

The “Business” of Clinical Research: How to Conduct Trials Efficiently and Ethically

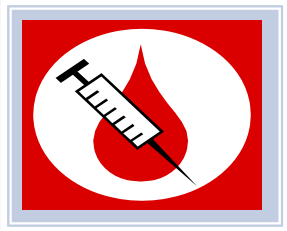
December 13, 2011
Maureen Coyne

Disclosures

- ▶ No industry relationships
- ▶ No financial conflicts of interests
- ▶ Recent experience weighted toward industry-sponsored clinical trials
- ▶ Information based on my experiences

With peer-reviewed data too!

Do we speak the same language?



IRB

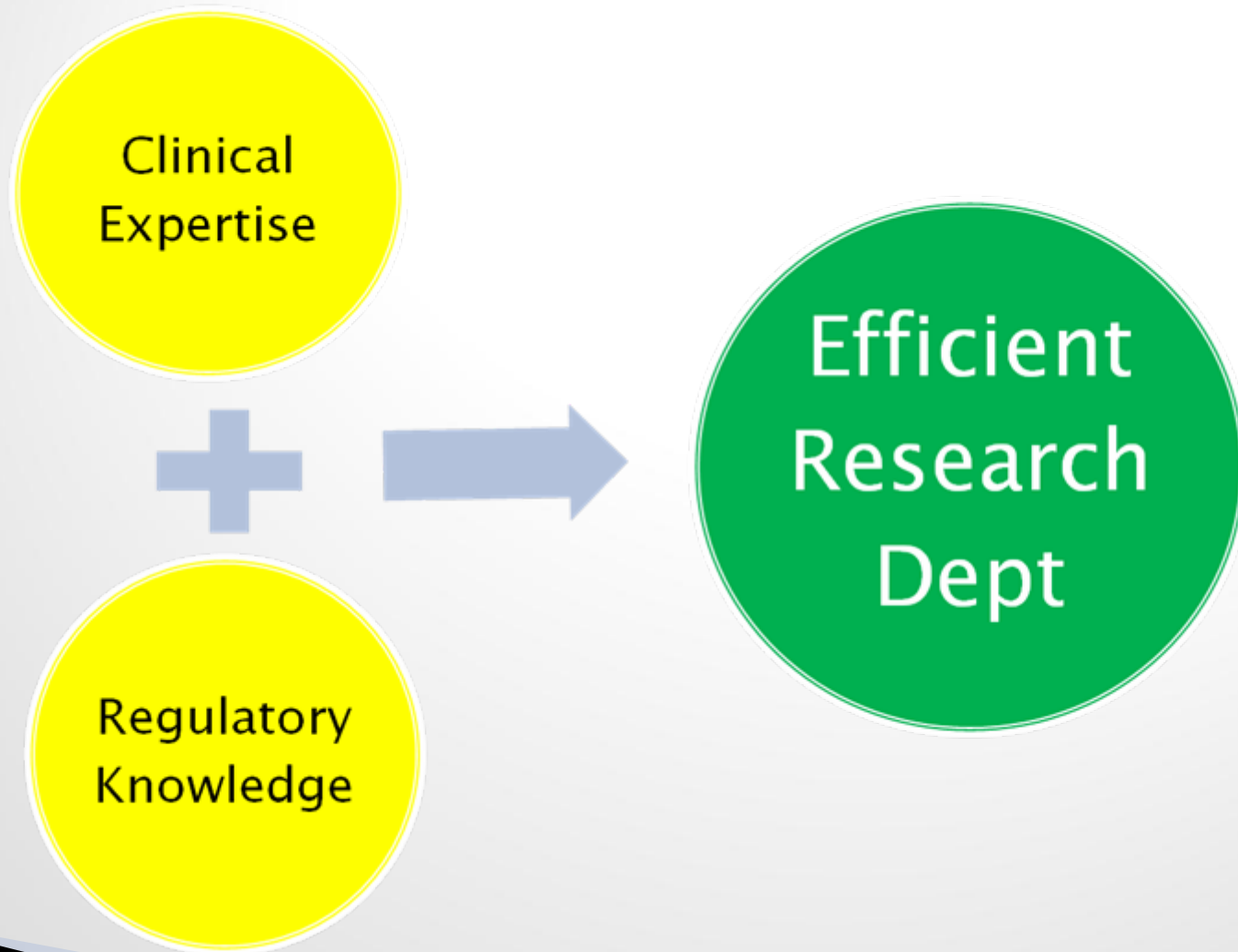
- How does this impact the *human subject*?
- Volume of blood being drawn?
- Precautions to prevent fainting?
- End result – sample obtained safely



Researcher

- How do I get the *lab results*?
- What color tubes do I collect?
- How do I prepare the sample?
- Do I send sample to central lab or process locally?

