# Investigator Initiated Research: Risks, Responsibilities, and Rewards

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# A Growing Concern

- PhRMA recently reported that spending on IIR had increased by 20%
- IIR spending is rising faster than on Phase I through III studies
- OIG suggests IIR activity be carefully watched to ensure that the activity is legitimate, and not just a pretext to expand a product's market
- Recipe for risk and corporate liability
- Research professionals must manage the risks

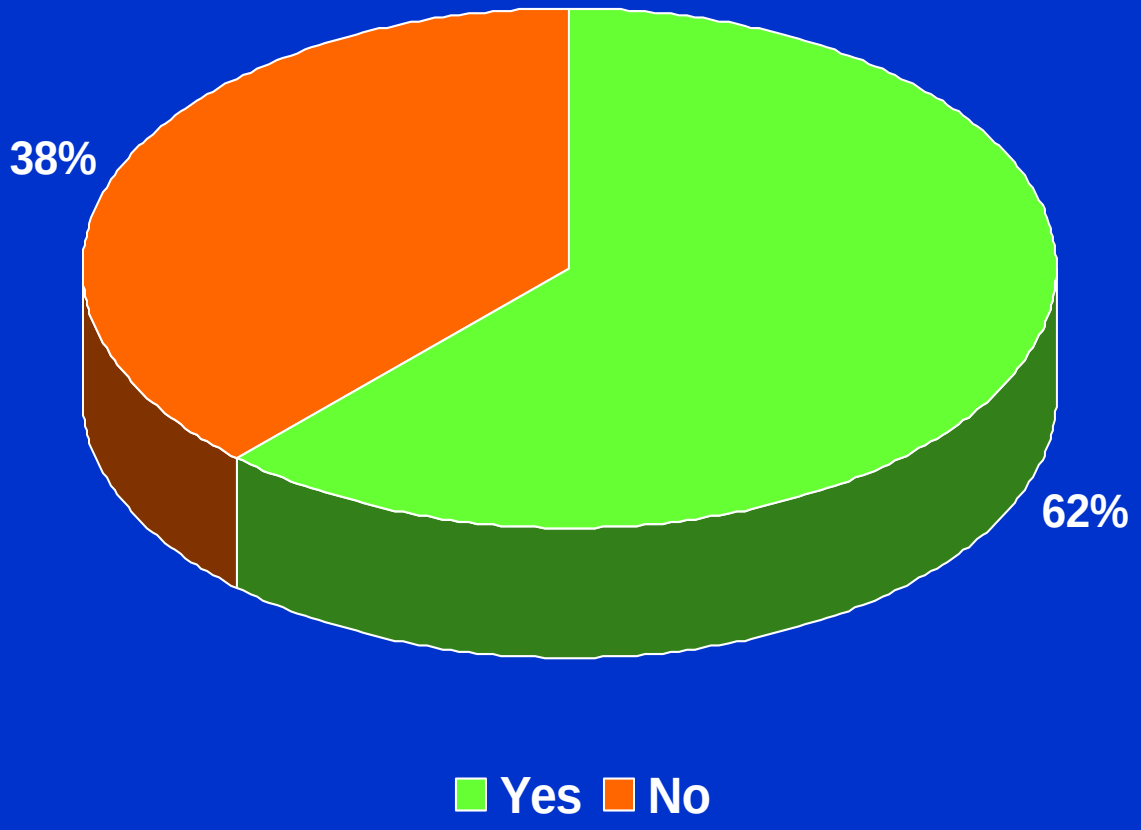
# Considerations

- Who are the parties?
- What are their roles?
- How can you manage the risk of IIR?
- What are the criteria for an appropriate IIR project?
- How should IIR be reviewed and processed?

# Survey Details

- Online survey
- Distributed through central office of ACRP in February, 2007
- *n*=285
- Demography of participants includes response from Industry and Academic Research

# Does your standard contract language clearly indicate when the investigator was the sponsor?



# Undefined Roles



# Ambiguous Roles and Responsibilities





Taking on responsibilities outside the scope of an assigned role

# What Am I?
## (And what are they?)

Sponsor

Collaborator



Investigator



Investigator-Sponsor

# Sponsor

A person who takes responsibility for and initiates a clinical investigation. . .**may be an individual or company, government agency, academic institution, private organization, or other organization**. . .

*21 CFR 312.3*




- Financial Support
- Protocol Development Assistance
- Provision of Product
- Anything other than a contractual statement and/or listing on the 1571 designating “Sponsor”

# Investigator

An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject).

*21 CFR 312.3*



# Sponsor-Investigator

Individual who both initiates & conducts a clinical investigation, and under whose immediate direction the investigational drug is administered or dispensed.

**The term does not include any person other than an individual**. The **requirements applicable to a sponsor investigator under this part include both those applicable to an investigator and a sponsor**.

