

Sponsor-Investigator Clinical Trials with FDA Regulated Products



2008/UK/bms

Sponsor-Investigator

- An individual who both conceives, initiates, designs and conducts a clinical trial and under whose immediate direction the study drug is administered. 21 CFR 312.3
- Investigator submits and holds FDA Investigational New Drug Application
- Must comply with requirements of both investigator and sponsor – plans, designs, conducts, monitors, manages data, prepared reports, oversees regulatory & ethical issues, publishes manuscript

Sponsor-Investigator Initiated Trials

(also referred to as investigator-initiated trials)

- **Benefit from investigators expertise, experience, ingenuity, academic resources and creativity.**
- **Offer opportunity to explore off-label therapeutic areas, populations and treatment regimes.**
- **Are economical means to produce valuable data**
- **Held to the same standards and regulations as industry sponsored trials.**
- **Potential challenge for safety & data quality.**
- **Carry greater risk and liability.**

Industry involvement

- **IIT may benefit from consultation with sponsor for strategic input. Submit letter of intent to industry sponsor.**
- **Add to the companies safety profile for the product and lends academic credibility to product research.**
- **Allow IIT to tag onto the sponsor's IND**
- **Allow for collaboration or regulatory guidance.**
- **May or may not provide funding or test product at no or reduced cost.**
- **If new indication that company considers for labeling, can tag onto or transfer IND to company.**

Primary Investigator (PI) Responsibilities

**UK Principal Investigator's Guide to
Responsibilities, Qualifications, Records and
Documentation of Human Subjects Research**

**[www.research.uky.edu/ori/SOPs_Policies/9-
PI_Responsibility_guidance-noDMS.pdf](http://www.research.uky.edu/ori/SOPs_Policies/9-PI_Responsibility_guidance-noDMS.pdf)**



***Tasks may be delegated,
but responsibility can not.***

Task Delegation

- **Delegation of tasks – The PI may delegate many tasks to study staff provided that they are qualified to perform the task and it is within their scope of practice.**
- **It is recommended to have written task delegations that both parties' sign.**
- **Exception: medical decisions (decisions regarding cause, treatment and response to adverse events, abnormal lab values, drug dosing, dropping a subject, breaking blind, etc), must be made by a physician investigator.**

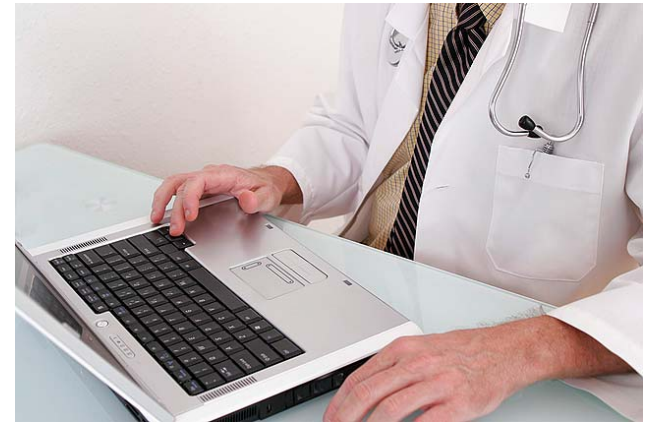
Sponsor-Investigator Responsibilities

Responsibilities

Drug Responsibilities Document

Responsibilities may include:

- Protocol development
- Submit IND/IDE application & required documents to FDA
- Register the trial on Clinicaltrials.gov per ICMJE publication requirements
- Select qualified investigators, sites and monitors
- Provide all information needed to conduct investigation
- Ensure that study sites get appropriate IRB approval
- Develop Case Report Forms and data collection tools
- Provide investigational drug or device



Sponsor-Investigator Responsibilities cont.

Responsibilities



- Monitor and ensure study conducted according to protocol and good clinical practice
- Ensure compliance with regulations
- Provide study supplies and/or investigational product
- Inform FDA and PIs regarding adverse events and safety reporting
- Monitor data for safety and efficacy - Data Safety Monitoring Plan (DSMP)
- Perform data analysis and report findings
- Final reports
- disposition of study article – assure return or destruction of any unused investigational drug

Protocol Elements

21 CFR 312.23(a)(6)(iii) & GCP Guidelines

- **Background Information**
- **Primary purpose or outcome – determine sample size**
 - **Power to detect difference in primary outcome**
- **Objectives, end-points**
- **Names & qualifications of investigators**
- **Inclusion/exclusion criteria and number of subjects**
- **Selection of subjects (with demographic illustrative of real patient population & withdrawal of subjects**
- **Trial design, blinding, controls**
- **Statistical plan & methods to minimize bias**
- **Study product –dose & duration of exposure**
- **Methods, observations, safety & efficacy measurements**
- **Risk, benefits**
- **Clinical procedures to monitor effects of study product**

Protocol - Eligibility Criteria Pitfalls

- **Inadequate statistical power assessment**
- **No subject feasibility assessment**
- **Methods of recruitment not considered**
- **Demographic intent – not convenience sample**
- **Protections for vulnerable populations**
- **Diagnostic criteria for the condition being investigated are vague – need specific indicators**
- **Adequate description of “healthy volunteer”**

Protocol - Treatment Plan

- **Specific details of what is required of patients/subjects.**
- **Delineate standard treatments vs. those conducted for research purposes.**
- **Detailed randomization plan (how assigned, straight or stratified)**
- **Details regarding study product administration**
- **Study procedures - description & schematic**
- **Data collection plan**
- **Privacy and confidentiality provisions**

Protocol - Risks discussion - *include*

- Study treatment
- Procedure associated events or exposure
- Drug side effects
- Discomforts of drug administration
- Inconvenience
- Confidentiality
- Social, psychological, well being
- Illustrate the probability of risks from procedures (radiation exposure = to X amount of naturally occurring background radiation).
- Include specific guidelines for assessing causality of adverse events or alert lab values (ie. Temporary discontinue drug, re-assess, re-challenge with drug, permanent discontinuation of drug)

Protocol - Benefits

- **Describe benefits that could reasonable be expected.**
- **Identify benefits to society in general**
- **If no benefit, say so**

Protocol - Alternatives

- **Any standard alternatives available**
- **Is drug available without being in the study?**
- **Include any behavioral treatments?**
- **Is doing nothing an alternative?**

- **Exemption from the law that requires that drug be approved to transport across state lines**
- An application to FDA including manufacturing, pharmacology, & toxicology of the drug to support its use in human testing
- **Focus of review is on safety and efficacy**
- **Response in 30 days**



FDA Frequently Asked Questions-

<http://www.fda.gov/cder/about/smallbiz/faq.htm>

IDE – When is it required?

