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# The Food and Drug Administration and pragmatic clinical trials of marketed medical products

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## Abstract

Pragmatic clinical trials (PCTs) can help answer questions of comparative effectiveness for interventions routinely used in medical practice. PCTs may examine outcomes of one or more marketed medical products, and they are heterogeneous in design and risk. The Food and Drug Administration (FDA) is charged with protecting the rights, safety, and welfare of individuals enrolled in clinical investigations, as well as assuring the integrity upon which approval of medical products are made. The FDA has broad jurisdiction over drugs and medical devices (whether or not they are approved for marketing), and as such, clinical investigations of these products are subject to applicable FDA regulations. While many PCTs will meet the criteria for an exemption from the requirements for an investigational new drug application (IND) or investigational device exemption (IDE), in general all clinical investigations of medical products that fall under FDA jurisdiction must adhere to regulations for informed consent and review by an institutional review board (IRB). We are concerned that current FDA requirements for obtaining individual informed consent may deter or delay the conduct of PCTs intended to develop reliable evidence of comparative safety and effectiveness of approved medical products that are regulated by the FDA. Under current regulations, there are no described mechanisms to alter or waive informed consent to make it less burdensome or more practicable for low-risk PCTs. We recommend that the FDA establish a risk-based approach to obtaining informed consent in PCTs that would facilitate the conduct of PCTs without compromising the protection of enrolled individuals or the integrity of the resulting data.

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Clinical research oversight; Food and Drug Administration; informed consent; medical devices; pragmatic clinical trials; regulations

## Introduction

In contrast to explanatory clinical trials, pragmatic clinical trials (PCTs) are designed to evaluate the comparative effectiveness of interventions within routine clinical settings.[1,2] These trials are "pragmatic" because they focus on understanding how interventions work in real life as opposed to "explanatory" where the goal is to determine if and how an intervention works.[1,3,4] Key aspects of PCTs are broad population inclusion, study design and data collection procedures that minimally disrupt routine clinical care encounters, and an emphasis on patient-centered health outcomes.[2] PCTs are expected to be a major vehicle for comparative effectiveness research for products that have been previously FDA-approved and for evaluating healthcare strategies that involve FDA-regulated products.[3] For this reason, it is important for investigators, sponsors, institutional review boards (IRBs), and patients to understand how current FDA regulations concerning the conduct of clinical investigations and the protection of human subjects may affect PCTs.

FDA's jurisdiction and oversight over clinical investigations, developed iteratively over the last half-century, centers primarily on the need to mitigate the risks to human subjects in explanatory trials intended to demonstrate safety and effectiveness of novel investigational therapies with unknown risks. PCTs exclusively involving FDA-approved treatments considered to be standard of care in clinical practice present different and often much smaller risks to human subjects,[5] and therefore less intensive regulatory oversight may be sufficient to protect human subjects.

In this article, we explain the FDA regulations that are applicable to the conduct of clinical investigations, and we illustrate important considerations with examples of PCTs. We discuss the potential for the FDA's informed consent regulations to impede or deter the conduct of PCTs and whether consent that adheres to FDA requirements is best suited to the conduct of lower-risk PCTs. We also suggest that the FDA apply a risk-based approach to determining whether alternative strategies to obtaining informed consent may be appropriate in low-risk PCTs. We then provide a schema for identifying low-risk PCTs and highlight the need for a regulatory mechanism to permit alteration or waiver of informed consent in certain low-risk PCTs.

While PCTs involving FDA-regulated products may be subject to both FDA regulations and U.S. Department of Health and Human Services (HHS) regulations governing human subject protections in federally funded research (45 CFR Part 46, known as the Common Rule[6]), the scope of this paper is limited to *FDA regulations* and their unique challenges for PCTs.

## FDA history and regulations

The Food, Drug, and Cosmetic Act (FD&C Act[7]) of 1938 gave FDA the authority to oversee the safety of food, drugs, and cosmetics before they entered the U.S. market.[8] The Kefauver-Harris Drug Amendments of 1962 gave rise to modern FDA oversight. These amendments require substantial evidence of a medical product's effectiveness for its intended use to obtain approval for marketing, and the evidence must consist of adequate and "well-controlled" trials.[9] The 1962 amendments also provided the FDA with jurisdiction over clinical investigations intended to demonstrate safety and effectiveness, including a requirement to obtain informed consent from study subjects enrolled in clinical investigations. In general, the FDA considers a clinical investigation to be:

