to recruit all agree to this practice if you receive clinical trial funding from NIH.

Understand the Processes

Depending on the IRB's requests, any pre-submission discussions with FDA, or other research plans, it may be appropriate to request a study risk determination from FDA. Like a pre-submission meeting, study risk determinations are part of the Q-Submission program, as noted above. However, unlike pre-submissions, study risk determinations do not usually include a meeting with FDA. As mentioned above, FDA has final authority on whether a study is SR or NSR, and the study risk determination is how FDA issues a formal ruling.

After the pre-submission meeting for SR devices, prepare the IDE documentation and submit it to FDA. FDA will review the IDE and provide comments or approval within 30 days. If no communication is received, the study is automatically allowed to proceed. This is a strong commitment from CDRH to provide timely review of IDE applications and to facilitate clinical evaluation of your new device.

Regulatory Resources

- Guidance documents and FDA resources
  - Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies – resources for determining risk classification
  - Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions – overview of regulations related to clinical data submissions
  - IDE Approval Process – overview of IDE approvals
  - Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (Section III.C addresses study risk determinations specifically)
- NIH network
  - Work with program officers and obtain regulatory feedback within NIH
  - NIH awardees can request a meeting with the NIH Small Business Education and Entrepreneurial Development (SEED) Innovator Support Team to ask questions about this process and request they review the draft cover letter and overall approach. However, the SEED office does not review or comment upon the scientific validity or data elements of the submission.

- Direct links to NIH SEED resources on related topics
    - Written communication
    - 510(k)
    - De Novo

Developing Your Submission

When seeking an IDE, compile the required materials, device descriptions, and justifications into a PDF document (or collection of documents) and submit the IDE application to FDA. The document should be as concise as possible, while providing evidence supporting the proposed research plan.

Submission Process

Documents are submitted through FDA's eCopy Program for Medical Device Submissions. In the pre-submission, include a cover letter specifying the intent of either a general pre-submission or a study risk determination request and provide documentation to support that request. There is no fee to submit the request.

What to Expect

Timeline

FDA intends to provide feedback on pre-submissions within 70 days of submission or five days prior to a scheduled meeting, whichever is sooner.

Regarding an IDE application, if the IRB approved the protocol, the clinical investigation may begin 30 days after FDA receives the IDE application unless FDA notifies you otherwise. If you do not have IRB approval, you cannot begin the clinical trial regardless of the status of the IDE application.

Format of Interaction

The IDE application itself may result in approval, approval with conditions, or disapproval. For approval with conditions, you may initiate your study after receiving IRB approval, but will need to respond to deficiencies identified in the FDA decision letter within 45 days. For disapproval decisions, FDA will provide all deficiencies that must be addressed in order to approve the IDE. The rationale contained in the deficiencies may be beneficial for further development of the product. Typically, there is no meeting to discuss FDA's decision or the submitted materials; however, follow-up questions may be sent to the lead reviewer listed in the decision letter or a follow-up meeting can be requested via a submission issue request (SIR) under the Q-Submission program.

Whether or not the IDE application is approved, you may schedule subsequent Pre-Submission Meetings prior to the marketing submission.

General Tips

- Overall, an NSR device must comply with abbreviated IDE requirements, including IRB approval and informed consent. With an NSR device, IRB approval is required before starting the clinical study. With an SR device, you must receive FDA approval of an IDE application, in addition to IRB approval, before starting the clinical study.
- In putting together an IDE submission, it is useful to review the outlined grounds for disapproval and to use a checklist to ensure each point is addressed and supported by evidence.
- It is a best practice to get questions about intended use, study design, and data requirements answered before submitting an IDE application. If you have regulatory questions at any point during device development, you can request feedback through a pre-submission.
- Involve the IRB as early as possible in the design stages of a product and associated clinical trial. This provides a better understanding of the potential regulatory requirements related to any clinical study conducted to support device's safety and effectiveness prior to bringing it to market.

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