*21 CFR 312.3*

# Why Do Investigator Initiated Research?

- Improve Science/Data
- Patient Benefit
- Support a New Use/Indication
- Supports Product Strategy

# Potential Risk Perspective

**Industry**

- Ineffective use of resources (financial and personnel) that do not support strategic plan.
- Lack of up front planning leading to potential non-validated data that can not be utilized for publication or support of FDA submission.
- Data results oppose current data results or strategic plan.
- Inappropriate budgets suggesting marketing influence
- Legal issues from non-compliance

# Potential Risk Perspective

**Institution / Investigator**

- Local sponsorship ambiguity
- Inadequate resources to act as sponsor
- Presentation / publication of data that may not have been validated (False Claims).
- Pivotal impact for research subject safety
- Legal issues from non-compliance to regulation
- Lack of indemnification of site from funding sources.

# Subject: Risk to Benefit Ratio

An invalid study resulting from the inappropriate/incomplete conduct of any study, places the subject at risk, potentially without providing any benefit….even to medical generalizable knowledge.

# Categories of IIR

- Traditional IND/IDE
- Non-IND/IDE Drug or Device studies
- Non-Drug or Device studies
- Each may be industry/association sponsored or not







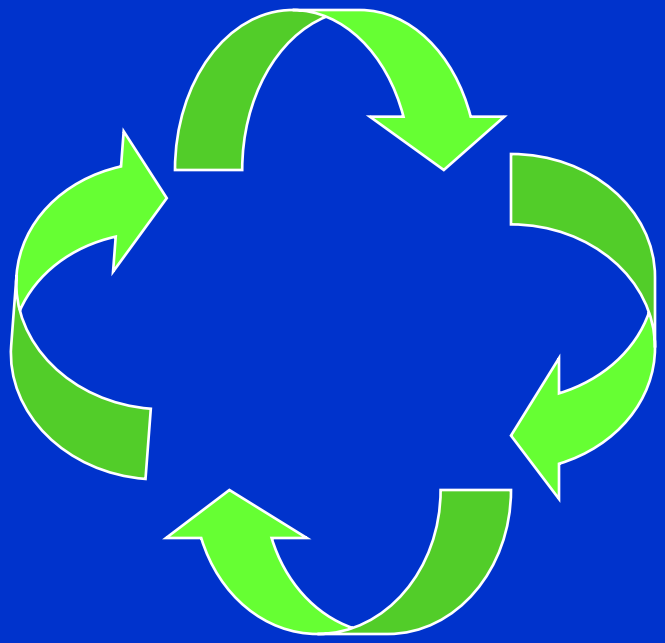
# Standards of Accountability

- Federal Regulation
- ICH Guidelines
- State Laws
- Institutional Policy
- Contractual Agreements
- The Protocol
- Investigator SOPs