> "… any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit."[10]

FDA jurisdiction over clinical investigations of regulated products extends throughout the product lifecycle, including clinical investigations of marketed products.[11] FDA maintains that even clinical investigations in which the marketed products are used according to their labeled indications are within its jurisdiction because the studies pose risks that patients' interests will be subordinated to the interests of the study and, therefore, should be subject to regulations intended to protect human subjects.[11]

### Investigational new drug and investigational device exemption regulations

The IND regulations[12] and IDE regulations[13] describe FDA's primary requirements for the conduct of clinical investigations of drugs and medical devices, respectively. The IND regulations describe the information that must be submitted to FDA to conduct a clinical investigation with an investigational drug, the criteria by which FDA determines whether a clinical investigation subject to IND regulations can proceed, and obligations and responsibilities of sponsors and investigators who conduct clinical investigations of investigational drugs. The IDE regulations describe similar responsibilities for clinical investigations of medical devices. However, in the case of medical devices, a clinical investigation is more narrowly defined as one that studies the safety and/or effectiveness of a device.[14] Clinical investigations conducted under an IND or IDE are subject to ongoing FDA oversight and reporting requirements, including submission of annual reports describing the progress of the clinical investigation, and expedited safety reports of serious, unexpected adverse events.

Both the IND and IDE regulations contain provisions that would generally exempt from those requirements studies of marketed products that are of low risk to patients (Table 1).[14-16] These exemption criteria would generally apply to low-risk PCTs of drugs or medical devices— that is, clinical investigations of marketed drugs and devices as they are

used in clinical practice—conducted by institutions other than the entities that market the studied products.[17] For example, the Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial[18] is a cluster-randomized PCT examining whether longer dialysis times compared with usual care will improve quality of life and survival. The trial is being conducted in more than 320 dialysis facilities owned by Fresenius Medical Care North American and DaVita. This trial was reviewed by the Center for Devices and Radiological Health (CDRH) at FDA and deemed exempt from the IDE requirements because the marketed devices are used in accordance with the indications in their FDA-approved labeling.[17]

Clinical investigations of drugs and medical devices that are exempt from the IND and IDE requirements, respectively, must still comply with regulations for informed consent of human subjects[19] and for IRBs.[20]

### Informed consent regulations

Informed consent is a process intended to enable individuals to make informed and voluntary decisions about participating in research with an understanding of the purpose, procedures, risks, and benefits of the investigation.[21] FDA's informed consent regulations describe the necessary elements of informed consent for patients participating in FDA-regulated investigations, including a statement that the study involves research, a description of foreseeable risks, a description of potential benefits, disclosure of alternative procedures or courses of treatment, a statement describing the extent to which study records are confidential (or not), compensation (if any), whether medical treatment is available for study-related injury, contact information, and a statement that participation is voluntary.[19] Only in very limited circumstances can the requirement to obtain informed consent be waived. In particular, section 50.23 provides an exception from the informed consent requirements for emergency treatment use, a presidential waiver for military personnel under certain circumstances, and in life-threatening situations necessitating the use of an investigational *in vitro* diagnostic device. Further, section 50.24 provides for an exception from informed consent for research conducted in an emergency setting.

### Institutional review board regulations

The IRB regulations describe the composition, operation, and responsibility of IRBs reviewing FDA-regulated clinical investigations. These regulations describe the criteria for IRB review of FDA-regulated investigations, including review of informed consent to determine whether it complies with the informed consent regulations as well as IRB procedural and recordkeeping responsibilities.[20] The IRB regulations also provide for the possibility of waiver of the need to document informed consent if the study is determined to constitute minimal risk and involves no procedures for which written consent is generally required outside the research context.[20,22]

## Informed consent issues raised in pragmatic clinical trials

As discussed above, PCTs of FDA-regulated products that are exempt from IND and IDE requirements are still be subject to informed consent and IRB requirements.[15] Therefore,

these trials will generally require documentation of informed consent as described in Table 2. These informed consent regulations are generally interpreted to require extensive and highly detailed consent that may be unnecessary and onerous in PCTs in which individual patients are randomized to interventions that they may well have been prescribed in the course of usual clinical practice and for which the risks and benefits are not known to be materially different. Additionally, such detailed consent may dissuade patients from participating because they may believe the medical products used in the PCT are more risky than those used in clinical practice.[23]

