University of California
2019 Ethics, Compliance and Audit Symposium
REACHING NEW HEIGHTS

Clinical Research: Staying in Compliance with **FDA** and **ClinicalTrials.gov** Requirements

Speakers

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Audience Poll

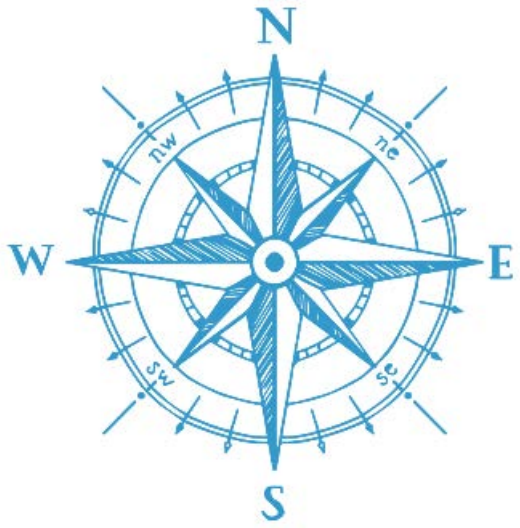
- Experience with ClinicalTrials.gov?
- Experience with preparing/submitting an IND or IDE application?
- Experience with an FDA Inspection?

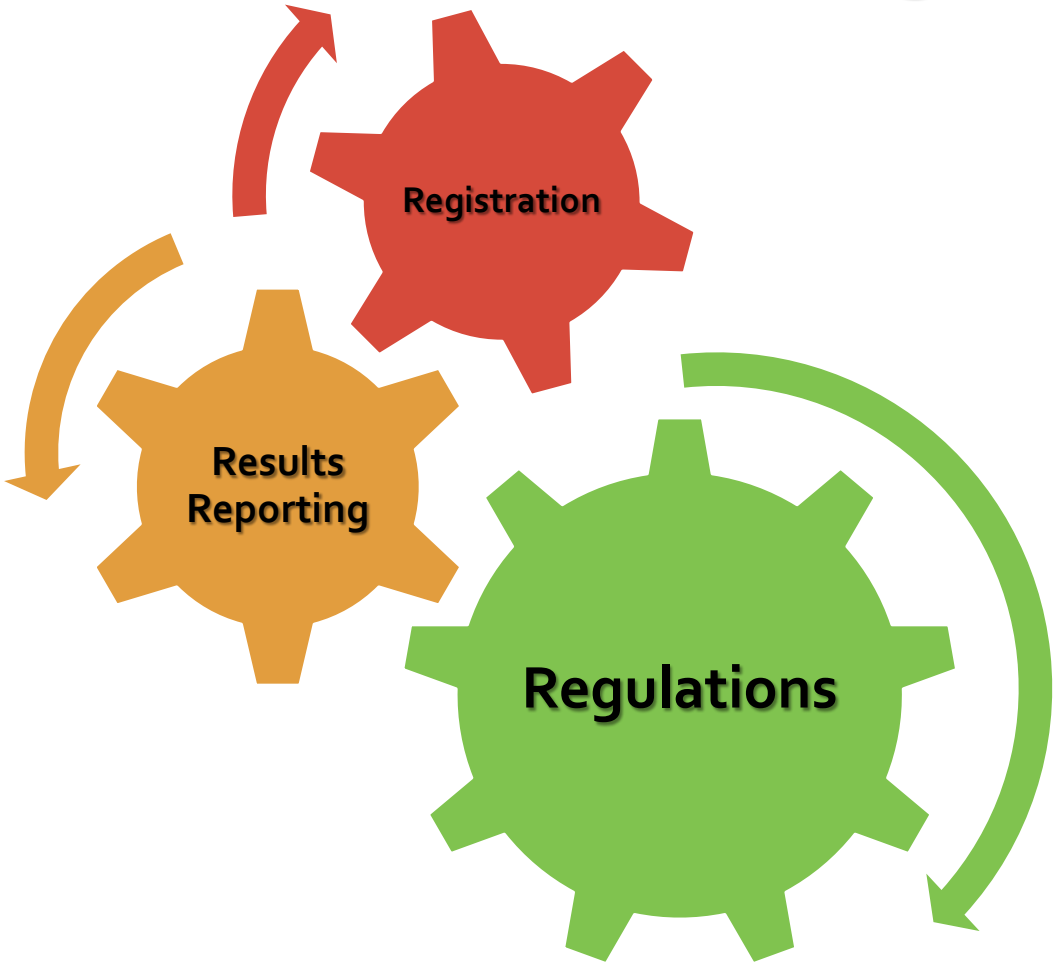
Audience Poll

What is your role?

