Sponsor-Investigators of Medical Device Studies: Creating Front-Line Institutional Compliance Systems

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FDA regulations for clinical investigations with medical devices

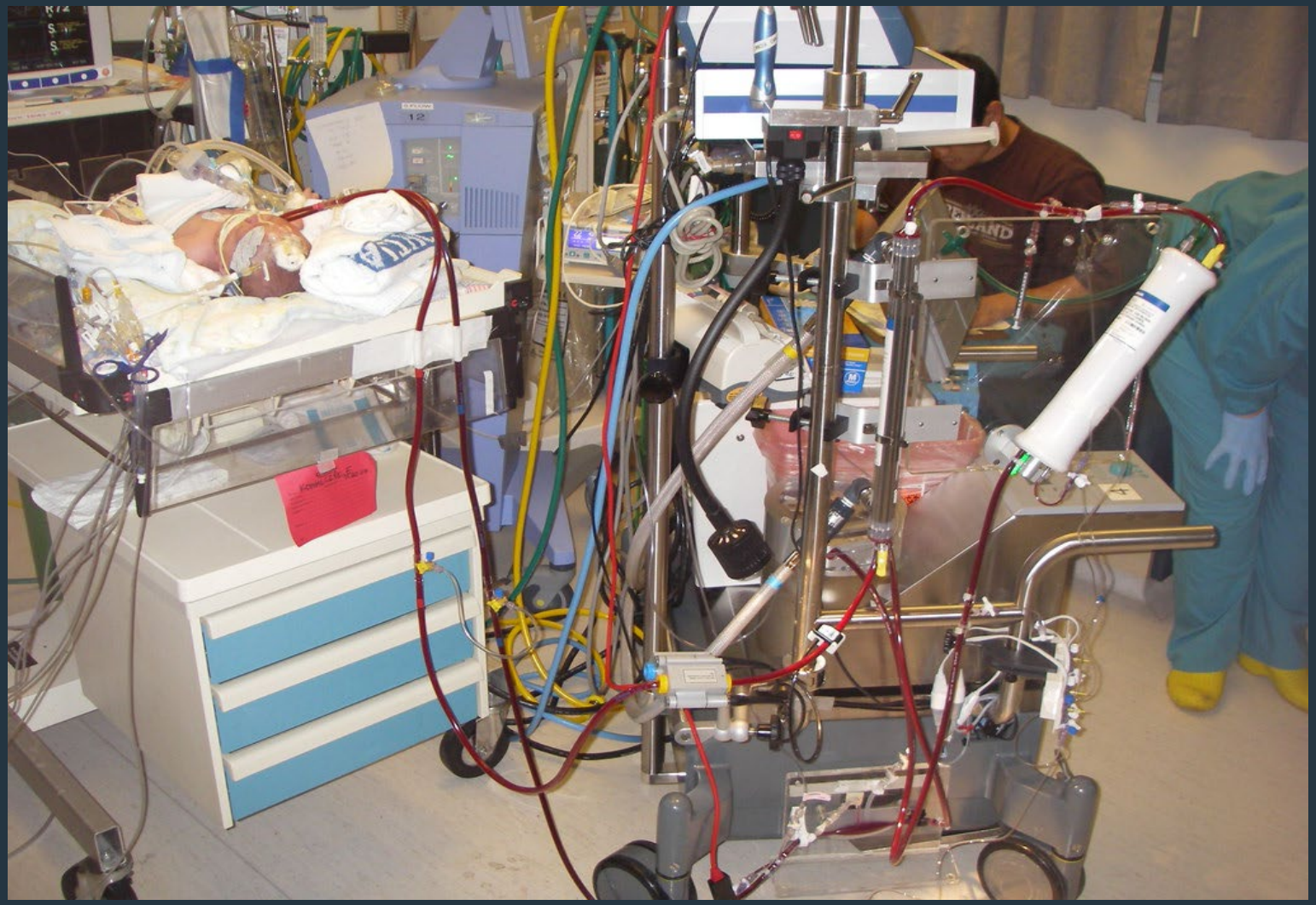
Elements to assess prior to study initiation for regulatory compliance

Examples of institutional level gatekeeping systems

Regulatory requirements

What is a Medical Device?

The Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposed by chemical action or by being metabolized.



