FDA and Pragmatic Clinical Trials of Marketed Medical Products

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Objectives

• Review FDA regulations applicable to clinical investigations
• Discuss implications for FDA’s informed consent regulations on the conduct of PCTs
• Present case examples that highlight potential issues with PCTs involving FDA-regulated medical products
• Describe writing group recommendations to the FDA to help facilitate the conduct of low-risk PCTs
• Highlight interim solutions to clarify FDA regulations for low-risk PCTs
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Introduction

• PCTs are designed to evaluate the comparative effectiveness of interventions within routine clinical settings\textsuperscript{1,2}
• Key aspects of PCTs are:
  • Broad population inclusion
  • Study design and data collection procedures that minimally disrupt routine clinical encounters
  • Emphasis on patient-centered health outcomes\textsuperscript{2}
• PCTs are expected to be a major vehicle for CER for products that are FDA approved (or cleared) and for evaluating healthcare strategies that involve FDA-regulated products\textsuperscript{3}
• Important for investigators, sponsors, institutional review boards, and patients to understand if and how current FDA regulations for medical products could affect PCTs (particularly cluster randomized trials)

FDA Jurisdiction and PCTs

- Developed iteratively over the last half-century\(^1\)

- Primarily established to mitigate the risks to human subjects in explanatory trials of investigational therapies\(^1\)

- PCTs that involve FDA-approved treatments considered to be standard of care present different and often much smaller risks to human subjects

- Less intensive regulatory oversight may be sufficient to protect human subjects

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1. U.S. Food and Drug Administration (FDA). Promoting safe and effective drugs for 100 years, [http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/](http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/)
FDA History and Regulations

• 1938: Food, Drug, and Cosmetic Act (FD&C)
  • FDA given the authority to oversee the safety of food, drugs, and cosmetics before they enter the US market\(^1\)
• 1962: Kefauver-Harris Drug Amendments\(^2\)
  • Modern FDA oversight
  • Substantial evidence of a medical product’s effectiveness for its intended use to obtain approval for marketing
  • Evidence must consist of adequate and “well-controlled” trials
  • FDA also given jurisdiction over clinical investigations intended to demonstrate safety and effectiveness
  • Rise of modern informed consent requirements in clinical investigations

2. U.S. Food and Drug Administration (FDA). Promoting safe and effective drugs for 100 years, http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/ (accessed 17 April 2015).
Clinical Investigation

• 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 FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.¹

Clinical Investigations of FDA Approved Drugs

- FDA jurisdiction extends throughout the product life cycle, including clinical investigations of marketed products\(^1\)
- FDA maintains that even clinical investigations in which the marketed products are used according to labeled indications are within its jurisdiction
  - FDA concerned with safety and welfare of patients in clinical trials
    - Patient’s interests subordinated to study interests; human protections needed
  - FDA concerned about public health, and making certain that decisions about product approvals are based on credible and interpretable data

## FDA Regulations for Clinical Investigations

<table>
<thead>
<tr>
<th>Code of Federal Regulations</th>
<th>Name</th>
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<tr>
<td>21 CFR 312</td>
<td>Investigational New Drug Application</td>
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<td>21 CFR 812</td>
<td>Investigational Device Exemption</td>
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<td>21 CFR 50</td>
<td>Protection of Human Subjects</td>
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<td>21 CFR 56</td>
<td>Institutional Review Boards</td>
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</table>
Investigational New Drug (IND) Regulations (21 CFR 312)

- Primary requirements for conduct of clinical investigations of drugs
- Describes information that must be submitted to the FDA to conduct a clinical investigation with an investigational drug
- Describes the criteria the FDA utilizes to determine where a subjected clinical investigation can proceed
- Describes the obligation and responsibilities of sponsors and investigators conducting the clinical investigation
- Clinical investigations under an IND are subject to FDA oversight and reporting requirements:
  - Submission of Annual Reports on progress of CI
  - Expedited safety reports of serious and unexpected adverse events

Investigational Device Exemption Regulations (21 CFR 812)

• Describe similar responsibilities for clinical investigations with investigations of medical devices\(^1\)

• For IDE, a clinical investigation is more narrowly defined as one that studies the safety and effectiveness of a device\(^2\)

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IND/IDE Exemptions

• Both the IND and IDE regulations contain provisions that would generally exempt studies of marketed products that are of low risk to patients

• Exemption criteria would generally apply to low-risk PCTs of drugs or medical devices
  • Clinical investigations of marketed drugs and devices as they are used in clinical practice
  • Conducted by institutions other than sponsors that market the studied products (no intent to pursue labeling changes)

21 CFR 50: Informed Consent

- 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.
  - Statement that study involves research
  - Description of foreseeable risks
  - A description of potential benefits
  - Disclosure of alternative procedures or courses of treatment
  - 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
  - A statement that participation is voluntary
FDA Regulations for Waiving Informed Consent

- **Section 50.23**
  - Exception from the informed consent requirements for emergency treatment use
  - A presidential waiver for military personnel under certain circumstances
  - Life-threatening situations necessitating the use of an investigational in vitro diagnostic device.