- research coordinator
- IRB staff
- IRB member
- research compliance
- privacy officer
- other

Navigating the key elements of ClinicalTrials.gov





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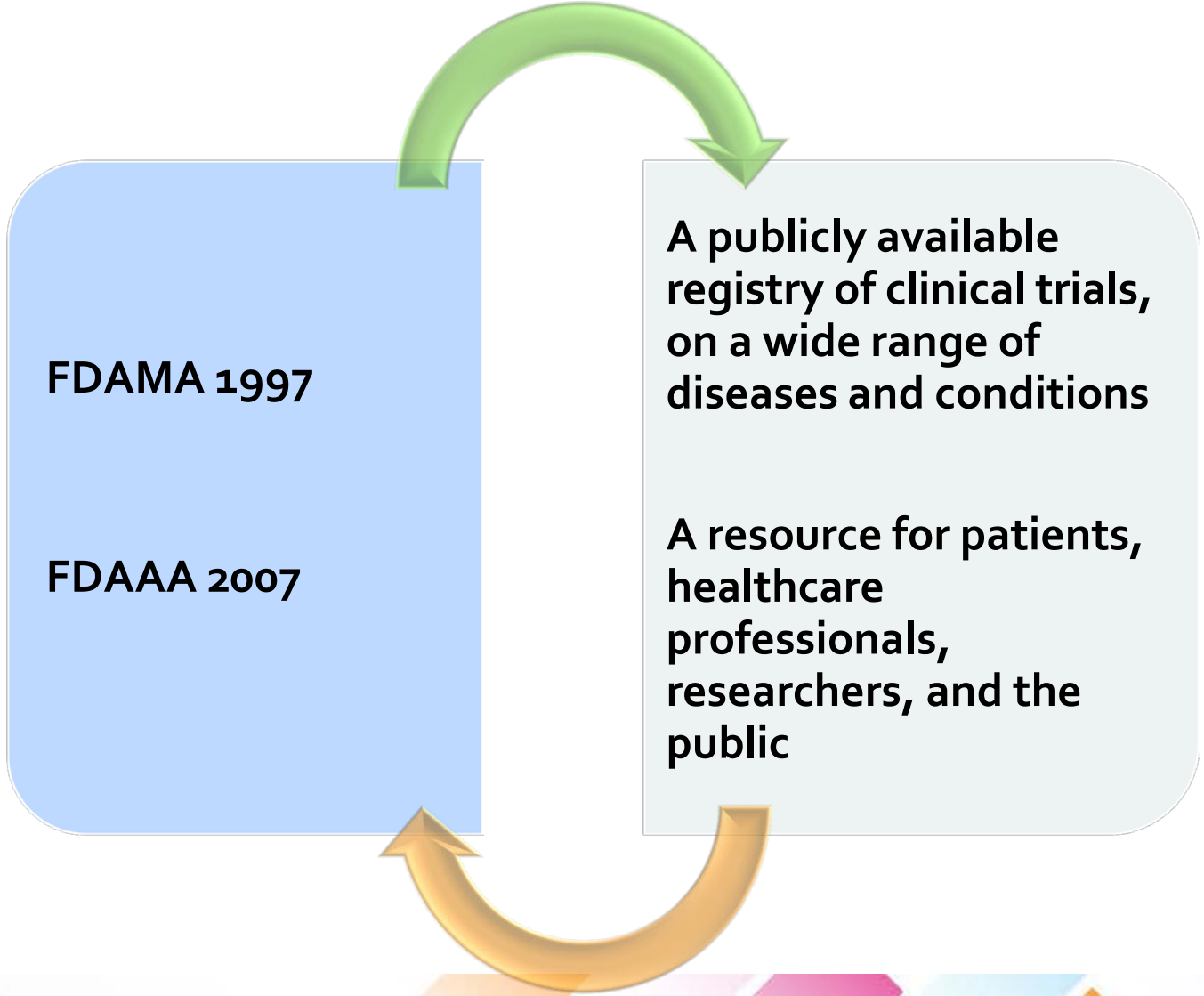
Assistant Director, Human Research Protections

UCI Office of Research Administration

UNIVERSITY OF CALIFORNIA Ethics, Compliance & Audit Symposium
REACHING NEW HEIGHTS


Purpose
History
Civil Penalty
Regulations
And
Policies
CLINICALTRIALS.GOV
Resources for
Compliance
PROCoM
What Studies
Should Be
Registered
Responsible
Party
Timelines
Registration
Updates
Results Reporting

HISTORY AND PURPOSE



REGULATIONS AND POLICIES

Laws Regulation Guidance

- FDAMA 1997
- FDAAA 2007, and 42 CFR Part 11
- 45 CFR Part 46, and Posting of Clinical Trial Consent Forms