We need a translator!



Who does what?

- I'm in favor of splitting **regulatory** and **clinical** tasks...

To an extent!



- Use talents wisely.
- If you don't know, ASK!
Who, What, When, Where, Why?

What else is needed?

- ▶ Medical Coding
- ▶ Billing Compliance
- ▶ Financial Savvy
- ▶ Legal Knowledge
- ▶ Public Relations / Marketing

It works!

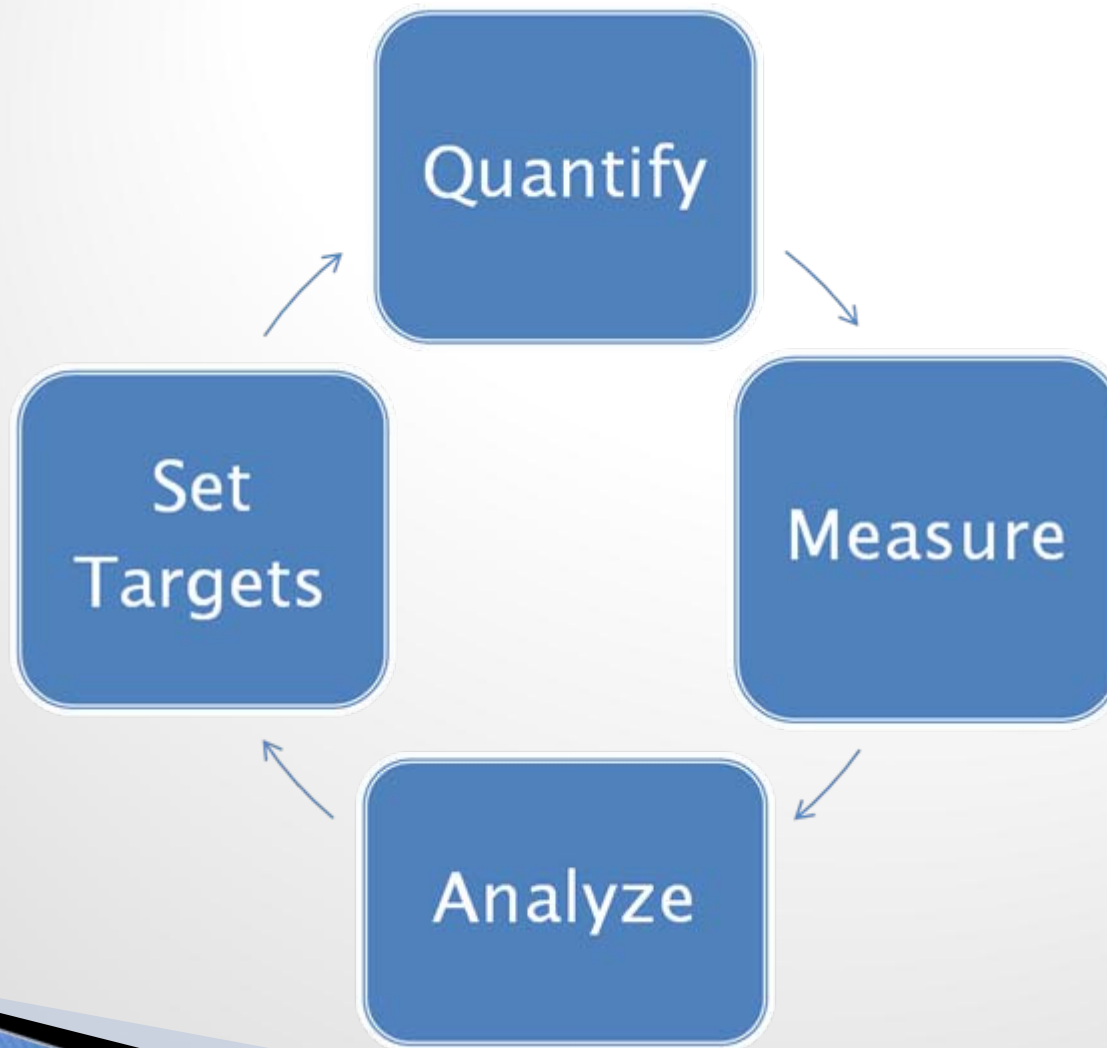


A culture of transparency can produce results.

How are you doing?

- ▶ Significant time is spent collecting data for the sponsor.
- ▶ But what data do you collect about your department?
- ▶ Have you ever said this?
 - *The IRB takes forever.*
 - *Legal said no.*
 - *The sponsor rejected our budget requests.*

Data is your friend.



Recruitment Sources

- ▶ Where do you find potential subjects?
- ▶ Who sends referrals? (regardless of enrollment outcome)
- ▶ Do subjects self-refer? Where did they see your ad?
- ▶ This will identify waste and focus your efforts.

Trial Offers

- ▶ What type of trials are being presented to you?
- ▶ By whom?
- ▶ How did they get your name?
- ▶ Why are you turning trials away?
- ▶ Are you diversified? Are you strategic?

News to Me! (and to sponsors)

- ▶ IRB approval is just one of many steps on the path to study activation

Project Timelines

- ▶ What is required to start a study?
- ▶ Where are the bottlenecks?
- ▶ What is and isn't in your control?
- ▶ What steps can be done in parallel?
- ▶ Create a process map.

Detailed Tasks From Timeline

| | Tasks | Responsible | Duration (weeks) | Details of Tasks |
|----|------------------------------------|--------------------------------|------------------|--|
| 1 | CDA to Protocol | PI /Medical Director | 2 | 1. Dr. Rubenstein & selected PI to sign CDA |
| 2 | Sponsor Feasibility | PI / Research Staff | 1 | 1. Review over sponsor's feasibility sheet |
| 3 | Protocol Analysis | PI / Research Staff | 18 | 1. In depth look at study design 2. Location of study IN / OUT Pt trial 3. Type of procedures involved 4. Ancillary departments involved 6. Review eCRF from sponsor to estimate coordinator time 7. Estimate Coordinator time on trial 8. Estimate how many coordinators needed 9. Site resources analysis 10. Central vs. local labs |
| 4 | CRC Meetings (1 day) | PI / Research Staff | 3 | 1. Vote to approve or reject protocol 2. Determine who the PI will be 3. PI to identify Sub-I's (ongoing till IRC submission) |