- **Section 50.24**
  - Exception from informed consent for research conducted in an emergency setting
21 CFR 56: Institutional Review Boards

- Regulations describe composition, operation, and responsibility of IRBs reviewing FDA-regulated clinical investigations under the FD&C Act

- Regulations describe criteria for IRB review
  - Informed consent review for determination of compliance with FDA regulations
  - IRB procedural and recordkeeping responsibilities

- 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

Informed Consent Issues in PCTs

- PCTs exempt from IND/IDE are subject to IC and IRB regulations.
- PCTs will generally require documentation of informed consent.
- Informed consent must include all elements.
- FDA regulations are generally interpreted to require extensive and detailed IC that may be onerous or impracticable for low-risk PCTs:
  - Interventions prescribed in the course of usual clinical practice where risks and benefits are not known to be materially different.
  - Such detailed consent may dissuade patients from participating; may believe risk of medical products in PCTs > clinical practice.
Example 1: ABATE Trial

- Active Bathing to Eliminate Infection Trial
- PCT in which individual hospitals are randomized to one of two strategies commonly used to reduce multidrug resistant and healthcare-associated infections in non-critical care settings
- Study compares FDA-approved decolonization drugs, chlorhexidine and mupirocin, to routine hospital showering practices
- During study duration, all non-intensive care unit ward patients admitted to greater than 50 hospitals are being enrolled
- This example illustrates a potential problem with obtaining informed consent, written or oral, in a cluster-randomized trial (CRT) where all patients in a cluster must participate to answer the research question
- Informed consent is understood to include the option to decline to participate

Example 2: ADAPTABLE Trial

• Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness
• First PCT of PCORnet
• 3-year PCT is comparing the effectiveness of two doses of aspirin for secondary prevention of atherosclerotic cardiovascular disease in 20,000 patients
• Data are being collected periodically from the electronic health records of enrolled patients and from patients via the internet
• The risks and benefits related to aspirin are well known, and a patient could be prescribed either dose within the course of clinical practice
• Study uses an electronic informed consent process

Issues with IC in PCTs with FDA-approved products

- ABATE and ADAPTABLE PCTs highlight scenarios with IC as required by the FDA could deter enrollment and threaten the ability to conduct the study in a timely way, if at all

- In each trial, the risks from participating in the study closely track the risks patients would be exposed to in a clinical practice setting

- Alternatives to extensive, documented consent may better meet the needs of enrolled patients
Research on Medical Practices: Attitudes toward Informed Consent

- 1095 adults completed a web-based questionnaire on risks and preferences for notification and informed consent for research involving usual medical practices
- 3 animated videos that focused on clinical trial scenarios
  - Medical record review comparing the outcomes of 3 FDA-approved medications in patients with newly diagnosed hypertension
  - Unblinded, random assignment of FDA-approved medications based on physician judgment and patient preferences
  - Randomized study comparing 3 medications for “a more serious condition that increases your risk of stroke”

Research on Medical Practices: Attitudes toward Informed Consent

- 97% (74.3% strongly) respondents agreed that health systems should evaluate standard treatments
- 92.8% acceptable for health systems to use randomization for standard treatment comparisons
- 75.2% to 80.4% wanted to be asked permission to participate even if research only involved a medical record review
- 70.2% to 82.7% would accept oral or general notification for consent if written permission makes research conduct difficult
- 64.0% to 81.6% perceived additional risk from each research scenario

Low-risk PCTs involving FDA-regulated products: Writing Group Summary

- Nature and goals of PCTs challenge the notion that complex federal regulatory requirements for IC are required for protection of human subjects in PCTs.
- For PCTs that track clinical practice where IC not needed, it is unclear what information patients find helpful and in what format.
- Extensive and detailed consent is not necessary.
- When the institution is the randomization unit, individual subject consent may not be meaningful, practicable, or permit choice.
- Additional research is needed.
- Alternative approaches are needed.
Writing Group Recommendations

• We recommend FDA adopt a risk-based policy for obtaining IC to permit alternatives to conventional written IC

• Policy would build upon FDA’s current risk-based policy for determining the need for INDs and IDEs

• We propose that risk-based categories of PCTs fall on a spectrum of risk levels based on the nature of the evidence to support the use

Risk-based IC Approach
Category 1 PCTs

- Category 1 PCTs would compare approved drugs or devices used according to their approved or cleared labels.
- Safety and effectiveness profiles are well-known and therapies are used according to FDA-approved labeling.
- Balance of risks and benefits between the two comparators would not be known to be materially different.
- Incremental risk of approved drug/device in the trial is minimal compared with its use in clinical practice.
- PCT comparing rosuvastatin to atorvastatin to reduce cardiovascular events in patients at high risk for atherosclerotic events.
- Alternatives 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.
Risk-based IC Approach
Category 2 PCTs