Key US Policies

- NIH Policy on Registration and Results Submission of NIH-Funded Clinical Trials
- National Cancer Institute (NCI) Clinical Trial Access Policy
- Department of Veterans Affairs (VA) Clinical Trial Registration and Results Submission Policy
- Center for Medicare and Medicaid Services (CMS) and Reporting of ClinicalTrials.gov Identifiers on Claims
- Patient-Centered Outcomes Research Institute (PCORI) Process for Peer Review and Public Release of the Results

International Policies

- International Committee of Medical Journal Editors (ICMJE)
- World Health Organization (WHO)

What studies should be registered / Responsible Party

Primary

- DHHS (2016) *81 FR 64981*
- NIH (2016) *81 FR 64922*

Other

- CMS
- ICMJE
- WHO
- NIH mechanistic clinical trial
- Expanded Access
- Voluntary Submissions
- NCI
- VA
- PCORI

Note

- the definitions of a study that should be registered are *very narrow*
- there are many definitions of a "clinical trial" [i.e., column "other", FDA, UCOP, Common Rule, NCI,DOD, VA (same as ICMJE), etc]
- Review the ***terms and conditions* of an award** to **determine definition and registration requirements; *as well as international requirements***
- *Being unfunded does not exclude ACTs from the requirement to register*

Responsible Party

- The IND / IDE holder, or the PI if delegated by the sponsor
- For clinical trials not conducted under an IND / IDE, the sponsor is considered to be the person or entity who initiated the trial

Registration, Updates, Results Reporting

Registration

No later than 21 days after enrollment of the first research participant

Updates

Within 30 days of a change to: recruitment status, overall recruitment status, and completion date

Update annually even if there are no updates

Results

No later than 12 months after primary completion date (some exceptions)

Resources for Compliance

REFERENCES / TRAINING

- CITI course
- ct.gov: training, FAQs
- NIH NOT-OD-19-126 (Prospective Basic Experimental Studies with Human Participants)
- NIH Clinical Trial Policy: Implications for SBE research

CHECKLISTS

- NIH (FAQ, Case Studies)
- DHHS (ACT)
- Responsible Party
- Voluntary Submission
- Determining when the NIH Policy or the DHHS Final Rule applies ("Step 2")
- Studies initiated before/after 2007: table
- Registration criterias
- Results Reporting criterias

OTHER

- National Clinical Trials Registration and Results Reporting Taskforce
- PRS Newsletter
- http://fdaaa.trialstracker.net/
- UCLA PROCOM database
- Interest in a monthly UCOP listserv group?

PROCoM – online *PRS Record Oversight & Compliance Management* tool

- PRS Administrator oversight of institutionally registered studies
- Daily import of PRS* data (*ClinicalTrials.gov *Protocol Registration and Results System*)
- Filtering, sorting, reporting, administrator notes, additional contacts, progress metrics, email templates
- Identify problems that have newly arisen or been newly resolved
- Email merge fields create custom reminders in quantity, for example:
  - Choose all records with Late Results problem flag, apply Late Results email template, each study contact will receive email with notice of problem, study title, date of problem, instructions, links
  - Choose all records with results due in an upcoming timeframe (e.g. 6 months), apply Results-Upcoming email template, each study's contacts will receive email with study title, date of expected results, instructions, links
- Pilot-tested in 2019; intended availability in 2020 (details TBD)

Civil Penalty

DHHS

Under the statute, responsible parties, including, for example, grantee institutions, could be held accountable for **noncompliance**, with the potential for substantial civil monetary penalties, the withholding of grant funding from HHS agencies, and criminal proceedings

NIH

Noncompliance with the terms and conditions of the NIH award may provide a basis for enforcement actions

Effective Consultations for FDA-Regulated Studies

Melanie Hassel, MS

Regulatory Specialist, UCSF Office of Ethics and Compliance

UNIVERSITY OF CALIFORNIA Ethics, Compliance & Audit Symposium
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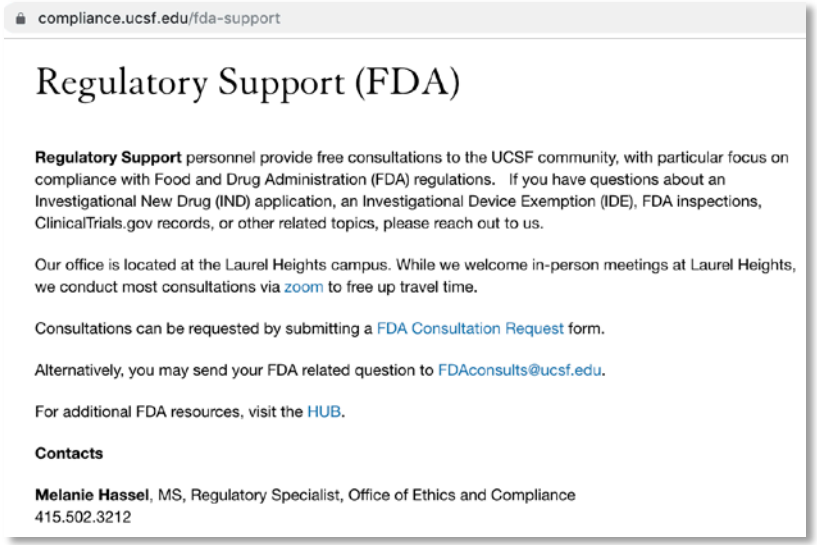
What are the benefits?