Commonalities between IDE (21 CFR Part 812) & IND (21 CFR Part 312)

- Describes investigator responsibilities
- Describes sponsor responsibilities
- Requires selection of qualified investigators
- Requires appropriate submission to be made to the FDA prior to initiating the study*
- Specifies labeling requirements
- Addresses waivers
- Requires study monitoring

Regulations common to device & pharmaceutical studies

21 CFR Part 11 – Electronic records, electronic signatures and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper

21 CFR Part 50 – Protection of Human Subjects, covers informed consent and additional safeguards for children in clinical investigations

21 CFR Part 54 – Financial disclosure by clinical investigators

21 CFR Part 56 – Institutional Review Boards

Device vs Pharmaceutical

Device Studies	Drug Studies
Pilot: Small study (10-30 patients with the condition) to determine preliminary safety and performance	Phase I: Small study (20-100 healthy volunteers with condition) to determine preliminary safety and dosage
Pivotal: Larger study (150-300 patients with the condition) to determine efficacy and adverse effects	Phase II: Larger study(up to several hundred people with the condition) to determine efficacy and adverse effects
Post approval: Post-approval study to collect long-term data	Phase III or Pivotal Study: Even larger study (up to thousands of people with the condition) to determine efficacy and monitor adverse effects
	Phase IV: Post-marketing study to collect long-term data

What is unique about device trials?

- Smaller than drug trials
- Many are difficult to blind randomize or control
- Many dependent on physician technique
- Device modifications can occur during the trial
- Designed to support “a reasonable assurance of safety and effectiveness” for the marketing application

Device Classification

	Class I	Class II	Class III
Example	Adhesive bandage Surgical Glove Tongue depressor Thermometer Stethescope Bedpan	Knee Prosthesis Single use scalpel Catheters Pregnancy test kits Contact lenses	Drug eluding stent Insulin pen Complex robotic surgery device Cochlear implants
	General controls Most are exempt from premarket submission	Special controls Premarket Notification [510(k)]	Premarket Approval Require Premarket Application [PMA]

21 CFR Part 812 Investigation Device Exemptions (IDE)

All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

- → Allows the investigational device to be used in a clinical study to collect safety and effectiveness data
- → An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act)

Risk Determination

Significant Risk Device Study

21 CFR 812.3(m), a SR device means an investigational device that:

- → 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 use 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.
- → Requires an IDE 812.20 (a)

Nonsignificant Risk Device

Nonsignificant risk device is one that does not meet the definition of a SR device.

- → NSR d**evices that do not pose a significant risk to the human subjects**.
- → Sponsor makes the initial determination and presents to IRB
- → IRB serves as FDA surrogate for NSR investigations and is required to determine whether a NSR device is a SR or NSR device
- → FDA can always be consulted and is the final arbiter
- → Examples include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and Foley catheters. A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study.

What are the requirements in 21 CFR 812 for NSR Device Studies?

- Abbreviated requirements at 21 CFR 812.2(b)
  - Labeling, IRB approval, informed consent, monitoring, record keeping, reports, and prohibition against promotions
- NSR Studies are considered to have an approved IDE, therefore no IDE is submitted to the FDA
- Sponsors and IRBs do not have to advise the FDA of NSR device studies
- IRBs **must** make a SR or NSR determination for every NSR study (21 CFR 812.66)
  - If the IRB makes a SR determination the investigator or sponsor must notify the FDA that a SR determination has been made for the device per 21 CFR 812.150(9).
  - The study can be conducted as an SR investigation following FDA approval of an IDE application.

Elements to assess prior to device study initiation for regulatory compliance

Clinical Trial Design

Part 46 of Title 45 of the U.S. Code of Federal Regulations (45 CFR 46) provides the regulatory framework for Protection of Human Subjects within the broader topic of Public Welfare. Importantly, 46.111(a)(1)(i) states that:

- → *Risks to subjects are minimized by using procedures that are consistent with **sound research design** and that do not unnecessarily expose subjects to risk…"*

→ Interpretation of these regulations requires that ***no scientific research experiment using one or more human subjects may be conducted without consideration of risk or in the absence of valid scientific design to benefit*** subjects and/or the larger society. Proposed scientific research that does not adhere to these principles is unethical and antithetical to Federal and University standards.

Clinical Trial Design - Master Protocol Document

→ A **Master Protocol Document** (‘MPD’ or ‘protocol’) is a repository for accumulated ideas, information, literature review, and references. **It is a working document** that specifies all the details, algorithms, procedures, strategies, and plans for study conduct, and serves as a master source of text used for reference and guidance. Beginning in the earliest stages of study planning, it is highly efficient to use a MPD template as a tool for collecting ideas, references, information, and evolving text for subsequent use in grant proposals, IRB applications, and publications.