The NIH Health Care Systems Research Collaboratory supports several ongoing and planned PCT demonstration projects[24]. One of these, the ABATE Infection trial, highlights considerations related to FDA regulations for informed consent. The ABATE Infection trial is a pragmatic, cluster-randomized controlled trial in which individual hospitals are randomized to one of two strategies commonly used to reduce multidrug-resistant organisms and healthcare-associated infections in non–critical care settings.[25] The study compares FDA-approved decolonization drugs, chlorhexidine and mupirocin, to routine hospital bathing and showering practices. For the duration of the study, all non-ICU ward patients admitted to more than 50 hospitals will be enrolled. This example illustrates a potential problem with obtaining informed consent, written or oral, in a cluster-randomized trial where all patients in a cluster must participate to enable the study to answer the research question. Informed consent is understood to include the option to decline to participate.

The Patient-Centered Outcomes Research Institute is preparing to initiate its first randomized PCT to be conducted within PCORnet, a national network integrating data from 11 clinical data research networks and 18 patient-powered research networks. This PCT called ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) will compare the effectiveness of two doses of aspirin for secondary prevention of atherosclerotic cardiovascular disease in 20,000 patients. Data will be collected periodically from the electronic health records of enrolled patients and from patients via the Internet.[26] The risks and benefits related to aspirin are well known, and a patient could be prescribed either dose within the course of clinical practice. ADAPTABLE plans to use an electronic informed consent process.

These examples illustrate scenarios in which documented informed consent consistent with FDA requirements could deter enrollment and threaten the ability to conduct the study in a timely way, or at all. Each study is a large, simple design in which the risks from participating in the study closely track the risks a patient would be exposed to in a clinical practice setting. In these scenarios, an alternative to extensive, documented informed consent may better meet the needs of enrolled patients and facilitate the conduct of the trial. We recognize that the size and simplicity of these trials are not independent bases for a less burdensome informed consent process, but we believe those factors support the case for alternatives to conventional written informed consent.

Recent empirical research supports the idea that people want to be informed about research and prefer to have the option to participate.[27,28] Of those surveyed in a recent study,[28] most understood that trade-offs may be needed and would support more practical approaches (oral

permission or general notification) if written permission made research impracticable. The nature and goals of PCTs challenge the notion that current complex federal regulatory requirements for informed consent are necessary to protect human subjects in PCTs.[22] For PCTs that track clinical practice and compare interventions for which conventional written informed consent would not be required in a clinical practice setting, it is unclear what information individuals would find most helpful in their decision to enroll in a PCT, in what format this information should be delivered, and whether informed consent adherent to the regulations is best suited to this context; additional research is needed. However, it seems clear that extensive and detailed written informed consent is not necessary. For cluster-randomized trials in which large institutions are the unit of randomization, individual subject consent may not be meaningful (as when the patient has no alternative to hospitalization), practicable (i.e., when trial validity is contingent upon uniform application of the study intervention within that institution or community), or permit choice (e.g., when the range of treatment options are protocol-driven or based on existing formulary). Alternative approaches are needed.

## Proposed risk-based approach to informed consent for PCTs regulated by the FDA

We recommend that FDA apply a risk-based policy for obtaining informed consent in PCTs that would permit alternatives to informed consent that meets current requirements in low-risk PCTs. This policy would build upon FDA's current risk-based approach to determining the need for IND and IDEs. In Table 3 we delineate categories of PCTs that fall on a spectrum of risk levels based on the nature of the evidence to support the use.

*Category 1* PCTs would compare approved drugs or devices used according to their approved or cleared labels. In these types of PCTs, the comparators are demonstrated to be effective in the manner used in the study according to FDA-approved labeling. This category would generally have well-known safety profiles (based on premarket studies and postmarket surveillance). The use of the products would be considered to be within the standard of care for the indications for which they are being studied. In addition, the balance of risks and benefits of the compared products would not be known to be materially different. Given these conditions, enrollment in the PCTs would be of no greater risk than receiving the approved drugs in a clinical practice setting. Therefore, the incremental risk of the research could be considered minimal. An example of such a PCT would be a comparison of rosuvastatin (FDA-approved 2003)[29] with atorvastatin (FDA-approved 1996)[29] to reduce cardiovascular events in patients at high-risk for atherosclerotic cardiovascular disease. The American College of Cardiology/American Heart Association (ACC/AHA) released guidelines in 2013 recommending moderate to high statin therapy for four groups at risk for atherosclerotic cardiovascular disease, including patients 40 to 75 years of age with a 10-year risk of atherosclerotic cardiovascular disease.[30] Here, there is no known difference in the risk–benefit balance of one drug compared to the other (clinical equipoise), so the risks associated with the exposure to these FDA-regulated products are no greater than what would be encountered in clinical practice. Alternates to a conventional

written informed consent processes are conceivable (e.g., notification, opt-out mechanisms). IND or IDE would not be required, as determined by exemption criteria.