| 5 | Site Evaluation / Selection | Sponsor / Research Coordinator | 4 | 1. Coordinate ancillary departments for visit 2. Schedule PI to meet with sponsor rep 3. If site approved: protocol given to ancillary department; & eIRB process begins 4. Legal REVIEW of protocol to determine if it is worth our time to invest in the study |
| 6 | eIRB Application | Research Coordinator | 10 | 1. Begin the application process to the IRC 2. Give investigator's brochure & study protocol to ancillary departments |
| 7 | Contract | PI Attorney | 4 | 1. Attorney reviews contract 2. PI reviews contract 3. Contract changes reviewed by sponsor 4. Contract BACK to site Attorney for FINAL REVIEW |
| 8 | Budget | PI / Research Staff | 4 | 1. Cost analysis begins 2. IRC fees \$2000 3. Pharmacy fees \$975 (start-up fee) 4. Pharmacy fees (close-out) 5. Administrative fees \$ 875 (up-front) 6. PI fees \$2500 7. Investigator reimbursement 8. Pt stipend fees 9. Coordinator's time fee 10. Misc fees |
| 9 | ICF | Research Coordinator | 4 | 1. Coordinator to modify original consent from sponsor 2. ICF changes to sponsor for approval 3. ICF from sponsor to IRC 4. IRC preliminary approval 5. PI reviews over ICF 6. ICF back to sponsor with IRC preliminary changes 7. IRC presentation of study by the PI 8. ICF to sponsor with FINAL IRC changes |
| 10 | Regulatory Document MD Recruitment | Research Coordinator PI | 4 | 1. Financial disclosures signed 2. Conflict of Interest signed 3. 1572 signed 4. Signature pages signed 5. Protocol education by the PI to sub-I's 6. Find Sub-I's for study |
| 11 | IRC Application & Approval | Research Coordinator PI IRC | 6 | 1. Submission until IRC meeting may take up to 3 weeks 2. IRB Meeting to Approval of study may take up to 3 weeks 3. Educate sub-I's that agree to do the study 4. Continue to find sub-I's for study 5. Schedule PI for IRC meeting and confirm 6. Create patient information sheet & submit to sponsor then to IRC for approval |
| 12 | Contract Executed | PI Attorney | 2 | 1. PI & VP of Medical & Academic Affairs sign contract |
| 13 | Site Initiation | Sponsor | 2 | 1. Sponsor rep visits site |
| 14 | Study Drug Shipped | Sponsor | 2 | 1. Sponsor ships drugs to pharmacy |
| 15 | Nursing Education | Research Coordinator | 3 | 1. In-services for nursing staff available |
| 16 | Patient Enrollment | Research Coordinator PI | ongoing | 1. Inclusion / Exclusion by investigator 2. Coordinator facilitates procedures and randomize pt into trials |