Clinicaltrials.gov Requirements

- → The study Sponsor/Investigator has overall responsibility for registering the trial.
- → CT.gov registration and results reporting is required for controlled investigations with health outcomes evaluating a device subject to FDA regulation other than a small (early) feasibility study or pediatric post market surveillance study.
- → CMS - Since January 1, 2014 CMS requires the National Clinical Trial (NCT) number on all clinical trial-associated claims submitted and is available only by registering at ClinicalTrials.gov. Claims submitted to CMS without the NCT number will be rejected.

PDF: Brief CT.gov Registration Highlights

Trial Registry Overview Chart

	Register WHEN?	Phase 1	Phases 2-4	Device	Other Interventional*	Observational	Post Results?
ICMJE	Before enrollment of 1st subject	Yes	Yes	Yes	Yes	No	No
NIH	Within 21 days of 1st subject's enrollment	Yes	Yes	Yes	Yes	No	Yes
FDA	Within 21 days of 1st subject's enrollment	No	Yes	Yes	No	No	Yes
CMS	Prior to claims submission (for Qualifying Clinical Trials)	Yes (if qualifying)	Yes	Yes	No	No	No

Examples of institutional level gatekeeping systems

Scientific or Protocol Review Committee

The goal of a Scientific Review Committee (SRC) or Protocol Review Committee (PRC) is to improve clinical research by providing review of the proposed research for scientific merit

The SRC or PRC review of a study protocol should be to complement existing resources available to the principal investigator and study team for the planning and implementation of interventional and observational studies involving human subjects.

The SRC or PRC should be composed of a transdisciplinary group of clinical and biological investigators.

IRB Review and Approval

USE OF INVESTIGATIONAL DEVICES MUST BE CONDUCTED ACCORDING TO FDA IDE REGULATIONS (21 CFR PART 812), AND OTHER APPLICABLE FDA REGULATIONS.

IRB APPROVAL MUST BE OBTAINED BEFORE THE STUDY BEGINS.

THE IRB MUST PROVIDE WRITTEN DOCUMENTATION OF APPROVAL TO THE INVESTIGATOR WITH DETERMINATION OF WHETHER THE DEVICE PRESENTS A SIGNIFICANT OR NON-SIGNIFICANT RISK.

ANY DEVICES DETERMINED TO BE SR REQUIRE AN IDE, THE INVESTIGATOR MAY BE ASKED FOR EVIDENCE OF THE IDE BY THE IRB

NSR DETERMINATION

Policy for the Storage & Control of Investigational Devices

The purpose is to provide consistent control of investigational devices used in clinical research to ensure complaince with Federal and institutional requirements

- → It is the responsibility of Sponsor/Investigator to maintain appropriate storage and handling of the investigational devices based on institutional policy.
- → The investigational device should be stored in **a limited-access location and according to instructions received from the supplier, distributor, or manufacturer**.
- → Proper storage conditions should address the temperature, light, moisture, ventilation, and sanitation needs of the study product.

Monitoring in Device Trials

The study sponsor/investigator is responsible for ensuring all study related activities are conducted in accordance with relevant regulations as well as the following the approved protocol

Key driver in the quality of the medical device trial

Imperative to ensure subject safety

Monitors must be qualified by training and expertise to monitor the investigational study in accordance with IDE and other applicable guidelines

Post Approval Reviews or Auditing

The Institutional Official is ultimately responsible for ensuring the protection of human participants.

- The Human Research Protections Program (HRPP) consists of various individuals, committees and offices, including a post approval review program.
- The purpose of a post approval review program is to improve the quality, efficiency and effectiveness of the HRPP by providing education and oversight for researchers conducting human subjects research approved by the IRB.
- A post approval review program functions to maximize the safety of research participants and ensure data integrity by reviewing studies to confirm that research is implemented in a manner consistent with the IRB approved protocol and in compliance with all applicable regulations and institutional policies.
- Routine reviews should be conducted based on a risk matrix.

Research Billing Compliance Program

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) allowed Medicare payment of the routine costs of care furnished to Medicare beneficiaries in certain categories of Investigational Device Exemption (IDE) studies. Covering the costs in these IDE studies removes a financial barrier that could otherwise discourage beneficiaries from participating.

→ Category A (Experimental) device refers to a device for which "absolute risk" of the device type has not been established (that is, initial questions of safety and effectiveness have not been resolved) and the FDA is unsure whether the device type can be safe and effective.