Unapproved products:

- IND/IDE is required when an unapproved drug (biologic or significant risk device) is used in a clinical investigation

Special Use Exemptions:

- Treatment IND ([21 CFR 312.34](#)) or Emergency IND ([21 CFR 312.36](#))

Approved products:

- is needed if data is to support a new indication or significant change in labeling or promotion
- is needed if involves a route of administration or dosage level or patient population that significantly increases risk

IDE – When is it required?

Generally not required when 5 criteria met:

1. Study not intended to support FDA approval of new use or labeling change.
2. Not intended to support a significant change in advertising.
3. Does not involve a route of administration, dosage, population, or other factor that significantly increases risks.
4. Is conducted in compliance with human subject protection and IRB regulations.
5. Is conducted in compliance with FDA requirements concerning promotion and charging for investigational drugs.

21CFR312.2

Repercussions of non-compliance:

Johns Hopkins Hexamethonium Inhalation Trial

An [FDA Warning Letter](#) following the death of a healthy volunteer in a Johns Hopkins study, using a chemical compound (drug) not approved for marketing, sited ...

- Failure to submit an IND
- Failure to provide adequate animal toxicity data
- Failure to provide previous human data
- Failure to provide dosing rationale & procedures to identify, collect and report adverse events
- Failure to notify and obtain IRB approval for protocol changes
- Failure to promptly report unanticipated problems

IRB Ruling

- **Recent changes in FDA guidelines allow IRBs to determine if the PI needs to pursue an IND for an investigator-initiated study.**
 - Documented in letter to investigator as part of IRB revisions.
 - Investigator contacts FDA and provides IRB with written response



Include IRB Attachment 0-1 with original submission

FORM 0-1 Questions

1. Are the results of the investigation intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug?
2. Is the investigation intended to support a significant change in the advertising of a lawfully marketed prescription drug product?
3. Does the investigation 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?

IND Contents

Application Process –

http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

- **Form FDA 1571**
- **Table of Contents**
- **Introductory statement**
- **General investigational plan**
- **Investigator's brochure**
- **Protocols (study, investigator, facilities, IRB, Form FDA 1572)**
- **Chemistry, manufacturing, control data and environmental impact statement**
- **Animal pharmacology and toxicology data**
- **Previous human experience**
- **Additional information**

FDA Guidance Resources

- FDA IND Information -
<http://www.fda.gov/cder/about/smallbiz/faq.htm>
- Center for Drug Evaluation & Research
[http://www.fda.gov/cder.](http://www.fda.gov/cder)
- For a review of the IND process and answers to frequently asked questions, consult the FDA web page- [Frequently Asked Questions on Drug Development and Investigational New Drug Applications.](http://www.fda.gov/cder/about/smallbiz/faq.htm)
<http://www.fda.gov/cder/about/smallbiz/faq.htm>

IND Consultation

Consult manufacturer/sponsor, IRB, FDA, Legal counsel

- The FDA Office of Drug Evaluation IV (ODE IV) Pre-Investigational New Drug Application (IND) Consultation Program is a resource to foster informal early communications between the divisions of ODE IV and potential sponsors.
- For more specific or complex drug inquiries, telephone the Drug Information Branch at (301) 827-4573 or send them an electronic mail message at druginfo@cder.fda.gov.
- Pre-IND advice may be requested for issues related to drug development plans; data needed to support the rationale for testing a drug in humans; the design of non-clinical pharmacology, toxicology, and drug activity studies; data requirements for an Investigational New Drug (IND) application; and regulatory requirements for demonstrating safety and efficacy.

<http://www.fda.gov/cder/ode4/preind/>

FDA

- **Financial Disclosure from each investigator**
- **IND**

- **1571**

- **1572**

Sponsor & Investigator obligations

**Instructions for completion located on FDA
website**

<http://www.fda.gov/cder/about/smallbiz/Forms.htm>

- **Document any sponsor responsibilities transferred to contract service**
- **Name who will be monitor study conduct & evaluate drug safety**

1571 Commitments *legal contract*

- Wait 30 days post IND submission before beginning the study
- Not begin or continue the study if placed on clinical hold
- IRB will be responsible for initial & continuing review and approval of the study
- Conduct the study in accordance with all applicable regulatory requirements
- Select qualified investigators based on training & experience
- Obtain FDA Form 1572 from any investigator(s).

Selecting qualified investigators

Considerations when selecting investigators at separate sites to conduct the trial include:

- Site & PI selection criteria – is the PI qualified and the site ability to conduct the trial. This may include conducting a survey and pre-study site-assessment visit
- Review FDA regulations and Good Clinical Practice Guidelines with site
- Review investigator commitments as outlined on the FDA Form 1572
- Investigator failure to follow the protocol should result in termination.