Checklists

- ▶ *“The Checklist Manifesto: How to Get Things Right” – Atul Gawande, MD*
- ▶ Well-designed checklists improve outcomes
- ▶ Airline industry → Medicine
- ▶ WHO Checklist – reduces surgical complications by one third
- ▶ SC Hospital Assc. partners with Gawande to implement 1st statewide surgical checklist

“It’s the overconfidence of experts that can result in spectacular mistakes.”

– Malcolm Gladwell



Who has time to do all this?!

- ▶ Use a shared drive accessible to all staff
- ▶ Document control / naming conventions
- ▶ Repository of data for Site Evaluation Surveys
- ▶ Keep a central calendar to track deadlines, subject appointments, etc.
- ▶ It is *essential* that this information is accessible to staff at all times.

How do I put the data to use?

1. Budgeting

2. IRB

3. Informed Consent

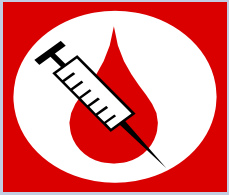
Preparing the Study Budget

- ▶ Know the protocol inside and out.
- ▶ Review CRFs for exact data points.
- ▶ Know your site's research rates. Create a procedure template.
- ▶ Know what your time is worth – this is the study's biggest expense!
- ▶ Know your site's pass-through costs and overhead rates

Document Administrative Costs

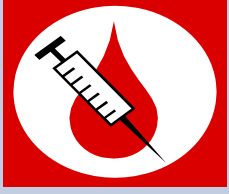
- ▶ Training of ancillary staff
- ▶ Regulatory preparation (please sign this!)
- ▶ Protocol analysis
- ▶ Contract review
- ▶ Medicare Coverage Analysis
- ▶ Monitoring visits
- ▶ Office supplies
- ▶ Source document creation
- ▶ Record archiving

Staff Time and Effort



Sponsor

- 10 minutes to draw blood from the subject
- 30 minutes to enter lab results/ data into the CRF



Researcher

- Schedule visit with the subject
- Prepare source documents for visit
- Trek across campus to the visit
- 10 minutes to draw blood from the subject
- Local – take sample to lab, or...
- Central – process sample, spin blood, get dry ice, package sample, take package to mailroom.
- 30 minutes to enter lab results/ data into the CRF
- Respond to queries