→ Category B (Non-experimental/investigational) device refers to a device for which the incremental risk is the primary risk in question (that is, initial questions of safety and effectiveness of that device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA premarket approval or clearance for that device type

https://www.cms.gov/Medicare/Coverage/IDE
https://www.cms.gov/Medicare/Coverage/IDE/Downloads/MM8921pdf.pdf

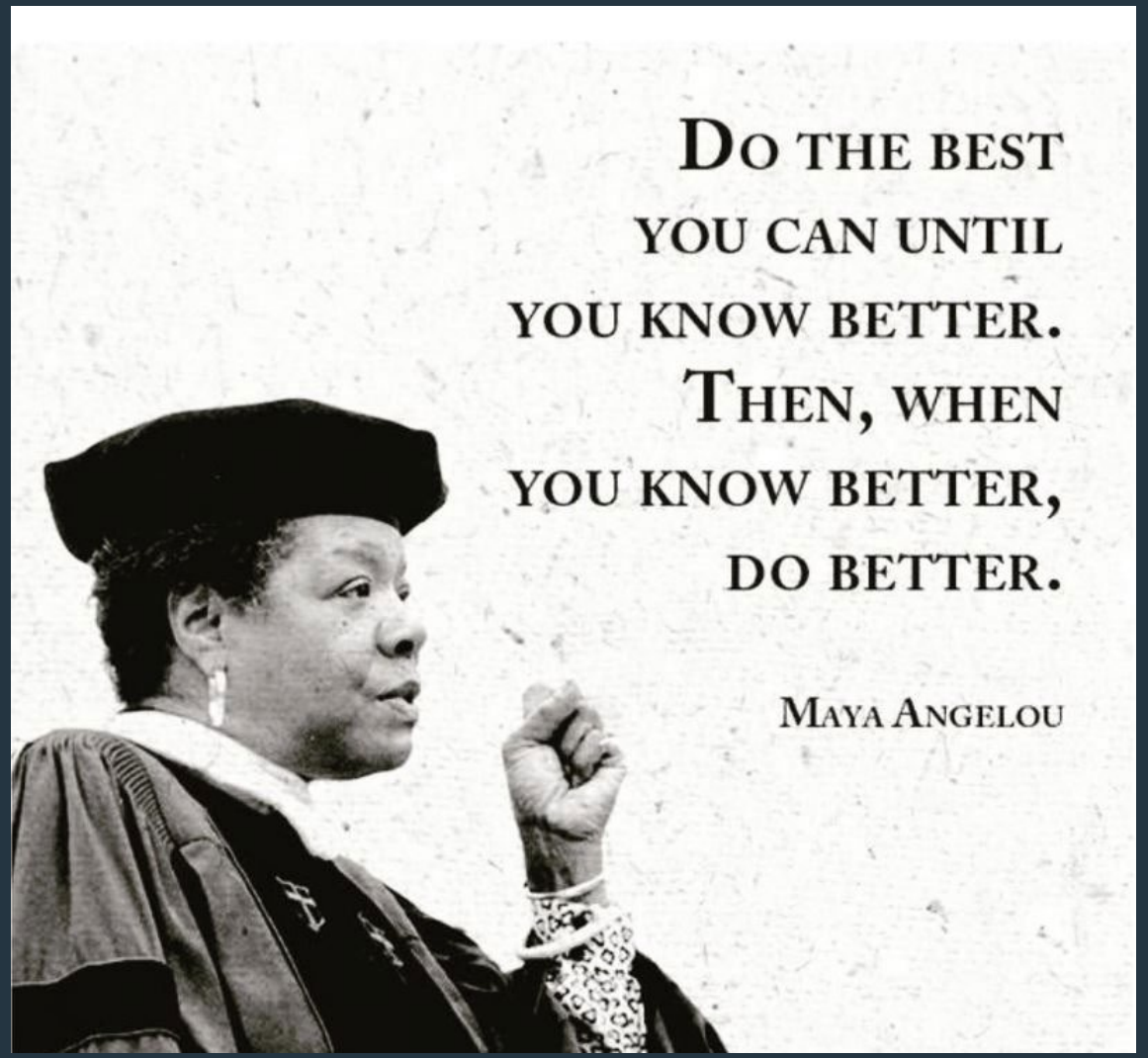
Research Billing Compliance Program

A Research Billing Compliance program is dedicated to ensuring billing compliance for clinical research.

Conducts coverage analyses on clinical trials protocol.

Ensures congruency between the budget, contract and informed consent to determine what is billable to insurance based on federal/state billing regulations including Medicare's National Coverage Decision (NCD) 310.1 as well as other third-party billing rules.

It ensures consistent application of Medicare rules across studies, and consistent application of study documents.


DO THE BEST
YOU CAN UNTIL
YOU KNOW BETTER.
THEN, WHEN
YOU KNOW BETTER,
DO BETTER.
MAYA ANGELOU

Questions?

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