# IIR: Responsibilities
# Plan to Succeed
# (or failing to plan is planning to fail)

Make a Plan

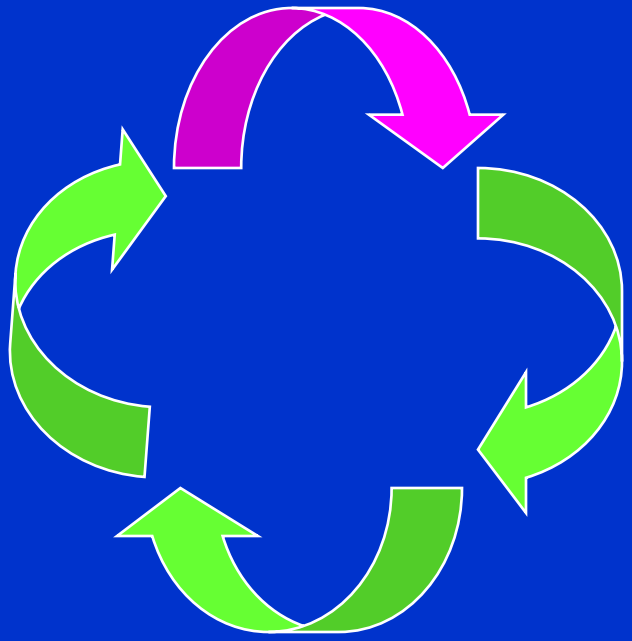
Report on the Plan



Follow the Plan

Record the conduct of the Plan

# Make A Plan



- Protocol (including oversight)
- Infrastructure Review
- Contracts

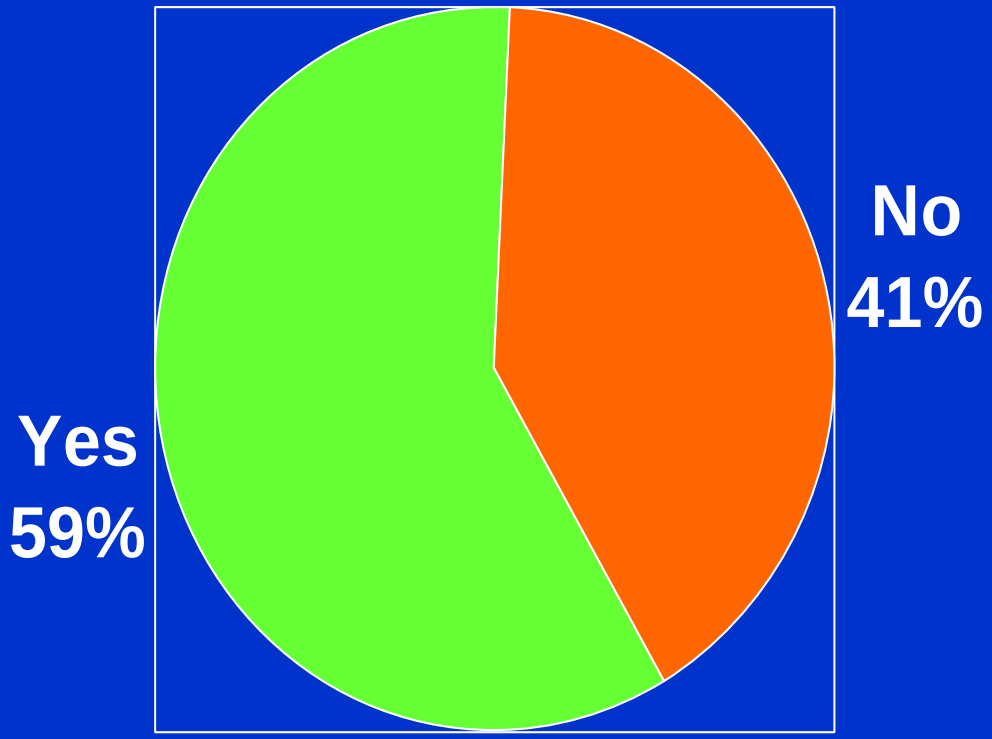
# Protocols and Oversight Plans

- Sample size (power) of study appropriate for study design and purpose.

- Appropriate Endpoints

- Detailed plan for oversight of study conduct, subject safety, validity of data

# Does your company/institution have a formalized policy and/or procedures for oversight of IIS?



# Review of Infrastructure

- Knowledge Base
- Personnel Resources
- Facility (space, services and equipment) Resources
- Recruitment Potential
- Financial Resources



# Functional Infrastructure

Infrastructure appropriate for:

- monitoring regulatory submissions
- oversight of study conduct (including qualification and education of staff)
- oversight of data and research subject safety

# Start Responsibly



- Spell out roles and responsibilities in contracts with industry collaborators.
- Read all agreements or conditions of awards

# Financial Budgets

Assure that budget is representative of full study costs.

- Personnel
- Procedures
- Supplies
- Facilities
- Recruitment
- Training
- Monitoring



# Warning: Assure not in violation of anti-kickback statute.

**OIG:**

**[A]ny remuneration from a manufacturer provided to a purchaser that is expressly or impliedly related to a sale potentially implicates the anti-kickback statute and should be carefully reviewed.**

**To reduce risk, manufacturers should insulate research grant making from sales and marketing influences.**

**Source: OIG Pharma Compliance Guidance – 68 Fed. Reg. 23736**

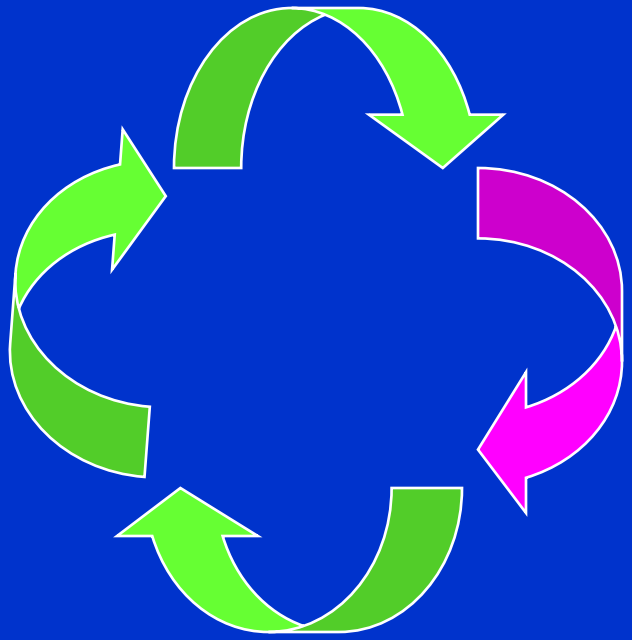
# Contract Financial Considerations

- A written budgetary agreement should be in place, specifying the type of the research services to be provided and the basis for payment for those services
- Investigator compensation should be reasonable for services performed
- Payment should not be tied to study outcome.
- The Investigator team (or their families) should not have conflict of interest related to the product being studied.

