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The Difference is in the Details

DRUGS vs DEVICES

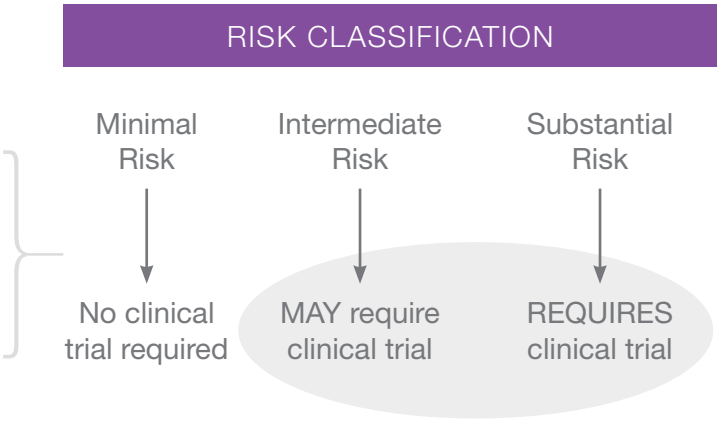
Whether investigating drugs or devices, the common thread that ties the seemingly different clinical research processes together is simple….patients. Human beings.

Real people on the other side of that investigational product that face innate risks in choosing to be part of this thing called clinical research. So while the investigations of drugs and devices have their differences, by design these differences are intended to accomplish the same goal: to safeguard those research participants while bringing safe and effective products to the market as quickly as possible. Understanding the similarities and appreciating the differences is important for clinical researchers who are involved in both drug and device trials.

Is a clinical trial necessary?

In the situations of a drug, a clinical trial will always be required, period. However, not all devices will need to undergo a clinical trial. The determination of whether or not a device clinical trial is required is based on a risk stratification, as illustrated in the diagram below. Minimal risk devices would not require a clinical trial, whereas some intermediate risk devices and all substantial risk devices will require a clinical trial. Currently, the FDA is considering providing additional guidance to assist researchers in determining whether a particular Class II device would require a clinical trial.

CLASS	DESCRIPTION
Class I	*Least risky, general controls adequate; no clinical trial needed*
Class II	*Intermediate risk, special controls needed (510K)*
Class III	*Substantial risk devices, pre-market approval needed (IDE)*