FDA Form 1572

<http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf>

Expiration Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0014. Expiration Date: May 31, 2009. See OMB Statement on Reverse.
STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312) (See Instructions on reverse side.)		NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).
1. NAME AND ADDRESS OF INVESTIGATOR		
Principal Investigator Information – affiliation & address match CV		
2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.		
<input checked="" type="checkbox"/> CURRICULUM VITAE <input type="checkbox"/> OTHER STATEMENT OF QUALIFICATIONS		
Education, Training, Experience		
3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.		
Study Locations		
4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.		
Laboratory Information – Central &/or Local		
5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).		
IRB Information		
6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).		
List of Sub-Investigators		
Modify if any change occurs		
7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.		
Study Title, Protocol Number		

Attach CV or documentation demonstrating qualifications

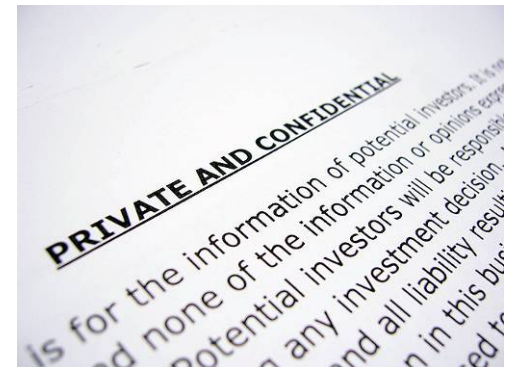
Responsibilities on the flip side

By signing a Form 1572 you are committing to:

- ☞ personally conduct/supervise
- ☞ adhere to protocol
- ☞ meet investigator requirements/obligations
- ☞ inform subjects that drug is investigational
- ☞ obtain informed consent
- ☞ report serious adverse events
- ☞ know the Investigator Brochure (IB)
- ☞ maintain records & make available
for inspection – FDA could audit at any time
- ☞ IRB compliance
- ☞ inform staff re: obligations

HIPAA

- 45 CFR Part 160 – rights over protected health information (PHI)
- Consider options for how protect PHI – Waiver, Authorization, De-identify
- HIPAA Website:
<http://www.research.uky.edu/ori/forms%20HIPAA.htm>
- Questions: ORI Joe Brown, Research Privacy Specialist, at (859) 257-9084 or Helene Lake-Bullock, Research Compliance Officer, at (859) 257-9428.
For questions regarding HIPAA patient rights or accounting of disclosure, contact Brett Short, Privacy Officer, at (859) 323-9817



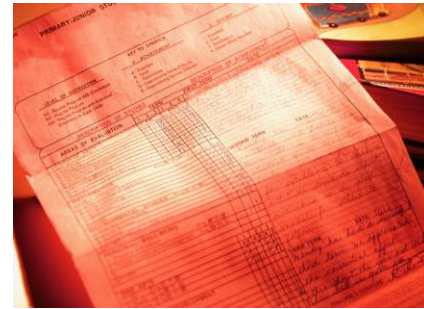
Informed Consent Principles

More than a document, informed consent is a continuing process that starts with advertising and carries through to the end of the individual's participating in the trial.

- Informed Consent form must be signed/dated prior to study participation (including any wash-out).**
- Provide quiet place, ample time and privacy to review the document and ask the subject if they have any questions in private.**
- Avoid coercion, influence and exculpatory language.**
- Ask open ended questions to confirm subject understanding.**
- Provide subject with photocopy (Complete Document)**
- Place original in their charts/files.**

See ORI & IRB [Standard Operating Procedure on Informed Consent](#) for additional guidance and special circumstances

IRB Reporting Obligations



The investigator should promptly report to the IRB

- (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects
- (b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.
- (c) All serious adverse drug reactions or problems that are both related and unexpected.
- (d) New information that may affect adversely the safety of the subjects or the conduct of the trial.
- (e) Continuation review – progress report

FDA Investigational Drug Reporting

The sponsor-investigator must provide the following reports in a timely manner to FDA, the IRB's, and/or other investigators

- **IRB review – initial & continuing**
- **IRB correspondence for modifications, unexpected or serious adverse events, protocol violations**
- **1571 with any additions/revisions**
- **FDA Progress or Final Reports**
- **Discontinuation of the trial**

Adverse Events (AE)

Investigators:

- Review solicit, record, track and assure care of all AEs
- Assess causality
- Follow any protocol guidelines for withdraw or re-challenge with study drug
- Discontinue study drug if there is a safety concern
- Follow open AEs through resolution or at least 30 days past subjects participation in trial
- Report per IRB requirements

Sponsors:

- Discontinue the study if the investigational drug presents and unreasonable & significant risk to subjects.
- Report to FDA, IRB & other investigator sites

Serious Adverse Events (SAEs)



- **SAE per FDA**
<http://www.fda.gov/medwatch/report/DESK/advevnt.htm>
- A serious adverse event (SAE) is any untoward medical occurrence that results in
 - death
 - is life-threatening
 - requires inpatient hospitalization or prolongation of a hospitalization (with exception of in-patient procedures planned prior to study enrollment)
 - results in persistent or significant disability or congenital anomaly or
 - requires intervention to prevent permanent impairment.

requires intervention

- **May be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject's health or welfare and may require medical or surgical intervention to prevent one of the outcomes listed in the previous slide.**
- **Example: allergic bronchospasm requiring intensive treatment in an emergency room or at home**

Adverse Event Reporting

Drug Studies

- **Sponsor-Investigator must inform the FDA of any SAE that is unexpected and related:**
 -  **Telephone report within 7 days of occurrence**
 -  **Written report within 15 days – identify all previous IND safety reports concerning a similar SAE and their relevance to this event**

Serious Adverse Event Reporting

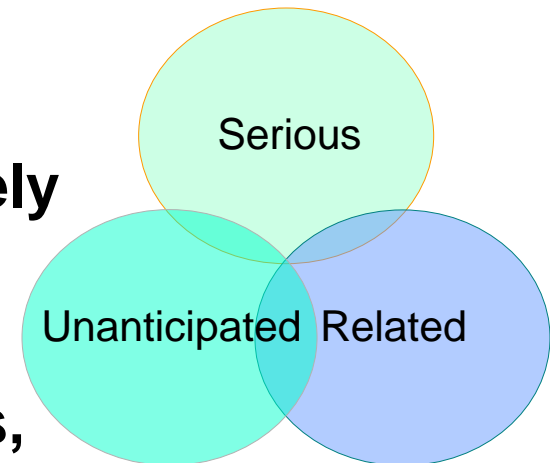
- As Sponsor-Investigator you must determine a process that includes collection of subjective and objective information. Can choose to use MedWatch format.