*Category 2* and *Category 3* PCTs would involve one or more comparators that are commonly used for the indication being studied but used in an unlabeled (also referred to as off-label) manner; that is, outside of its labeled indication granted by the FDA for marketing. Within this category, the quality and quantity of evidence to support the unlabeled use could vary considerably. There would thus be a spectrum of risk associated with the unlabeled use, and varying levels of FDA oversight may be warranted. In Category 2, a PCT involves an unlabeled use of an approved drug identified as a standard-of-care medical product and endorsed by clinical practice guidelines. For example, hydralazine is approved only for hypertension—except in blacks where BiDil (an isordil/hydralazine combination pill) is approved for heart failure.[31,32] However, the ACC/AHA currently recommends the use of hydralazine and nitrates in non-blacks with heart failure with reduced ejection fraction (class IIa) if angiotensin-converting enzyme inhibitors or angiotensin receptor blockers cannot be tolerated.[32,33] Thus a trial seeking to compare standard of care plus isordil/hydralazine and standard of care for a broader population of patients with systolic dysfunction could conceivably be conducted without FDA oversight and with simplified or altered consent that still adheres to FDA requirements.

Similarly, coronary stents are considered standard of care in patients with acute ST-elevation myocardial infarction (STEMI) based on extensive experience in controlled clinical trials[34-39] and authoritative professional guidelines.[40] A PCT of STEMI comparing outcomes with different types of drug-eluting stents (e.g., sirolimus versus zotarolimus) for which there is no known material difference in risks and benefits would present only minimal incremental risk above routine clinical practice in this setting. Again, in these PCTs, an IND or IDE may not be needed and consent could be altered or simplified here.

*Category 3* PCTs also involve an unlabeled use of a medical product used some in clinical practice but not formally endorsed by clinical guidelines[41] and for which there is limited evidence of safety and effectiveness. For example, intravenous or intramuscular lidocaine is commonly used off-label to relieve pain and other symptoms associated with drug-resistant fibromyalgia and other chronic pain syndromes,[42-46] but there is not conclusive evidence to support that use. In a PCT comparing lidocaine with other interventions for fibromyalgia, more extensive informed consent may be warranted to explain the limited evidence to support the unlabeled use and the potential risks related to the limited evidence. In such cases, the risks presented by the unlabeled use could be significantly increased relative to labeled uses of the product, in which an IND or IDE is needed and consent should be comprehensive and documented.

*Category 4* PCTs involve 1 or more products for investigational use. Accordingly, in such trials, an IND or IDE is needed and consent should be comprehensive and documented.

## Interim Recommendations

We recognize that formal implementation of a risk-based approach for informed consent will require a change to FDA regulations, which is typically a lengthy process. In the

interim, we encourage FDA to provide guidance for IRBs, sponsors, and investigators to help facilitate the conduct of PCTs under existing regulations, as it has done in other contexts.[47] FDA's IRB regulations permit IRBs to waive documentation of informed consent if the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.[20] We recommend that the FDA provide guidance that describes criteria for minimal risk that would explicitly encompass low-risk PCTs and which interprets the waiver of documentation provision for informed consent for minimal-risk trials to permit alternatives to conventional written informed consent that strictly adheres to the required elements in the current regulations. We recommend that the guidance include discussion of simplified elements and acceptable innovative methods of obtaining and documenting consent (e.g., simple-to-use, interactive electronic options). In addition, we recommend that the guidance describe possible alternatives to conventional written informed consent for low-risk cluster-randomized trials where individual consent may not be feasible or possible. Empirical data and evolving knowledge about the goals of informed consent (e.g., respect, protection, and authorization) will be imperative in guiding the FDA (as well as others) in adapting informed consent processes to this new paradigm of research.[22,48]

## Conclusion

With evolving clinical trial designs meant to address large evidentiary gaps in our knowledge of the relative effectiveness and safety of various treatment options in clinical practice settings, some of FDA's informed consent requirements may impede the ability to routinely perform PCTs that are essential to answering comparative effectiveness questions. FDA has spearheaded multiple efforts that demonstrate its willingness to be innovative in enhancing the efficiency and utility of the clinical research enterprise in meeting important public health goals (e.g., revisions to adverse event reporting and clinical trial monitoring). To facilitate broader use of PCTs so that data may be generated to help advance public health, we recommend that FDA adopt a risk-based approach to its jurisdiction for IND- and IDE-exempt trials. We believe that the FDA should have the explicit authority to consider alteration or waiver of individual informed consent when deemed appropriate.