- specialized knowledge
- parse guidance
- support IRB review
- get ahead of possible compliance issues

Referrals and Requests for Consultations

- IRB analyst reviewing a new study
- Consultation Request Form
- Study teams preparing IRB application
- FDAconsults@ucsf.edu
- CTSI
- Phone call



compliance.ucsf.edu/fda-support

Regulatory Support (FDA)

Regulatory Support personnel provide free consultations to the UCSF community, with particular focus on compliance with Food and Drug Administration (FDA) regulations. If you have questions about an Investigational New Drug (IND) application, an Investigational Device Exemption (IDE), FDA inspections, ClinicalTrials.gov records, or other related topics, please reach out to us.

Our office is located at the Laurel Heights campus. While we welcome in-person meetings at Laurel Heights, we conduct most consultations via zoom to free up travel time.

Consultations can be requested by submitting a FDA Consultation Request form.

Alternatively, you may send your FDA related question to FDAconsults@ucsf.edu.

For additional FDA resources, visit the HUB.

Contacts

Melanie Hassel, MS, Regulatory Specialist, Office of Ethics and Compliance
415.502.3212

UCSF
University of California
San Francisco

FDA Consultation Request Form

The Office of Ethics and Compliance provides free FDA consultations to the UCSF community.

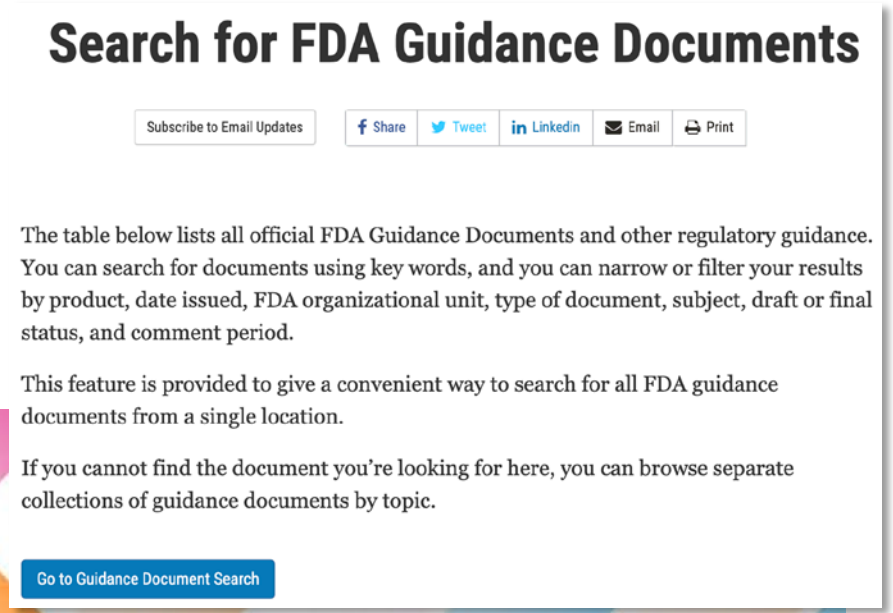
To initiate a consultation, please complete the form below. Providing this information with your request helps us to expedite a response and track where resources are needed.

We look forward to working with you.

Briefly describe the aim of your project:

How do I Prepare for a Consultation?

- Obtain IRB number
- Read IRB application
- Determine scope
- Take notes on investigational product or investigational use of a legally marketed product
- Review and compile relevant guidance documents and resources (search FDA Guidance Document Database)



Consultation Flow

Request Received

- Simple - resolved via email
- Complex- schedule consultation call

Overview

- Scope of consultation services – what I can and can't do
- Study team provides brief overview

Discuss Investigational Product

- Drug: Legally marketed or Investigational New Drug
- Device: Legally marketed or Investigational, Mobile Apps (enforcement discretion)

Consultation Flow (continued)

FDA Guidance/ Resources

- Discuss relevant guidance documents
- Which Division? (CDER, CBER, CDRH)
- Initiate contact with FDA division for further guidance, as needed

Conclusion

- Summarize discussion
- Clarify questions
- Outline next steps

Follow-up after call

- Email detailed summary of consultation to study team and IRB analyst
- Schedule additional calls, if needed
- Instruct study team to include consultation correspondence in IRB application

Drug Studies

Studying a legally marketed drug?

Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND

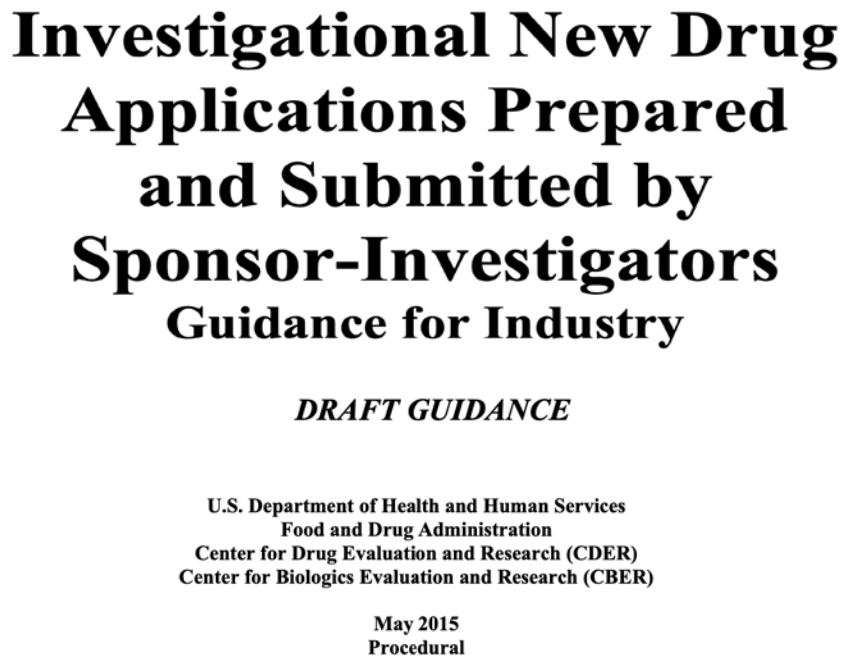
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Food Safety and Applied Nutrition (CFSAN)

September 2013
Clinical/Medical

Studying an *Investigational* drug?

FDA has very helpful website for Investigator Initiated INDs and a Draft Guidance:

IND Applications for Clinical Investigations (*Product Development*)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (*Expanded Access*)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Treatment of a Single Patient in Emergency Setting
Non-clinical Components	Safety Reports	Clinical Hold	Treatment of a Single Patient in Non-emergency Setting
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients



Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2015
Procedural

Device Studies

- Studying to determine safety and effectiveness
- Is the device solely a measurement tool?

Legally marketed device?

- IDE Exemption
- Non-Significant Risk Device
- Significant Risk Device / IDE

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INVESTIGATOR CHECKLIST FOR:
IDE Exempt, Non-Significant Risk, or Significant Risk Device Studies

Version	DATE	PAGE
6	10/09/18	1 of 2

The purpose of this checklist is to help investigators and the IRB determine whether a clinical investigation designed to determine the safety or effectiveness of a device is **IDE Exempt**, **Non-Significant Risk**, or presents **Significant Risk**.

Note: Determinations of IDE Exempt, Non-Significant Risk, or Significant Risk are needed only for devices that meet the FDA's definition of a medical device, which is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

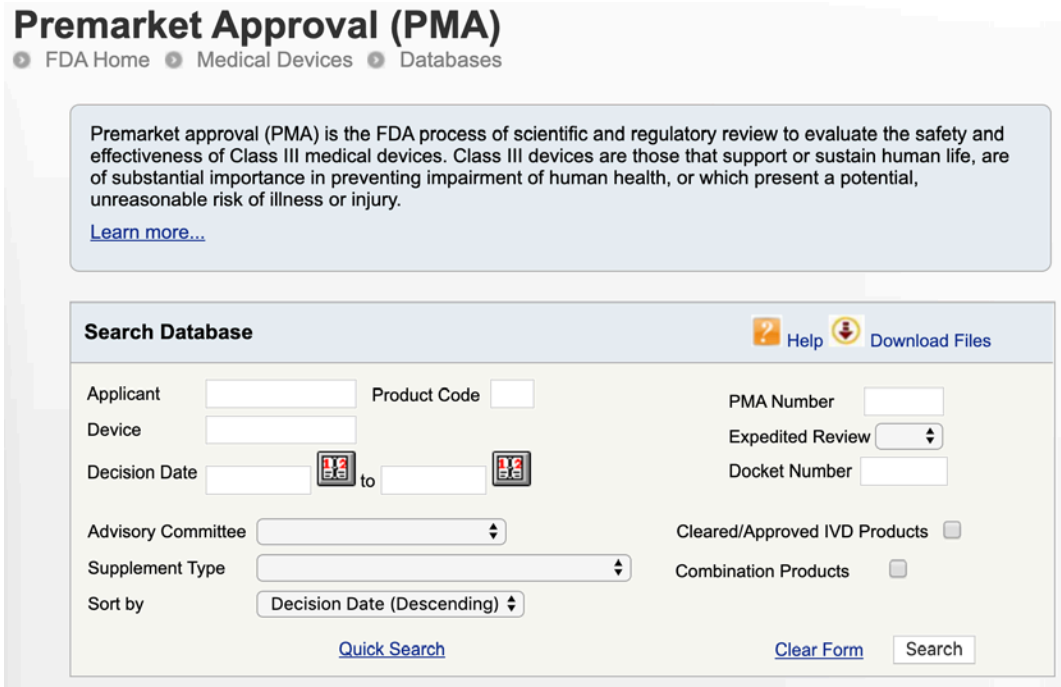
Device Name & Manufacturer:	IRB#:	Principal Investigator:

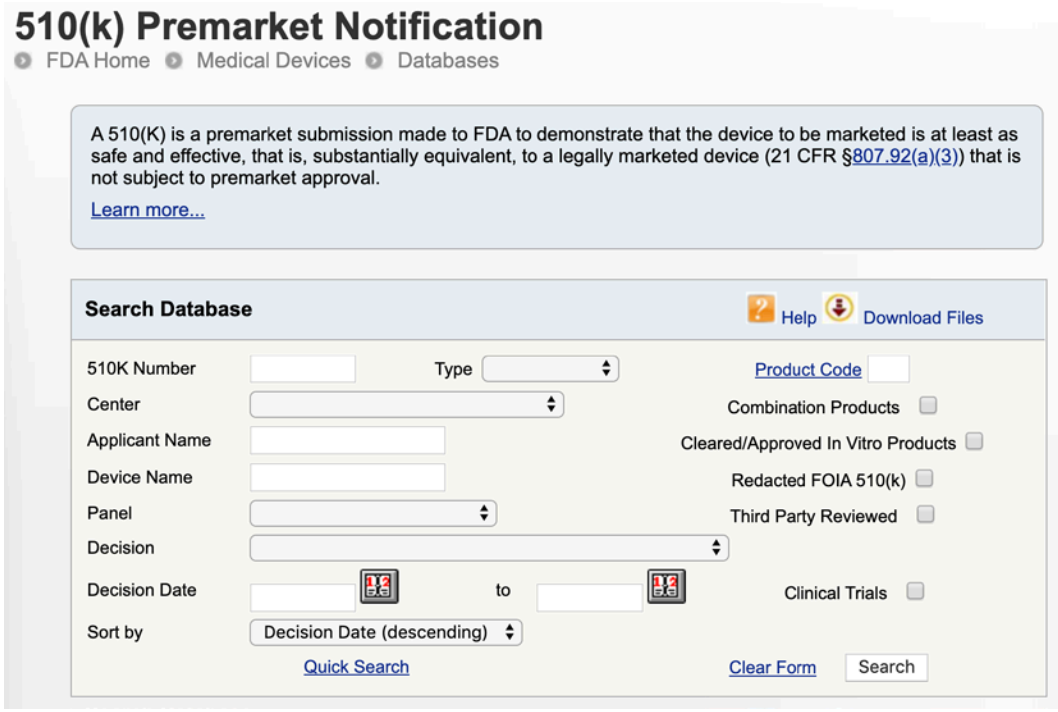
Instructions: Start with Section A. If you are unsure whether the criteria are met, complete Section B. If not met, continue to Section C.

Include this completed checklist in the Other Study Documents section of your iRIS submission to the IRB, and any correspondence from the FDA and/or study sponsor regarding the device. *Complete one Checklist for each device.*

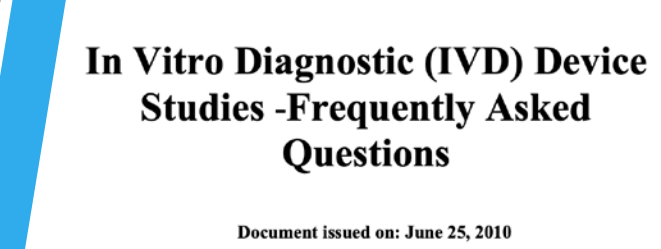
For consultations regarding medical devices, including help determining whether your device meets the FDA definition of a medical device, see FDA Regulatory Support at UCSF or e-mail: FDAconsults@ucsf.edu.