- <http://www.fda.gov/medwatch/report/instruc.htm>
- Documentation (*discharge summary, autopsy report, death certificate* – remove identifiers replace with study ID)
- Details, Details, Details

IRB Event Reporting

- All that are **serious** and **unanticipated** and which are possibly, probably or definitely **associated** with study procedures must be reported to the IRB using UK Internal, Unanticipated Problem/Adverse Event Reporting Form
- **Any death that is related to the study procedures - report immediately (i.e. within 48 hours)**
- **life threatening and unanticipated, and related* to the study procedures, should be reported within 7 calendar days**
- other internal serious and unanticipated problems/adverse events that are related* to study procedures, must be reported within 14 calendar days



Drug Accountability Obligations



- Read and know investigator's brochure
- Maintain strict control
- Adhere to special conditions
- Secured storage with limited access
- Inventory and separate from non-investigational or expired study drug
- Provide only to study subjects
- Provide subject education (inform investigational)
- Maintain records of receipt and disposition of all test article/drug – should MATCH inventory
- Track dispensing and reconciliation
- Monitor compliance & provide counseling
- Return, use or destroy per sponsor instructions at trial conclusion
- Archive documents

Sample Drug Accountability Record

Investigational Product Dispensing & Returns Log

Investigator:	Sponsor-Investigator:	Sponsor Protocol#:			Subject Initials:		
Address: University of Kentucky Hospital 800 Rose St Lexington KY 40536					Subject Number:		
	Dispensed By (initials)	Product Dispensed			Product Returned		
		Lot#	Date (mm/dd/yy)	# tablets	Date (mm/dd/yy)	# tablets	Comments
1							
2							
3							
4							
5							
6							
7							
8							
9							

Investigational Drug

- **Perpetual drug inventory log**
 - Reordering and pre-determined points
- **Packaging**
- **Labeling – PI Name; Drug name & Strength; Subject ID# & initials; Date dispensed; Directions; Precautions; Expiration Date; if multiple package noted (1 of X); visit number; Investigational Use Statement -**



**Caution: New Drug- Limited by Federal Law
to Investigational Use**

Investigational Drug Service

The investigator may transfer the task of study drug management to the Investigational Drug Service (IDS), as documented on the task delegation log, however the ultimate responsibility remains with the PI.

Use of the IDS is required for inpatient trials conducted in the hospital (PH 10-01)

It is encouraged, but optional for outpatient studies to utilize the IDS -*however IDS may audit sites to ensure compliance with state and federal regulatory standards* (PH 10-06)

Research of Investigational Drugs HP 01-32) requires...

- The principal investigator must provide a copy of the approval letter to the IDS before an investigational drug can be dispensed.
- The principal investigator must supply to IDS a copy of any amendments to the protocol made during the course of the study.

Investigational Drug & the IRB Submission

If your research involves administration of an Investigational New Drug (IND), and you will not be utilizing the Institutional Drug Service, the IRB must determine the risk/benefit ratio, and that SOPs are in place for receiving, storing, dispensing, and accountability control are appropriate for human subject protections.

 In order for the IRB to consider approval for your protocol involving an IND, complete Form O and include it with your application submission.

Data - General Requirements

“All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.” – [ICH GCP 1.51]

- Study documents should be maintained in a dedicated and secure area throughout the trial
- All clinical trial documents must be available on a long-term basis for review by auditors or regulatory authorities

Sample Regulatory

Protocol and amendments

Signed Protocol Signature Page

Signed FDA Form 1571 & 1572

IRB approvals (informed consent, advertisements, etc)

IRB Membership Roster

Calibration records for equipment

FDA & IRB correspondence

Site Delegation of Authority Log

Explicit Regulatory Requirement

- 312.62 (b) An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug....
- Case histories = Case Report Form (CRF) + Supporting Data (Source)
- Source = All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
- Source documents are the original document where patient information was first recorded
(regardless of the medium)



Guidelines & Tips

- Document every subject visit, communication or interaction including phone contact
- Record documentation of eligibility
- Record in consistent units of measure – European date, kg vs. lb
- Explanations of missing data
- If data must be changed, single horizontal line through original, enter correction, initial and date change.
- Any late additions may be inserted as a “late entry” or “addendum”.
- Indicate any follow-up testing or treatment for AEs
- Provide subjects with expectations and tools to collect all needed data between visits
- Explanation of any protocol deviations or violations
- Continued progress notes through to termination of study.

Case Report Forms (CRF)

Sponsor-Investigator designs CRFs to capture concise translation of pertinent data that reflect a subjects status while participating in a research trial

Enrollment:

- Date the patient entered the study
- Patient number
- Randomization, Study Number
- Confirmation of written informed consent prior to study or screening procedures
- Confirmation subject meets inclusion/exclusion criteria
- Concomitant medications- should include dates begun and discontinued; the dose received; and indication
- Medical history and the patient's health status prior to entry into the study

All study visits include:

- Procedures conducted
- Concomitant meds-new, changed or discontinued
- Unexpected complaint or adverse event, the date and time of onset; severity; relationship to study article, duration; and for treatment
- Study drug compliance

Final visit:

- Condition of subject completion or termination of study article

Data Retention & Recordkeeping

- The federal code specifies that study documents must be retained by the site for a minimum of two years following date of marketing approval (or two years past discontinuation of the NDA).
- Specific trials such as multi-site international or pediatric trials have longer requirements.
- However in order to comply with HIPAA requirements, the IRB requires investigators to retain research records for six years after completion of the study.
- Records must be maintained in a secure fashion with limited access, including additional controls to ensure password protection, authenticity, integrity, confidentiality of electronic records.
(FDA regulation 21 CFR 11)

Monitor for Data Integrity

- **Appoint a monitor to oversee the progress of the investigation. (21 CFR 312.53)**
 - **Can assume this responsibility yourself but must clearly document thorough monitoring during study**
 - **Qualified internal candidate or contract monitor**
 - **Scientific/clinical knowledge**
 - **Familiar with product, regulations, protocol, consent process**



Monitoring trial for assurance of...