Cost Analysis for FUN Trial

Site Resources - Hourly Rates: Investigator - \$30, Manager - \$20, Coordinator - \$10

| Start-Up Costs | Role | Hours | Cost |
|-----------------------------------|--------------|-------|-------------------|
| Contract Review | Investigator | 0.25 | \$7.50 |
| Contract Review | Manager | 3 | \$60.00 |
| Cost Analysis | Manager | 6 | \$120.00 |
| Cost Analysis | Investigator | 0.25 | \$7.50 |
| IRB Meeting Presentation | Coordinator | 0.5 | \$5.00 |
| IRB Meeting Presentation | Investigator | 0.5 | \$15.00 |
| Medicare Coverage Analysis | Manager | 6 | \$120.00 |
| Project Start-up Preparation | Coordinator | 20 | \$200.00 |
| Protocol Analysis | Coordinator | 3 | \$30.00 |
| Protocol Analysis | Investigator | 1 | \$30.00 |
| Regulatory Preparation | Coordinator | 16 | \$160.00 |
| Regulatory Preparation | Investigator | 0.5 | \$15.00 |
| CMS Application Preparation | Manager | 5 | \$100.00 |
| Study Initiation Meeting | Coordinator | 4 | \$40.00 |
| Study Initiation Meeting | Investigator | 0.5 | \$15.00 |
| Training - Hospital Nursing Staff | Coordinator | 2 | \$20.00 |
| Training - Physicians | Coordinator | 2 | \$20.00 |
| Subtotal | | | \$965.00 |
| Total with 15% Overhead | | | \$1,109.75 |

| Screening / Enrollment Costs | Role | Hours | Cost |
|--------------------------------|--------------|-------|-----------------|
| ID & Consent Participant | Coordinator | 1.5 | \$15.00 |
| Coordinator Time & Effort | Coordinator | 2 | \$20.00 |
| EKG | CPT 93005 | n/a | \$172.85 |
| Health History Documentation | Coordinator | 2 | \$20.00 |
| Investigator Time & Effort | Investigator | 1 | \$30.00 |
| Lab - CBC, Auto, No Diff. | CPT 42658 | n/a | \$42.11 |
| Lab - HDL | CPT 12574 | n/a | \$61.00 |
| Lab - Total Cholesterol | CPT 96254 | n/a | \$29.33 |
| Subtotal | | | \$390.29 |
| Total with 15% Overhead | | | \$448.83 |

Too much detail?

Or not enough?

Budget Language

- ▶ Start-up payment vs. per patient payment
- ▶ Fair approach by the sponsor, but the site must know its “break even” point.
- ▶ Non-refundable
- ▶ Don't forget screening time
- ▶ You have the justification!



Budget Red Flags

- ▶ Holdback of more than 10%
- ▶ Payments dependent on monitor visits
- ▶ Infrequent payments
- ▶ Requiring invoices for routine payments
- ▶ No payment for screen failures

Continuous Financial Monitoring

- ▶ Add expected payment dates to your shared calendar
- ▶ Demand itemized payments
- ▶ Reconcile every check
- ▶ Projections
- ▶ Accounts Receivable Aging Report

UNPAID PATIENT VISITS

| <u>DAYS OUT</u> | <u>0 - 30</u> | <u>31 - 60</u> | <u>61 - 90</u> | <u>91 - 120</u> | <u>121 - 150</u> | <u>151 - 180</u> | <u>181 +</u> | <u>SUBTOTAL</u> |
|----------------------|---------------|----------------|----------------|-----------------|------------------|------------------|--------------|---------------------|
| TRIAL 1 | \$ 0.00 | \$ 0.00 | \$ 85.20 | \$ 0.00 | \$ 0.00 | \$ 0.00 | \$ 0.00 | \$ 85.20 |
| TRIAL 2 | \$ 607.00 | \$3,862.00 | \$ 0.00 | \$ 552.00 | \$ 0.00 | \$ 0.00 | \$ 0.00 | \$ 5,021.00 |
| TRIAL 3 | \$ 536.00 | \$1,914.00 | \$ 535.40 | \$ 191.40 | \$ 151.00 | \$ 171.80 | \$6,229.60 | \$ 9,729.20 |
| GRAND TOTALS: | \$ 1,143.00 | \$5,776.00 | \$ 620.60 | \$ 743.40 | \$ 151.00 | \$ 171.80 | \$6,229.60 | \$ 14,835.40 |

Medicare Analysis

- ▶ Medicare's Clinical Trial Policy (CTP) covers “routine costs” of clinical trials
 - If not paid for by sponsor
 - If not promised free in the consent
 - If the trial is deemed and qualified

3 Requirements to Be Qualified

- ▶ Purpose of the trial is an evaluation of an item or service that falls within a Medicare Benefit Category
- ▶ Trial has therapeutic intent. Not designed exclusively to test toxicity or disease pathophysiology.
- ▶ Trial enrolls patients with diagnosed disease, not healthy volunteers.