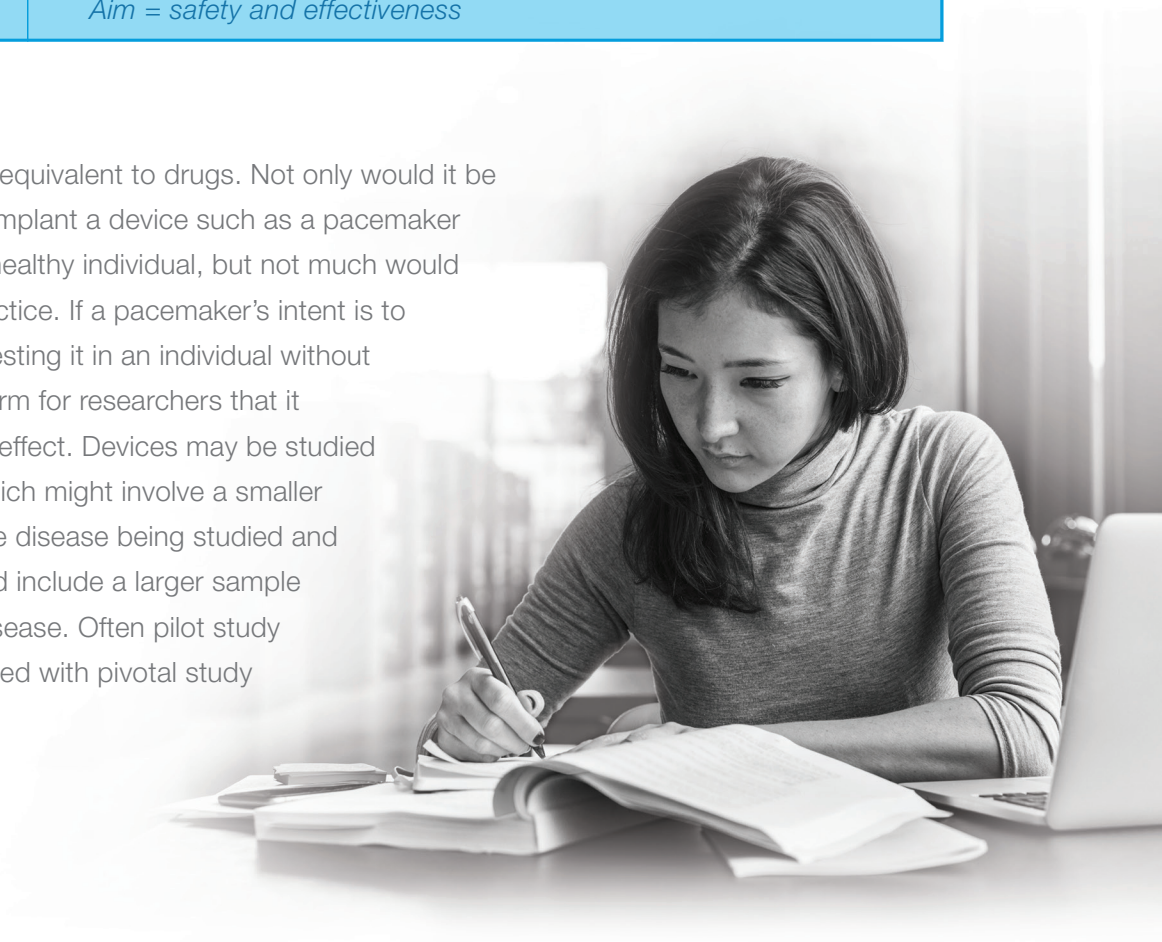


What do the clinical trials look like?

Drugs studies are conducted in phases as described in the table below with phase 1 aimed at safety and tolerance, phase 2 aimed at safety and efficacy, and phase 3 aimed at safety and efficacy in a larger population. Because of the systemic affect, more patients than are typically enrolled in a device trial are needed in a drug trial to determine how the chemical interaction affects the human body and how it potentially interferes with the metabolism of other drugs.

CLINICAL TRIALS ALWAYS REQUIRED FOR NEW DRUGS	
Phase I	*Normal healthy volunteers* *Determine metabolism and pharmacologic actions* *Aim = safety and tolerance*
Phase II	*Patients with the disease or condition* *Small sample* *Aim = safety and effectiveness*
Phase III	*Patients with the disease or condition* *Larger population* *Aim = safety and effectiveness*

Devices have no “phase I” equivalent to drugs. Not only would it be unethical, for instance, to implant a device such as a pacemaker or a coronary stent into a healthy individual, but not much would be gained from such a practice. If a pacemaker’s intent is to normalize an arrhythmia, testing it in an individual without an arrhythmia will not confirm for researchers that it accomplishes its intended effect. Devices may be studied in terms of pilot studies which might involve a smaller number of patients with the disease being studied and pivotal studies which would include a larger sample size of patients with the disease. Often pilot study data are eventually combined with pivotal study data for analysis purposes.



How are the clinical trials regulated?

Once it is determined that a clinical trial is necessary, the applicable regulations will need to be followed. The regulatory requirements for conducting a clinical trial are exactly the same for drugs and devices when it comes to electronic medical records (21 CFR 11), human subject protection (21 CFR 50), financial disclosure (21 CFR 54), and IRB requirements (21 CFR 56). The differences exist in the investigational new drug regulations (21 CFR 312) and the investigational device exemption regulations (21 CFR 812), however, even within 21 CFR 312 and 21 CFR 812, the similarities far outweigh the differences.

Some of those similarities are described in the table below.

FEDERAL REQUIREMENTS	DRUGS	DEVICES
21 CFR 11	*Required*	*Required*
21 CFR 50	*Required*	*Required*
21 CFR 54	*Required*	*Required*
21 CFR 56	*Required*	*Required*
21 CFR 312	*Required*	*Not Required*
21 CFR 812	*Not Required*	*Required*

SIMILARITIES	312	812
Requires that the appropriate submission be made to the FDA before beginning an investigation	✓	✓
Requires annual updates on study progress	✓	✓
Requires amendments when changes are made	✓	✓
Addresses the issue of promotion and charging for the product	✓	✓
Specifies requirements for labeling	✓	✓
Addresses waivers	✓	✓
Describes both sponsor and investigator responsibilities	✓	✓
Requires that the investigation be conducted in compliance with the investigational plan, signed agreement, federal regulations, and conditions of approval imposed by the IRB	✓	✓
Requires the selection of qualified investigators	✓	✓
Requires that sponsors provide information to investigators	✓	✓
Requires that the investigation be properly monitored	✓	✓
Requires that IRB approval be obtained prior to beginning the investigation	✓	✓
Specifies to whom significant new information should be provided	✓	✓

What are the differences?