- **Subject rights and well being protected**
- **Safe and responsible conduct of trial**
- **Submission, review & approval by IRB & FDA**
- **Adequately informed staff**
- **Documentation of task delegation**
- **Adherence to protocol**
- **Adequate informed consent process**
- **Proper storage & disposition of study product**
- **Accurate, complete & verifiable data**

Monitoring Plan Outline

- Regulatory documents complete
- Tracking log of screened & recruited subjects
- Only eligible subjects enrolled
- Documentation informed consent process
- Drug accountability & disposition
- Reconcile CRF with source data
- Errors dated, initialed
- Reporting – Adverse events (IRB, FDA, Subjects)
- IRB reporting – modifications, deviations, violations
- Missed visits, missed data, withdrawals

Monitoring Reports

- **When**
 - **Before**
 - **During (after 1st subject enrolled, periodically)**
 - **After (annual & final report to IRB & FDA)**
- **Comprehensive report after each review**
- **Date, site, monitor, investigator, others**
- **Checklists**
- **Summary of review findings, deficiencies, conclusions, action taken**
- **Review & follow up by sponsor-investigator**

Data Safety Monitoring

All clinical trials require safety monitoring plans.

Certain trial designs, sponsor requirements or federal regulators may also necessitate an independent monitoring committee be established.

FDA guidance for Clinical Trial Sponsors on establishing DSMC

<http://www.fda.gov/cber/gdlns/clintrialdmc.pdf>

DSMP

Plans for:

- Monitoring
- AE reporting
- Data security
- Data accuracy
- Protocol compliance
- Reporting a suspension
- Multi-Center communication

Registering trials on... *ClinicalTrials.gov* Protocol Registration System

- Per the Food and Drug Administration Amendments Act (FDAAA) of 2007 sponsors or sponsors of investigator initiated trials must have their studies registered by defined deadlines.
- Registration is also a requirement for publication in many medical journals per the **International Committee of Medical Journal Editors (ICMJE)** .
- See the UKCRO trials registration website for more information including:
 - NIH guidelines regarding expanded requirements
 - Clinicaltrial.gov Registration Data Element Definitions
- To obtain an access code to the UK Organizational Account on ClinicalTrials.gov, send a request with Name Department and Email address to:
- Jessica Wehle, jlwehl0@email.uky.edu, (859) 323-6623

State law

- **Federal law takes precedence over State or Institutional Policy UNLESS state or local mandate is more stringent**
- **Refer to the ORI sop's which include consideration of state law**
- **Consult with ORI attorney when question**
- **Examples**
 - **Consent**
 - **Emancipated minor**

Institutional Considerations at UK

- Department chairs knowledge and approval of research and any cost-sharing agreements (as acknowledged by the IRB Signature Assurance Sheet and the UK Internal Approval Form)
<http://www.rgs.uky.edu/ospa/forms/IAFInstructions.htm>
- Interaction with the Office of Sponsored Projects Administration for contractual and legal issues
- Guidance from the Biostatistics Consulting Unit
- Data Retention & Ownership Policy
- Conflict of Interest Policy & Management
- Other Review Committees that may be required depending on the protocol

What does the Department Chair's signature on the IRB Assurance sheet signify?

- **Trial has scientific merit deserving of conduct in humans including**
- **Key personnel are qualified and have sufficient time and resources**
- **Potential access to subject population**
- **Required facilities and equipment**
- **Chair will provide continued guidance and mentoring**

Clinical Trial Agreements

- Who holds the IND?
- What are the deliverables for the study?
- Liability risk – Is drug Investigational, marketed or new indication?
- Who will supply the contract?
 - Indemnification – committee review for risk
 - Subject Injury
 - Payment terms & milestones
 - HIPAA – what PHI will be provided to company
 - Data Ownership
 - Intellectual Property
 - Publication Rights

UK Boilerplate CTA



Conflict of Interest

Investigators who are also sponsors must pay particular attention to deification and management of conflict of interest.


While it is impossible to eliminate all conflicts, the following are potential ways to manage conflicts of interest:

- reduction of the financial interest?
- disclosure of the financial interest to prospective subjects?
- separation of responsibilities for financial decisions and research decisions?
- additional oversight or monitoring of the research?
- an independent data and safety monitoring committee
- modification of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change of investigator?
- elimination of the financial interest?



Conflict of Interest

UK Policy

 At UK, all key personnel for an externally funded or non-externally funded trials must complete a disclosure of financial interest form. UK will review and determine if the study will require COI management, oversight, limitations restrictions or prohibitions.

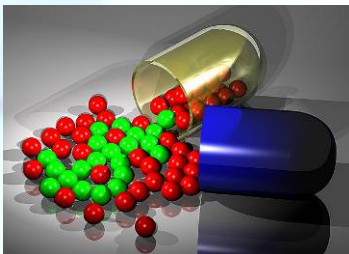
If you have questions or need assistance with a specific situation, please contact Carole Cole at 257-0579 or clcole2@uky.edu.

Third Party Reimbursement

Billing third party should only be done when approved and in congruence with language in the informed consent form. Co-pays and deductibles still apply.