- PCTs involve an unlabeled use of an FDA-approved drug/device commonly used in clinical practice (endorsement by clinical guidelines)

- For example, hydralazine is approved only for hypertension—except in blacks where BiDil (an isordil/hydralazine combination pill) is approved for heart failure
  - Only endorsed by AHA guidelines if non-blacks with CHF have intolerance to ACE or ARB therapies

- PCT comparing standard of care plus isordil/hydralazine and standard of care for a broader population of patients with systolic dysfunction could conceivably be done without FDA oversight and with simplified or altered consent that still adheres to FDA requirements

Risk-based IC Approach

Category 3 PCTs

- PCTs that also involve an unlabeled use of a medical product used some in clinical practice but not formally endorsed by clinical guidelines and with limited evidence of safety and effectiveness
- Intravenous or intramuscular lidocaine is commonly used off-label to relieve pain in drug-resistant fibromyalgia and other chronic pain syndromes, but no conclusive evidence to support that use
- For a PCT comparing lidocaine with other interventions for fibromyalgia, more extensive informed consent may be warranted to describe the potential risks related to the limited evidence
- IND or IDE is needed
- Informed consent should be comprehensive and documented

Risk-based IC Approach
Category 4 PCTs

- PCTs that involve one or more products for investigational use as with traditional explanatory RCTs
  - IND or IDE is needed
  - Informed consent should generally be comprehensive and documented

Interim Recommendations

• Broad implementation of a risk-based approach to IC would likely require change in FDA regulations (a lengthy process), but there is potential for more flexible application of existing regulations

• Recommendations:
  • FDA develop guidance for IRBs, sponsors, and investigators to facilitate the conduct of low-risk PCTs under existing regulations
    • Describe criteria for minimal risk that encompasses low-risk PCTs
    • Interpret the waiver of documentation provision for IC for minimal-risk trials in order to permit alternatives to conventional written IC while still adhering to required elements
    • Discuss and illustrate simplified elements and acceptable innovative methods of obtaining and documenting consent (e.g. simple-to-use, interactive electronic options)
Conclusions

- PCTs conducted within health systems are meant to address gaps in our knowledge of the relative safety and effectiveness of standard medical products.
- Some of the FDA informed consent requirements may impede the ability to perform PCTs that are essential to achieving these national priorities.
- To facilitate broader use of PCTs involving FDA-regulated medical products, our recommendation is that the FDA adopt a risk-based approach to its jurisdiction for IND- and IDE-exempt trials.
- In the future, FDA should develop a regulatory scheme that provides explicit authority to consider alteration or waiver of IC for low-risk PCTs when deemed appropriate.
Acknowledgements

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• Robert M. Califf, MD, for his contributions while Director of the Duke Translational Medicine Institute (through Feb 2015)
Additional Slides
Table 2. Elements of informed consent as required by FDA.

<table>
<thead>
<tr>
<th>Mandatory elements</th>
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<tr>
<td>(1) A statement that the study involves research, an explanation of the purposes</td>
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<td>which are considered experimental.</td>
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<td>(2) A description of any reasonably foreseeable risks or discomforts to the</td>
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<td>subject.</td>
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<td>(3) A description of any benefits to the subject or to others which may reasonably</td>
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<td>be expected from the research.</td>
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<td>(4) A disclosure of appropriate alternative procedures or courses of treatment,</td>
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<td>(5) A statement describing the extent, if any, to which confidentiality of records</td>
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<td>(6) For research involving more than minimal risk, an explanation as to whether</td>
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<td>information may be obtained.</td>
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<td>(7) An explanation of whom to contact for answers to pertinent questions about</td>
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<td>(8) A statement that participation is voluntary, that refusal to participate will</td>
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<td>Additional elements</td>
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<td>(1) A statement that the particular treatment or procedure may involve risks to</td>
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<td>(2) Anticipated circumstances under which the subject's participation may be</td>
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<td>(3) Any additional costs to the subject that may result from participation in the</td>
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<td>research.</td>
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<td>(4) The consequences of a subject's decision to withdraw from the research and</td>
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<td>(5) A statement that significant new findings developed during the course of the</td>
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<td>(6) The approximate number of subjects involved in the study.</td>
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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.”

FDA: Food and Drug Administration.
## Criteria for Exemptions from IND

### Code of Federal Regulations

<table>
<thead>
<tr>
<th>Title 21—FDA</th>
<th>Regulation Text</th>
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### Part 312—Investigational New Drug Application

#### Sec. 312.2 Applicability

**(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:
   1. 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;
   2. 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;
   3. 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;
   4. 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
   5. The investigation is conducted in compliance with the requirements of 312.7.

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Criteria for Exemptions from IDE

Part 812—Investigational Device Exemptions
Sec. 812.2 Applicability
(c) Exempted investigations. This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:

(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.

(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.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing
   (i) Is noninvasive,
   (ii) Does not require an invasive sampling procedure that presents significant risk,
   (iii) Does not by design or intention introduce energy into a subject, and
   (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(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.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.