Criteria to be Deemed

- ▶ Study funded by NIH, CDC, AHRQ, CMS, DOD or VA
- ▶ Study supported by centers or cooperative groups funded by above
- ▶ Studies conducted under IND application
- ▶ IND-exempt studies
- ▶ Studies conducted under the Coverage with Evidence Development process

What are “routine costs”?

- ▶ Conventional care
 - Requires objective evidence (treatment guidelines, medical journals)
 - PI can connect the reason for the diagnostic service to a known potential side effect of drug used in study
- ▶ Administration of the investigational item
- ▶ Detection, prevention and treatment of side effects

Site Responsibilities

Establish a process to:

- ▶ Analyze a trial to determine whether it is qualified
- ▶ Determine which study activities are a “routine cost”
- ▶ Document and communicate those results

*Journal of Clinical Research Best Practices
Vol 6, No 3, March 2010
Meade, Willenberg & Roach*

Requirements for Medicare Coverage of Routine Costs in Clinical Trials

Clinical Trial Title and Sponsor:

PI Name:

I. Does the trial meet the 3 requirements to be qualified?

| | |
|--------------------------|--|
| <input type="checkbox"/> | The purpose of the trial is the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids). |
| <input type="checkbox"/> | The trial has therapeutic intent. It is not designed exclusively to test toxicity or disease pathophysiology. |
| <input type="checkbox"/> | Trial will enroll patients with diagnosed disease rather than healthy volunteers (control arms are acceptable). |

II. Does the trial fall in any of the following 4 categories that are automatically deemed?

| | |
|--------------------------|---|
| <input type="checkbox"/> | Trial funded by NIH, CDC, AHRQ, CMS, DOD or VA. |
| <input type="checkbox"/> | Trial is supported by centers or cooperative groups funded by the NIH, CDC, AHRQ, CMS, DOD or VA. |
| <input type="checkbox"/> | Trial is conducted under an investigational new drug application (IND) reviewed by the FDA. Insert IND#: |
| <input type="checkbox"/> | Drug trial that is exempt from having an IND under 21 CFR 312.2(b)(1). |

III. If the trial is *not* automatically deemed, does it meet these 7 criteria to be deemed?

| | |
|--------------------------|--|
| <input type="checkbox"/> | The purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes. |
| <input type="checkbox"/> | The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use. |
| <input type="checkbox"/> | The trial does not unjustifiably duplicate existing studies. |
| <input type="checkbox"/> | The trial design is appropriate to answer the research question being asked in the trial. |
| <input type="checkbox"/> | The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully. |
| <input type="checkbox"/> | The trial is in compliance with Federal regulations relating to the protection of human subjects. |
| <input type="checkbox"/> | All aspects of the trial are conducted according to the appropriate standards of scientific integrity. |

PI Signature: _____ Date: _____

*CMS Centers for Medicare & Medicaid Services; National Coverage Decision (NCD) for Routine Costs in Clinical Trials (310.1).
Publication # 100-3, Manual Section #310.1, Version 2, Effective Date 7/9/2007.

Qualifying Trial Checklist

| Screening / Enrollment Costs | Resource | Billable? |
|-------------------------------------|-----------------|------------------|
| ID & Consent Participant | Coordinator | No |
| Coordinator Time & Effort | Coordinator | No |
| EKG | CPT 93005 | Yes |
| Health History Documentation | Coordinator | No |
| Investigator Time & Effort | Investigator | Yes |
| Lab - CBC, Auto, No Diff. | CPT 42658 | No |
| Lab - HDL | CPT 12574 | Yes |
| Lab - Total Cholesterol | CPT 96254 | Yes |
| Subtotal | | N/A |
| Total with 15% Overhead | | N/A |

**WHO is responsible for this cost?
The dollar amount is not relevant.**

IRB

- ▶ You've already done such detailed analyses... this will be apparent to the IRB and they will thank you for it!
- ▶ Application answers will come easily!
- ▶ The consent form will write itself!
- ▶ Again... use a checklist.