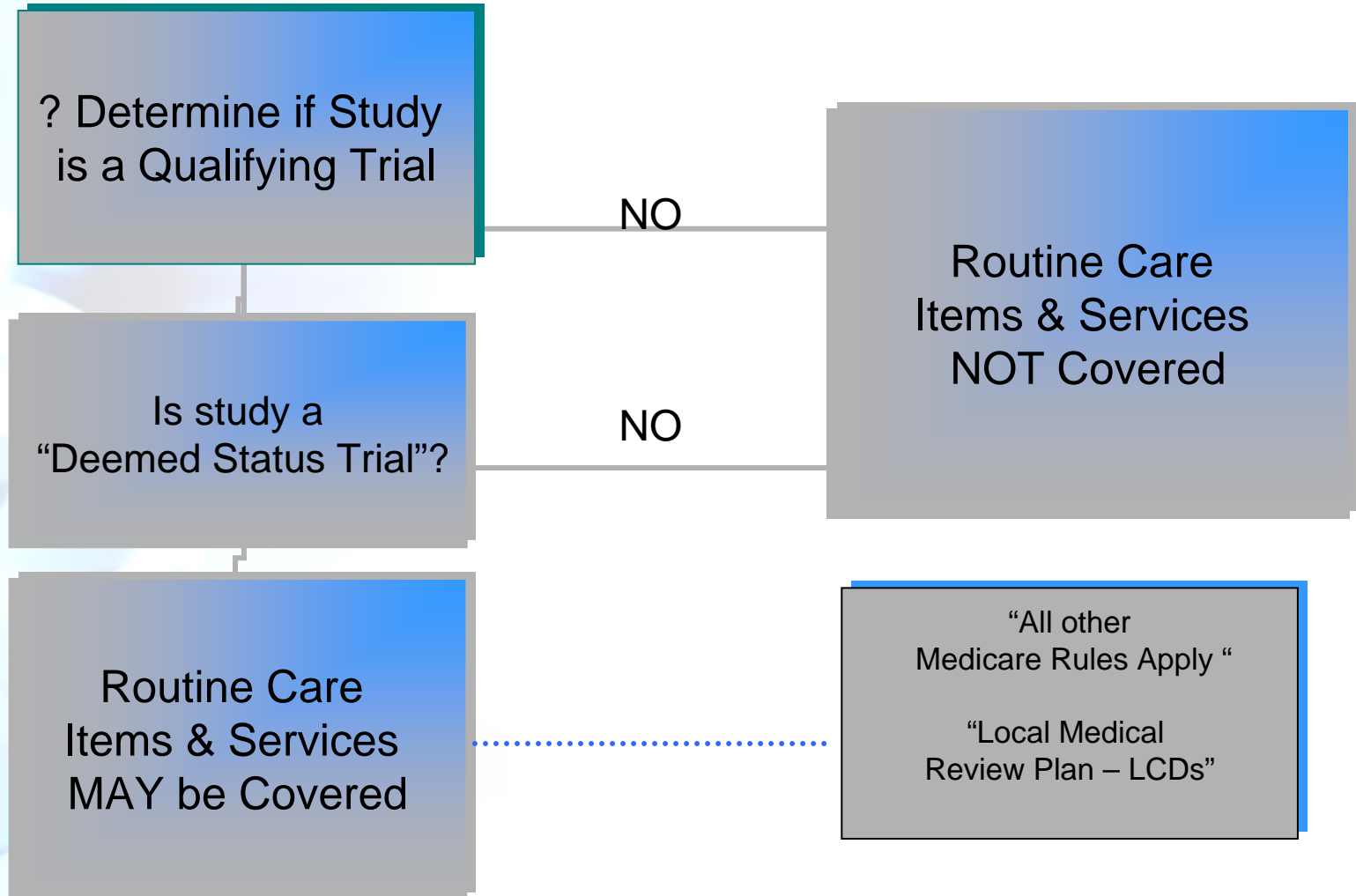
Adhere to Medicare and state Medicaid regulations-consult compliance for protocol analysis to determine if trial or procedures qualify for reimbursement.

**Rebecca Scott, Clinical Research Compliance Manager
Phone: (859) 323-1478, Fax: (859) 257-8325, Email:
rmwalt00@email.uky.edu**



See [Fiscal Management of Clinical Trials](#) for further guidance and billing compliance information

Medicare - Clinical Trials National Coverage Decision (NCD) of 2000



Clinical Trials NCD

- **Medicare may cover**

- Items and services typically provided absent clinical trial = medically necessary
- Items or services required solely for the provision of the investigational item or service (administer non-covered chemotherapy)
- Reasonable and necessary items and services used to monitor, diagnose, treat and prevent complications

- **Medicare does *NOT* cover**

- Investigational item or service itself
- Items and services *not* used in the clinical management of the patient
 - Data collection
 - Eligibility screening
- Items and services customarily provided by the research sponsor free of charge
- Items and services for which there is no Medicare benefit category
- Items promised free-of-charge in the informed consent

Device Development

- **Center for Devices and Radiological Health ([CDRH](#))**
- **Examples: surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, pregnancy tests, orthopedic pins**
- **Implant - a device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more.**



What Class?

- **Sponsor must verify the device classification in order to determine the necessary approval route.**
 - **Class I – minimal risk device that is exempt from FDA approval process.**
 - **Class II – devices with some risk and more regulatory oversight, some exempt and others nonexempt from approval.**
 - **Class III – devices intended for life support, are implantable or otherwise high risk.**

Product Classification Database can be found at:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>

Guidance on determining if you have a medical device:

<http://www.fda.gov/cdrh/devadvice/3121.html>

Is it Equivalent?

- **510(k) (or Pre-Market Notification) refers to the type of submission to FDA described under 21 CFR 807 Subpart E in which the applicant must establish that their device is substantially equivalent to a legally marketed device.**
- **This type of submission is used for most Class II devices and some Class I devices.**
- **FDA will make a determination of equivalency to allow immediate marketing or will require a Premarket Approval (PMA) (21 CFR 814.3) .**

Class III Devices

- Class III devices which require an approved premarket approval application (PMA) to be marketed are those devices found not substantially equivalent to devices marketed prior to May 28, 1976.
- Requires clinical trials to support claims for the device
- Examples of Class III devices which require a premarket approval include:
 - replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators.
- Must determine if significant risk (SR) or non-significant risk (NSR) device study.

 Include Form P with IRB application

Are Studies **SR** or **NSR**?

- The **Non-Significant Risk (NSR)** category was created to avoid delay and expense where the anticipated risk to human subjects did not justify the involvement of FDA (example: contact lenses).

The sponsor makes the initial decision whether the device studies will impart significant risk (**SR**) or **NSR** to study subjects.

- *Sponsor Says **SR**:* They must submit **IDE** to FDA for approval and be approved by an Institutional Review Board (IRB) before the study can begin.
- *Sponsor Says **NSR**:* Only require IRB approval .
- However, if the IRB considers the study to be **SR**, they override the sponsor and will require submission of an **IDE** to FDA before proceeding with clinical studies.