FDA Device Databases



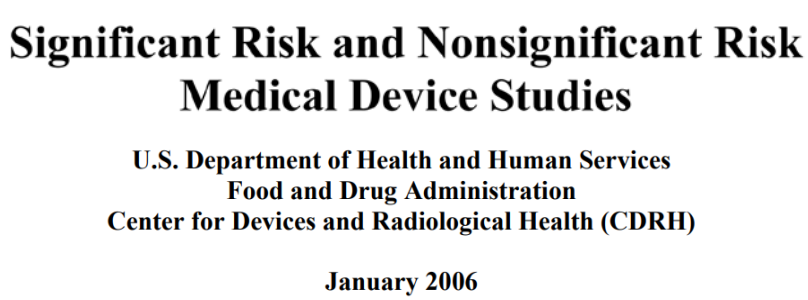


Additional Device Resources



In Vitro Diagnostic (IVD) Device Studies -Frequently Asked Questions

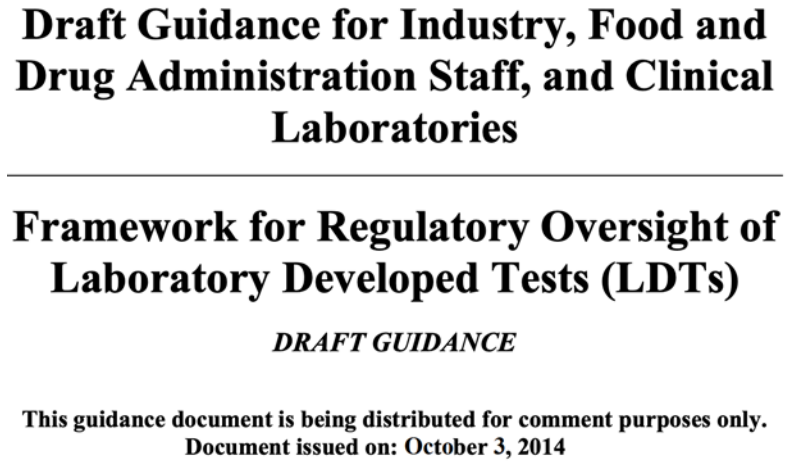
Document issued on: June 25, 2010



Significant Risk and Nonsignificant Risk Medical Device Studies

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)

January 2006



Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: October 3, 2014

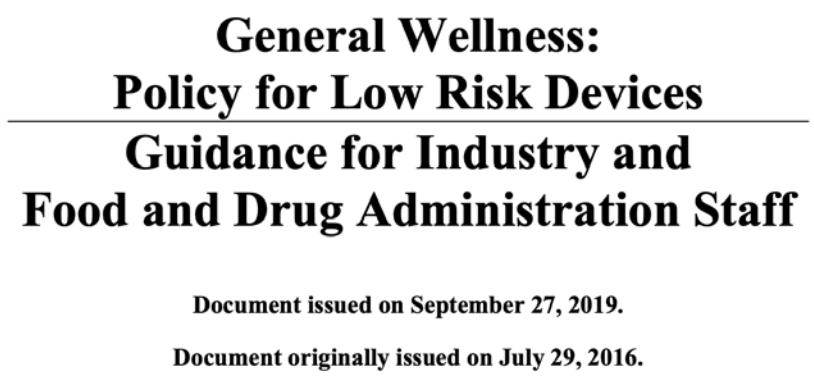
Policy for Device Software Functions and Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 27, 2019.

Document originally issued on September 25, 2013.

This document supersedes "Mobile Medical Applications" issued February 9, 2015.



General Wellness: Policy for Low Risk Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 27, 2019.

Document originally issued on July 29, 2016.

- Digital Health (mobile apps) DigitalHealth@fda.gov
- FDA Division of of Industry and Consumer Education DICE@fda.gov

Common Questions

Do I need an IND?

Why do I need an IND when I regularly use [product] in clinical care safely?

Is my mobile app a Medical Device?

How do I request an IDE exemption?

Does my device qualify for an NSR determination?

Why do I need device determinations for my CLIA certified laboratory test?

Additional Helpful Resources

- UCSF Clinical Research Resource HUB
- FDA
  - CDER Office of New Drugs
  - CDRH Management Directory
- FDA's Pre-IND Consultation Program
- FDA's Q-Submission Program for Devices
  - Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