# Sponsor-Investigators 21 CFR 312.50

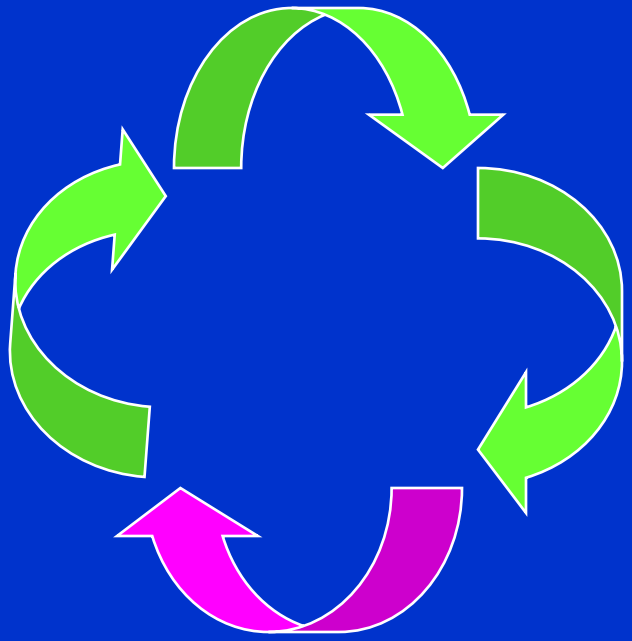
- Maintain the IND or IDE as required
- Qualify investigators and monitors (all sites)—CV's, 1572, financial disclosures
- Ensure proper monitoring (all sites)
- Ensure appropriate study conduct (all sites)
- Inform FDA and investigators of significant new AEs or risks with respect to the drug.
- Maintain accountability of investigational product (all sites).

# Follow the Plan



- Obtain approvals
- Stay the course

# Record the Conduct of the Plan



Essential Documents:

- Who?
- What?
- Where?
- Why?
- How?

# Essential Documents:
## (see ICH E6 Consolidated Guidance, Section 8)

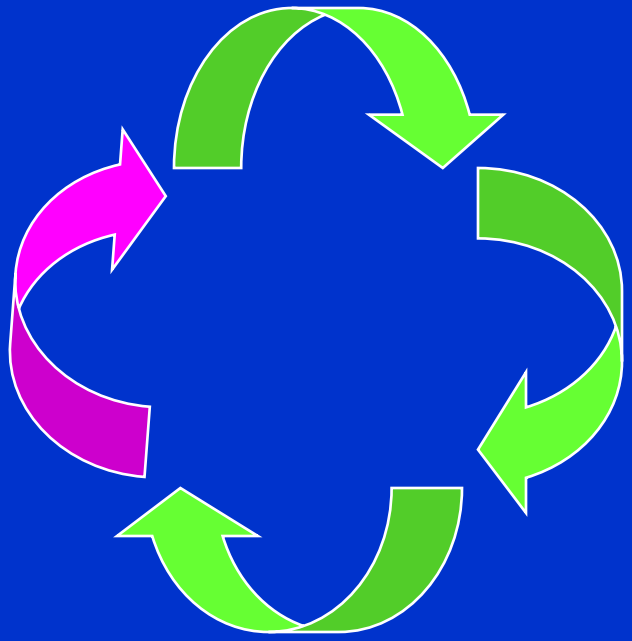
Examples:

- Protocol/Investigator Brochures
- Informed Consent and Recruitment Materials
- CV/License/Certifications
- Approvals
- Key Communication
- Accountability of test articles
- Training
- Staff permissions (not delegation)
- 1571 & 1572 when applicable
- Adverse Event reports
- Source documents and CRF when applicable

# The FDA's "ALCOA" requirement for source documentation

- **Attributable**: is it obvious who recorded it?
- **Legible**: can it be read?
- **Contemporaneous**: is the information in the correct time frame (how much time elapsed from the time of observation to the time of recording)?
- **Original**: is it a copy; has it been altered?
- **Accurate**: are conflicting data recorded elsewhere?

# Report on the Plan



- Waivers, Deviations, and Amendments
- Continuing Review
- Progress Reports
- Interim and/or Final Analysis
- DSMB reports
- Clinical Study Report/ Manuscripts to IRB, FDA, and perhaps collaborating group

# Rewards

- Promotes innovative thinking.
- For already approved drugs, there is a potential expansion of medical knowledge
- Less “resource” intensive for industry
- When partnered with industry financial support, a means to fund research programs.