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**Table 1**

**Criteria for exemptions of marketed products—investigational new drugs and investigational devices**

| Code of Federal Regulations Title 21—FDA | Regulation Text |
|---|---|
| ***Part 312—Investigational New Drug Application*** | |
| Sec. 312.2 Applicability (b) *Exemptions* | "(b) *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:<br>(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;<br>(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;<br>(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;<br>(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and<br>(v) The investigation is conducted in compliance with the requirements of 312.7." |
| ***Part 812—Investigational Device Exemptions*** | |
| Sec. 812.2 Applicability (c) *Exempted investigations* | "(c) *Exempted investigations.* This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:<br>(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.<br>(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.<br>(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:<br>(i) Is noninvasive,<br>(ii) Does not require an invasive sampling procedure that presents significant risk,<br>(iii) Does not by design or intention introduce energy into a subject, and<br>(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.<br>(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.<br>(5) A device intended solely for veterinary use.<br>(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).<br>(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution." |
| Sec. 812.3 Definitions (m) *Significant risk device* | "(m) *Significant risk device* means an investigational device that: |

| Code of Federal Regulations Title 21—FDA | Regulation Text |
|---|---|
| | (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;<br>(2) 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;<br>(3) 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<br>(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.” |

**Table 2**

**Elements of informed consent as required by FDA**

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| **Mandatory elements** |
| (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are considered experimental |
| (2) A description of any reasonably foreseeable risks or discomforts to the subject |
| (3) A description of any benefits to the subject or to others which may reasonably be expected from the research |
| (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject |
| (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records |
| (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained |
| (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject |
| (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled |
| ***Additional elements*** |
| (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable |
| (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent |
| (3) Any additional costs to the subject that may result from participation in the research |
| (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject |
| (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. |
| (6) The approximate number of subjects involved in the study |
| ***Applicable clinical trials*** |
| Must include the following statement in the Informed Consent Document: “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.” |

**Table 3**

**Risk categories of PCTs involving medical products in clinical research**

| Risk Category | Paradigm | Examples | Considerations |
|---|---|---|---|
| 1 | One or more regulated products **according to approved or labeled uses** | **1** Clinical trial comparing atorvastatin versus rosuvastatin according to labeled population and dose(s)<br>**2** Clinical trial comparing functional and anatomic evaluation of patients with chest pain | • Some labels are highly specific, which may result in a restrictive study population<br>• Likely to be low risk to study subjects<br>• In the case of devices, FDA regulations are not triggered unless safety and effectiveness are being evaluated<br>• Describes situations that would be encountered in clinical practice |
| 2 | One or more regulated products **NOT according to label but according to standard of care** | **1** Study involving the use of hydralazine in heart failure<br>**2** Study evaluating coronary stents in acute myocardial infarction<br>**3** Study involving the use of amiodarone to treat atrial fibrillation | • Risk profile of the product generally well understood<br>• Risk may vary according to the level of evidence supporting the “standard of care” ranging from low to high (amiodarone, apixaban)<br>• Professional guidelines are frequently discordant with product labels/approved use<br>• “Standard of care” may be variable by geography, medical specialty, or other factors<br>• Describes situations that would be encountered in clinical practice |
| 3 | One or more regulated products **NOT according to label and NOT according to standard of care** | **1** Study of renal denervation for uncontrolled hypertension<br>**2** Study involving apixiban for anticoagulation in patients with mechanical heart valves<br>**3** Study of intravenous or intramuscular lidocaine for pain relief in fibromyalgia | • Understanding of risk based on less experience and Likely less developed evidence base<br>• Newly approved products likely have less evidence base in unapproved indications |
| 4 | One or more regulated products **for investigational use** | **1** Pivotal device studies<br>**2** Phase II/III drug studies | • Unknown or minimally known safety and efficacy/effectiveness profile |