FDA Inspections

Joan Doherty Campbell, JD

Associate Director, UCSF Office of Ethics and Compliance

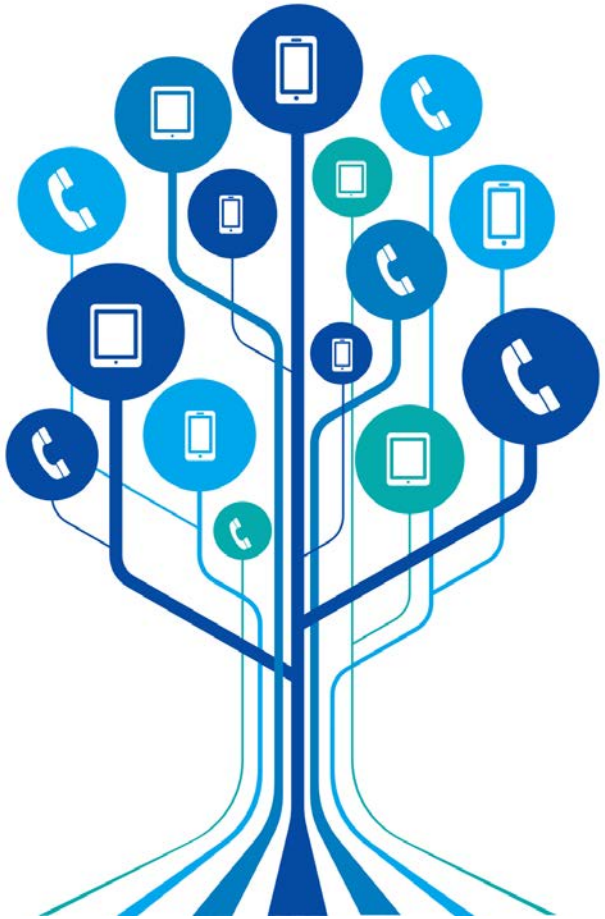
1. FDA NOTIFICATION

- FDA inspector typically contacts the Principal Investigator by phone
- Lead time: usually less than one week
- Gather information during the call:
  - Reason for the visit (for-cause or routine)
  - Scope: one protocol; all studies involving a particular drug/device; or all of the PI's studies
  - Anticipated length: ask about expected arrival date/time, and daily schedule

2. PREPARATION: Communication

Notifications to:

- Study sponsor (if applicable)
- Campus contacts
  - Institutional Review Board (IRB)
  - Compliance Office / Regulatory Support
  - Campus Counsel (who may include UC General Counsel)
  - Investigational Pharmacy (if applicable)
  - Laboratory (if applicable)
  - Others?



3. PREPARATION: Document Review

Verify that your regulatory binder is complete

- Content: https://hub.ucsf.edu/virtual-regulatory-binder

Strategically review study documents

- Reports to IRB / FDA of protocol violations/incidents, unanticipated problems and corrective actions
- Adverse events
- Consent form signatures and versions
- Delegation log
- Drug / Device accountability logs

Consult the IRB / Study Sponsor / Compliance with any questions or issues you anticipate!

4. PREPARATION: Logistics

- **Schedule a coordination call** with Compliance, IRB, and others as needed.
  - Create a **contact list** for questions (study personnel, study sponsor, IRB coordinator, compliance, legal).
- **Reserve separate space** for the inspector; notify nearby staff.
- **Clear schedules** (as much as possible) of **key personnel** (PI, CRC, the co-investigators most familiar with the study conduct).
  - Designate a **point-of-contact**/note-taker who can be available all day
- **Plan attendees** for **daily debrief** and recipients of **daily email summaries**

5. OPENING MEETING

- Review Inspector's credentials, give introductions
- Receive FDA Form 482, Notice of Inspection
- Tour the areas the inspector will need to access (office, restroom, cafeteria)
- Follow tips for answering questions (see notes)
- Ask about the plan for the next day and the anticipated length of visit
- Keep an extra copy of any documents requested, note any samples requested, take photographs of anything the inspector photographs
- Try to resolve as *many* issues as possible, as *soon* as possible

6. CLOSING MEETING

- FDA findings (Form 483): No action, voluntary action, official action indicated
- If there are findings, clarify that you will respond in writing, but would appreciate the opportunity to discuss questions during the meeting.
  - Ask for clarification, but demonstrate knowledge of the regulatory requirements, IRB requirements, and your own SOPs.
  - Adopt a collaborative approach (identify root cause), but don't over-promise corrective actions, particularly if they are inconsistent with standard practice.
- Clarify the due date: 15 business days vs. calendar days, consider differences between fed and state holidays, and agree on a specific date if possible.
- Confirm where to send your response (address and recipients)

7. WRITTEN RESPONSE TO FDA FORM 483

Study Team Drafts

IRB/Compliance Input

Sponsor Review

Legal Review

Make a plan to implement any proposed corrective actions

Helpful Links for FDA Inspections

- UCSF Clinical Research Resource HUB:
  - Inspection Tools: https://hub.ucsf.edu/fda-inspection-tools
  - Regulatory Binder: https://hub.ucsf.edu/virtual-regulatory-binder

Clinical Research Resource HUB

- FDA Guidance on Clinical Inspections of Investigators (June 2010): https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-inspections-clinical-investigators
- Compliance Program Guidance Manual for FDA Staff (Dec 2008):

  https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/compliance-program-guidance-manual-fda-staff

Questions & Answers

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Navigating the key elements of ClinicalTrials.gov

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