While there are many similarities, the differences lie in the details, and those details can sometimes lead to confusion and mixed messages among clinical researchers. The following paragraphs touch on some of the more noticeable differences between drugs and devices.

Agreements

In both drug studies and device studies, the FDA requires that the investigator comply with the agreements (21 CFR 312.56 and 21 CFR 812.46), however the agreements are not identical. The FDA Form 1572 is the agreement mandated by the FDA to be completed by all investigators involved in a drug trial. The agreement describes an investigator's qualifications and specifies his or her commitment to adhering to applicable FDA regulations. While the FDA does not require a specific form be completed for a device study, they do specify what needs to be contained in an agreement including investigator qualifications, their commitment to conduct the study in accordance with applicable regulations, their commitment to supervise device use, and a statement regarding involvement in research that was terminated, if applicable.

Training

Training should be approached slightly differently when beginning a drug study versus beginning a device study. In drug studies, the influence of physician technique is very low. Medication is dispensed and instructions are given to the patient to take the pill once daily, twice daily, etc. The brunt of the responsibility to comply with the drug regimen lies with the patient or the patient's caregiver. The focus on training at that point should be on first training the staff on the protocol requirements, mechanism of action of the drug, and possible side effects. The staff should then train the patient on how to use the medication, what signs and symptoms to take note of, and what to do if they have a negative reaction. Generally speaking, it would not be essential that the principal investigator oversee his or her sub-investigators dispensing the medication.

In device trials, the influence of physician technique can be very high depending on the complexity of the device being studied, and patients may have little to no outward affect on the process. Navigating a coronary stent into the correct position to open a stenosed vessel takes a specialized skill set. For this reason, training should be approached differently and should include not only protocol-specific training, but hands-on device specific training. This may require additional personnel to support the training that is usually done by a monitor (i.e., biomedical engineer, another physician, etc.) The principal investigator's supervision of his or her sub-investigators deploying or implanting a device may be necessary to ensure proper oversight.

Product reimbursement

Most often, drugs used in clinical trials are provided free of charge to clinical sites and patients. Devices can be expensive to produce and depending on the device, providing it for free could be a significant barrier to development. For some devices, investigators are charged for the devices and are then reimbursed by Medicare or private insurance. In the case of Medicare, a "Category B Investigational Devices" classification is granted by Medicare in order to allow for the billing of the investigational device.

Adverse events

The requirements for reporting adverse events are different for drug studies than for device studies. Due to the systemic nature of drugs, all adverse events will need to be captured and analyzed as potentially related to the drug. Contrary to this, devices have a local affect, and the likelihood of an adverse event being related to the device is easier to determine. For this reason, not all negative occurrences in a device study are reportable, and a smaller population is generally sufficient to determine what possible risks may be associated with a particular device.

Conclusion

Drugs and devices have differences, as described in this document, but they still share one unarguable similarity: patients. On the other end of that investigational product is a patient taking a risk. And for clinical research professionals, protecting them is their biggest responsibility. So whether completing a Form 1572 or signing a device agreement, whether reporting every stubbed toe, or just reporting a gangrenous toe, the activities that are incorporated into the processes are there to ensure a wellcontrolled, properly run clinical trial. The process of getting a drug to the finish line may look a little different than getting a device to the finish line, but either way, the road to that finish line requires an ethical commitment combined with proper controls and an understanding of the differences – in the details – between drugs and devices.

Sandra Maddock CEO and President

Under Sandra Maddock's leadership, IMARC Research was founded in 1999 to deliver the highest-quality clinical research monitoring, auditing, training/development and consulting services.

Sandra offers IMARC partners years of expertise covering:
coronary and peripheral stents, angioplasty balloons, combination products, thrombolytics, chemotherapy agents, endovascular grafts for treatment of thoracic and abdominal aortic aneurysms, wound care, and dura mater replacement grafts. Whether serving as a global auditor for a device study across the U.S., Japan and Germany, or working with U.S. sites establishing GCP Compliance in preparation for an FDA Inspection, Sandra's hands-on approach has become her trademark.

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