Significant Risk Investigational Device

- (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;**
- (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject;**
- (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**
- (4) otherwise presents a potential for serious risk to a subject**

Investigational Device Exemption

The PLAN

- **IDE Application Process**
<http://www.fda.gov/cdrh/devadvice/ide/application.shtml>
- **Cover letter content -**
<http://www.fda.gov/cdrh/dsma/797.html>
- **A description of the IDE process and information on FDA requirements for conducting a clinical study of an unapproved medical device can be found at:**
<http://www.fda.gov/cdrh/devadvice/ide/index.shtml>.
- **For device studies, the PI(s) must sign an investigator agreement (like FDA form 1572)**
- **While waiting on approval of an IND, an investigator can solicit potential subjects to ascertain interest, but cannot request informed consent prior to FDA & IRB approval**

Consultation

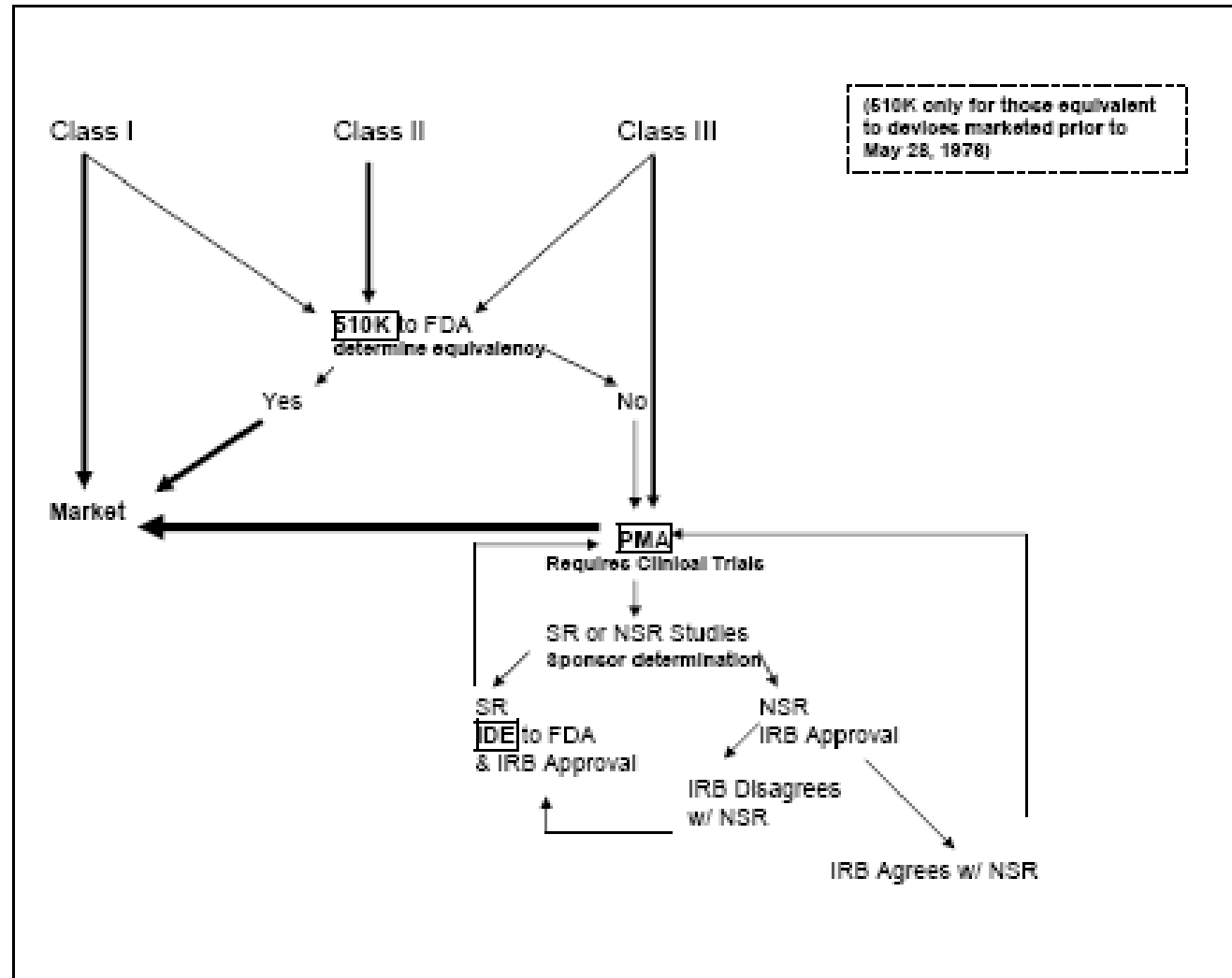
- **Frequently Asked Questions**
<http://www.fda.gov/cdrh/devadvice/ide/faq.shtml>
- **Ask a Question**
http://fdacdrh.custhelp.com/cgi-bin/fdacdrh.cfg/php/enduser/std_alp.php
- **"Goals and Initiatives for the IDE Program"**
<http://www.fda.gov/cdrh/d951.html>
- **"Pre-IDE Program: Issues and Answers"**
<http://www.fda.gov/cdrh/ode/d99-1.html>
- **Specific questions regarding IDE policies or procedures for the review of IDE applications, contact:**
 - **IDE Staff**
Investigational Device Exemptions Program (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850-3223
Telephone 301-594-1190

IDE Contents

- **Sponsor contact information**
- **Report of prior investigations**
- **Investigational plan**
- **Methods, facilities & controls for manufacture, packing, storage & installation of device**
- **Investigator agreement sample & list of participating investigators & institutions**
- **Participating IRBs**
- **Justification of any charge for device**
- **Labeling**
- **Copies of informed consent forms**

