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Non-Significant Risk Determinations: Just Because You Can Doesn't Mean You Should

By David Hammond

When I began my career as a clinical research coordinator working on pharmaceutical studies, the concept of a non-significant risk (NSR) product was unknown to me. Then, as now, the closest equivalent was a low-risk drug study that was eligible for expedited institutional review board (IRB) review. Any study submitted to the FDA in a New Drug Application (NDA) required an Investigational New Drug application (IND) prior to conducting the study.

When I started working with medical devices, I found a different set of rules: Studies with non-NSR devices required submission of an Investigational Device Exemption (IDE) application to the FDA, but low-risk studies with NSR devices did not. The sponsor's first question was thus always, "Can we do this as an NSR study?" Since then, I have learned that the correct question to ask is, "Can and should we do this as an NSR study?"

According to the FDA, a significant risk device is an investigational device that:[1]

- Is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject;
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
- Is 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 subject; or
- Otherwise presents a potential for serious risk to the health, safety or welfare of a subject.

Put simply, if a device presents a serious risk to the patient, it is a significant risk device.

There are four scenarios for medical device study applications:

- Sponsor determines that device is NSR. The IRB agrees.
- Sponsor does not submit an IDE to the FDA. When the sponsor submits study results to the FDA, the FDA agrees.
- Sponsor determines that device is NSR. The IRB does not agree. Sponsor submits an IDE to the FDA. Sponsor determines that device is not NSR. It submits an IDE to the FDA.

A non-significant risk device is a device that does not meet the definition of a significant risk device. The study sponsor determines whether the study device is significant risk or not. If the sponsor determines that the device and its use in the study are non-significant risk, it can make its case to an IRB. The IRB can either agree with the sponsor's determination or disagree if it believes there is a significant risk. If the IRB agrees with the sponsor that the device and its use in the study are non-significant risk, the IRB then takes on a dual role in the study: It continues with its traditional role of subject protection, and it also acts as a surrogate for the FDA, receiving and reviewing information usually submitted to the agency.[2] On the other hand, if the IRB determines that the study is significant risk, the sponsor has five days to notify the FDA of the IRB's decision, regardless of the path the sponsor chooses to follow.[3] This notification prevents "IRB shopping" – submitting the study

to different IRBs until one agrees that the device and its use in the study are NSR. Sponsors get only one shot for approval by one IRB before they have to notify the FDA.

The FDA has the final say and can wait to make its determination until it reviews the sponsor's Premarket Approval Application (PMA) or Premarket Notification (510k). The agency has the right to review the IRB's significant risk determination retroactively. If the FDA determines that the IRB was incorrect in its NSR determination, it may invalidate any data collected from the study for use in supporting a marketing application. (However, in future applications, it may consider any safety data collected.) Further, the FDA may conclude that the sponsor is too aggressive and needs extra scrutiny by the agency.

There are significant advantages of proceeding on the basis of an NSR determination: With only the IRB's approval required to initiate the trial, the timelines are shorter. The application to the IRB is much easier to assemble than an IDE application to the FDA. However, before pursuing an NSR determination for a device, the sponsor should consider the ramifications if the FDA later rejects the NSR designation: millions of dollars of wasted clinical data, years of delay, and a damaged reputation.

Even if the study device meets the FDA's definition of non-significant risk, pursuing an NSR determination may not be the wisest course. The following yes/no questions can help you determine whether you should proceed on that basis or not. The first six questions evaluate the relative risk of the device and the study, and the ability of the sponsor to guide the IRB to an NSR determination:

1. Can you explain every aspect of the device and its operation to the IRB simply and clearly with a straightforward justification of its safety? A device is not NSR until an IRB agrees it is. If it requires an MD and an engineer to explain the function of your device, it may be simpler to go to the FDA for IDE approval.
2. Does the IRB have experience in reviewing NSR studies? Any large academic or commercial IRB probably has adequate experience, but the IRB at a small community college may not have the experience to feel comfortable making an NSR determination.
3. Are any of the procedures outlined in the study dangerous, overly invasive, or beyond standard of care? Both the device and the study need to be non-significant risk. An NSR device study that requires a surgical procedure would likely not pass an IRB's definition of non-significant risk.
4. Are the individuals who will be using or implanting the device well-trained and familiar with it or with similar devices? An inexperienced operator may increase risk to the subject.
5. Will the device be operated in a non-chaotic environment with time for careful application and observation for subject safety and comfort? An endotracheal tube, in the hands of an anesthesiologist in an operating room with the presence of emergency equipment and drugs, would probably qualify as NSR. In contrast, that same device, in the hands of an emergency medical technician in the field, increases the risk.
6. Do the potential benefits outweigh the risks? NSR determinations depend on the context. A device that is NSR for terminal cancer patients may not be NSR for relatively healthy people.

These next six questions evaluate bigger-picture issues:

1. Are there other reasons to file an IDE application with the FDA? For example, if the sponsor is unsure what data the FDA will need to approve a marketing application, it may be in the sponsor's best interest to submit the IDE to the FDA to engage the agency in this discussion.

2. Will an NSR designation negatively impact the marketing value of the study? If the study device is classified as NSR, health care organizations, physicians and third-party payers may infer that it also offers non-significant benefits.
3. Will filing as NSR risk any FDA relationships? If your company has engaged the FDA in pre-IDE discussions, the FDA may have indirectly indicated their preference for reviewing any studies.
4. Will filing an NSR protocol with the IRB reduce the time to study initiation? Manufacturing may need 12 months to produce devices for the study.
5. Will the study (or follow-on studies) include international sites? The NSR concept exists only in the United States. Without an IDE, it may be time-consuming or impossible to obtain study approval in other countries.
6. Does the device involve a pharmaceutical component? If the device is a combination product, the FDA may designate the Center for Devices and Radiological Health (CDRH) as the lead center, but the other centers (without the NSR concept) may play a supporting role or even take over supervision.

NSR studies generally offer shorter timelines and require relatively simple submission documentation. However, focusing only on these potential benefits may yield significant unanticipated costs. The next time someone asks the question "Can we do this as an NSR study?" also ask "Should we to this as an NSR study?" Even if you can, it does not mean you should.

References

1. 21 CFR 812.3(m)
2. "INFORMATION SHEETS – Guidance for Institutional Review Boards and Clinical Investigators," September, 1998, last accessed 9/9/08 at http://www.fda.gov/OC/OHRT/IRBS/devices.html
3. 21 CFR 812.150(b)(9)

Author

David Hammond is the Clinical Affairs Manager at Calypso Medical Technologies, Inc. and an Affiliate Instructor in the School of Pharmacy at the University of Washington. Contact him at 1.206.650.7258 or david.t.hammond@gmail.com.