IRB, continued.

- ▶ Continuing Review – shared calendar tells you when it is due.
- ▶ Amendments – shared drive has the history of all your documents.

A Word on HIPAA

- ▶ Common mistake in IRB applications
- ▶ When is data truly de-identified?
- ▶ What is allowed by the HIPAA authorization in a clinical trial consent form?

| Sample Coding Category | Link Between Subject's Personal Identifiers and Genomic Biomarker Data | Traceability back to the Subject | Ability to Perform Subject Follow-up | Extent of Subject's Confidentiality and Privacy Protection |
|------------------------|--|----------------------------------|--------------------------------------|---|
| Identified | Yes (Direct) Allows for Subjects to be Identified | Yes | Yes | Similar to General Healthcare Confidentiality and Privacy |
| Coded Single | Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key) | Yes | Yes | Standard for Clinical Research |
| Double | Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys) | Yes | Yes | Added Privacy and Confidentiality Protection over Single Code |
| Anonymized | No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted | No | No | Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted |
| Anonymous | No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified | No | No | Genomic Data and Samples Never Linked to Subject |

IRB Review of CRFs

- ▶ Names
- ▶ ZIP Code
- ▶ Dates (except year)
- ▶ Phone numbers, Fax number, email address
- ▶ Social Security numbers;
- ▶ Medical record numbers; Health plan beneficiary numbers; Account numbers; Certificate/license numbers;
- ▶ Vehicle identifiers and serial numbers, including license plate numbers;
- ▶ Device identifiers and serial numbers;
- ▶ Web URLs and IP numbers
- ▶ Biometric identifiers, including finger and voice prints;
- ▶ Full face photographic images
- ▶ Any other unique identifying number, characteristic, or code

Prospective vs. Retrospective

- ▶ Another reason why the IRB wants to review your CRFs
- ▶ Retrospective data must be “on the shelf” at the time of IRB submission

Informed Consent

- ▶ IRB reviews for readability and required elements
- ▶ But informed consent is so much more than a document



Informed Consent

- ▶ The careful analysis you performed upfront will help you explain the study.
- ▶ Bottom Line – what's different about being in the study?
- ▶ Remember that the study goal is quality data. You want an informed participant.
- ▶ Collect the data! Why are people saying no?

Reasons for Decline

Data collected by National Institutes of Mental Health

- ▶ 36% – protocol issues (placebo, wash out)
- ▶ 33% – inconvenience
- ▶ 26% – non-specified reasons
- ▶ 3% – financial reasons
- ▶ 2% – want to participate in research elsewhere

Retention

- ▶ Continued informed consent
- ▶ Personal contact
- ▶ Clear communication
- ▶ Updates on study progress
- ▶ Thank you!!!

Why We Do What We Do

We owe our “customers” a debt of gratitude

- ▶ *Respect for Persons*

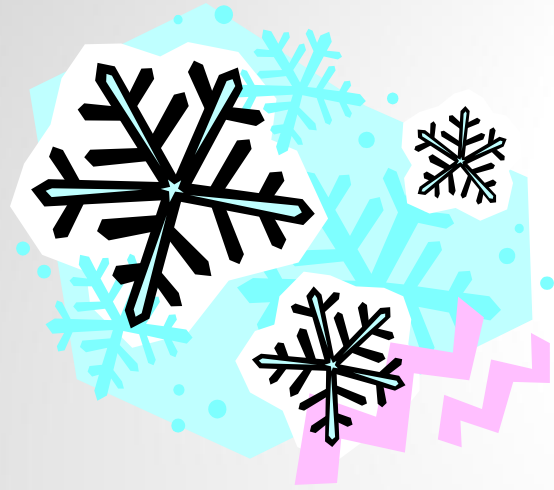
- autonomy; informed consent

- ▶ *Beneficence*

- minimize harm and maximize benefit

- ▶ *Justice*

- fairness in distribution



*Thank
you!*