Device Development

Device Development Flow



Additional Sponsor-Investigator Responsibilities for Device Trials

Device Responsibilities Document

- **Submit the IDE application to FDA**
- **Obtain a “signed investigator agreement” from any participating investigators**
- **Ship the device only after submitting certification of IRB approval to FDA and only to qualified investigators participating in the trial**
- **Select and Ensure proper monitoring of trial**
- **Maintain complete & accurate records pertaining to distribution & disposition of device**
- **Ensure patient informed consent is obtained**

By signing an Investigator Agreement you are committing to:

- **Protect rights, safety & welfare of subjects**
- **Adhere to the investigational plan & report any deviations**
- **Obtain informed consent**
- **Supervise use of the device**
- **Disclose financial interest during and one year following trial**
- **Maintain accurate & complete records**
- **Report unanticipated adverse device effects**

Device Recordkeeping

Records	Maintained by Investigator	Maintained by Sponsor
All Correspondence Pertaining to the Investigation	X	X
Shipment, Receipt, Disposition	X	X
Device Administration and Use	X	-
Subject Case Histories & Informed Consents	X	-
Protocols and Reasons for Deviations from Protocol	X	-
Adverse Device Effects and Complaints	X	X
Signed Investigator Agreements	-	X
Membership/Employment/Conflicts of Interest	-	X

Sample Device Accountability Record

Sample Investigational Device Accountability Log

[illegible]

Long-term accountability

Significant risk or implanted devices may necessitate tracking the research subjects patient even after the study is over in the event that there is ever a recall or problem.

Some device manufactures may also want an autopsy to explant the device in the event that the subject (patient) dies with the device still implant.



FDA Investigational Device Reporting

The sponsor-investigator must provide the following reports in a timely manner to FDA, the IRB's, and/or other investigators

- Unanticipated Adverse Device Effects**
- Withdrawal of IRB or FDA Approval**
- Current List of Investigators**
- Progress Reports**
- Recalls and Device Disposition**
- Final Report**
- Any usage without prior informed consent**
- Significant Risk Device Determination by the IRB when proposed to be non-significant risk**

Device Labeling

- an investigational device or its immediate package must bear a label with the following information:
- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of contents, if appropriate; and
- the statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."
- the label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
- storage requirements, calibration procedures, sufficient directions for proper administration, and detail procedures to follow in the event of subject injury

Device Promotion

- **Promotion is limited to IRB approved advertising and recruitment for research subjects**
- **Sponsor-investigator must not:**
 - **Promote or test market an investigational device**
 - **Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs**
 - **Unduly prolong an investigation**
 - **Represent that an investigational device is safe or effective**

Unanticipated adverse device events

...any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated adverse device events

Sponsor-Investigators are obligated to report unanticipated adverse device effects.

- Unanticipated = 10 days**
- If you determine that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible - no later than 5 working days and no later than 15 working days after first notice of the effect.**

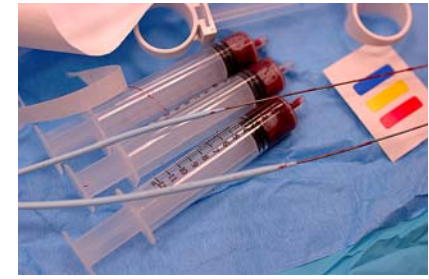
Device Reimbursement

The FDA permits a sponsor to charge an investigator or study subject for an investigational device. The charge is limited to the cost of manufacturing, research, development, and handling and the subject must be told of the charge in the informed consent. Medicare classifies these devices to assist in determining payment coverage during the clinical trial period.

Category B devices, as well as the hospital and physician services surrounding these devices, may be reimbursed by Medicare for Medicare patients.

In addition, routine cost associated with Category A devices that are used to treat an immediate, life-threatening condition, may also qualify but the device will remain non-covered.

Device Categories



Category A

A novel or innovative experimental device for which the absolute risk of the device type has not been established and initial questions of safety and effectiveness have not been resolved.

Category B

Those devices that are new generations of proven technologies. Initial questions about safety and efficacy have been resolved. Represent evolutionary changes in proven technologies.

Medicare Reimbursement

- **To receive Medicare reimbursement, the Hospital must gain approval from the Medicare Medical Director. This process is coordinated through the Managed Care Finance department of the Hospital and the required information must be submitted to Medicare at the inception of the Study. The Medicare approval process ranges from four to six weeks in duration.**

For more information:

- **Contact Elaine Younce at 859 257-9521.**
- **See the Special Considerations for Device Studies section of [fiscal management of clinical trials website](#) .**

Institutional Considerations at UK

UK Technology Assessment Committee

All investigational and non-investigational devices must be submitted for review and approval of the Technology Assessment Committee.

Complete the [request form](#) and submit with protocol and other supporting documents. If you have questions regarding your submission, contact Lorra Miracle, RN, Value Analysis/PI Facilitator/UHC Liaison at 323-4745. http://www.uky.edu/Purchasing/hosp_replaceform.pdf

Internal Guidance Resources

- UK IRB Standard Operating Procedures
http://www.research.uky.edu/ori/human/SOPs_&Policies.htm
- UK Human Research Education Materials & Guidance Documents
<http://www.research.uky.edu/ori/human/guidance.htm>
- IRB Survival Guide -
<http://www.research.uky.edu/ori/human/guidance.htm#IRBSurv>
- Clinical trial A-Z manual –
http://www.mc.uky.edu/ukcro/manual_page.htm
- Good Clinical Practice Guidelines
<http://www.fda.gov/cder/guidance/959fnl.pdf>
- Summary IIT Responsibilities for Drug IIT
http://www.research.uky.edu/ori/human/44-Revised_IND_Document.pdf
- Summary IIT Responsibilities for Device IIT
http://www.research.uky.edu/ori/human/45-Revised_IDE_Document.pdf

Clinical & Translational Resources

- In addition to internal support, there are several national efforts to advance innovation in translational medicine. The links below provide additional information and resources.
- [UK Center for Clinical & Translational Science](#)
- **FDA Critical Pathways – [Innovation/Stagnation – Challenge and opportunity on the Critical Path to new medical products](#)**
- [NIH Roadmap](#)