

Clinical Trial Budget Negotiation (W13)

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Objectives

- Discuss the four components of a clinical trial budget.
- Discuss differences between budgeting for clinical trials funded by industry versus federal sources.
- Describe a systematic approach to developing a clinical trial budget and coordinating the budget development and contract negotiation

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Drug Development Process

- 10-15 years concept to market¹
- Average cost \$802 million in 2000²
 - Up from \$138 million in 1978
- Increased to \$2 billion ('06)³
- 1 day delay to market costs \$600,000 to \$8 million⁵
 - In 2005, sales of Lipitor averaged >\$33 million per day

¹ Tufts University, 1995

² J A DiMasi, et al. 2003

³ Adams and Brantner, 2006

⁴ R&D Directions, October 2004

(CuttingEdgeInfo.com)

Budgeting Rules

- Anti-Kickback (civil penalties)
 - Fair Market Value
 - Unconditioned
- False Claim (civil and criminal penalties)
 - Prohibits submitting false information
 - » Charges , reports, grant proposals
 - Treble damages
 - Non-Government counterpart?
- Stark I and II

Sponsor's Budget

- How determined?
- Resources
 - National clinical trial databases
 - Example – Medidata Solutions Worldwide
 - » Medidata Grants Manager™
 - » Medidata CRO Contractor™
 - Internal databases
 - » Budgets, timelines, enrollment history
 - » Regional differences

Initial Offer

- Calculated for average site
 - Many sites are small private practice
 - » Likely to be first trial (and last)
 - » In recent 3-yr period, 50% of PIs on only 1 FDA Form 1572¹
 - Limited start-up expenses
- Not final offer (in most cases)
- Unlikely to affect selection as site

¹Glass HE. Contemp Clin Trials. 30:34-9 (2009)

Site's Budget

- Understand the protocol
- Study related procedures
 - Site related costs (e.g., interpretations)
- Usual (standard) care
- Labor costs (other than procedures)
- Draft the site budget early in process

Charge vs Cost

- ‘The’ cost of each study related item, procedure, labor hour exists, but may not be easily known
 - “it costs what it costs”
- Charge = Cost + Margin
- Reasonable goal is revenue \geq expenses
 - Excessive revenue looks like a kickback
 - » Insufficient revenue looks like a subsidy
 - COI reporting milestones
 - Medicare reimbursement + 20-25%?

Budget Categories

- Start-up Charges
- Per Subject Charges
- Contingent Charges
- Close-out Charges

Start Up Costs

- Negotiate as Non-Cancelable/Non-Refundable fees
- One-time charge
 - Not usually itemized by costs
 - Provide item list (not price list), if asked

Start Up Costs

- PI time
 - Protocol review
 - IRB Presentation
 - Investigator meeting
 - Initiation Visit
- Costs may vary with protocol complexity
 - Registry vs. Randomized trial with dose escalation
- Cost of doing business?

Start Up Costs

- Coordinator time
 - IRB application
 - Chart and/or database review
 - Site Initiation Visit
 - Protocol specific training
 - Investigator meeting
- Costs may vary with protocol complexity
- Cost of doing business?

Staffing Expenses

- Salary (or hourly) + Fringe Benefits
 - Staff cost, like time, marches on
 - “Missing payroll can adversely affect productivity” - Anonymous
- Biggest source of ‘hidden’ costs
 - Under budgeting commitment (‘donated’ time)
 - Time spent on non-revenue study activities
 - Uncontrolled contingencies
- What to charge?

Case Study: Cost of Staff Time

- Base Salary + Fringe Benefits
- Deduct time unavailable for research
 - Vacation, sick time, personal days
 - Holidays (if applicable)
 - Training time, required meetings
- Utilization - available time less non-billable hours
 - Late or canceled subjects, tests or procedures
 - Screening charts & admit lists, missed subject visits, initiation visit, monitor visits, answering queries

Case Study: Cost of Staff Time

- Scenario: Study Coordinator, RN, full time
- Direct Cost
 - Salary: \$50,000 (\$24/hr) + Benefits @ 25% (\$6/hr)
 - Direct cost to Institution: \$62,400 (for 2,080 hour year)
- Benefit Time
 - Vacation (15 days), sick (10 days), personal (3 days), holidays (6 days)
 - Total 272 hours
 - Leaving 1,808 usable hours

Case Study: Cost of Staff Time

- Institution Commitments
 - Department meetings (52 h), required training (8 h)
- Utilization - non-billable hours
 - Late or canceled subjects, tests, procedures (52 h)
 - Screening charts & admit lists (20 h)
 - Initiation visit (12 h)*, monitor visits (12 h x 4), queries (100 h)
 - Reviewing study subject bills for accuracy (100 h)
- Available time: $1,808 - 392 = 1,416$ hours

Case Study: Cost of Staff Time

- Staff networking time ('shrinkage')
 - 'Water cooler' meetings - 15 min/day (60 h)
 - Birthdays, holiday parties, lunches, etc (12 h)
- Available time: $1,416 - 72 = 1,344$ hours
 - $\$62,400/1,344 = \$46.43/\text{hour}$
 - Not including any overtime and/or shift differential
 - Not including the desired margin for this study
- Plus Indirect Costs (e.g., 30%) = $\$60.04/\text{hour}$
 - Break even for this position
- Different for every site

Start Up Costs

- Pharmacy
 - Protocol and pharmacy manual review
 - Study set up, maintenance, close-out
 - » Charged to study even if no subjects enrolled
- Laboratory
 - Protocol review
 - Study set up, tests (phlebotomy charge)
 - Special reports

Start Up Costs

- Direct Administrative costs
 - IRB submission preparation
 - Contract negotiation time
 - Budget negotiation time
 - Regulatory review
- Special equipment or facilities
 - Dedicated fax/modem line
 - Secure internet link
 - » Electronic data capture, Video conferencing

Indirect Costs

- Might have different rates for federal and industry
- Federal rate negotiated
 - Salary and wage basis
 - Direct cost basis (Total or Modified)
- Industry
 - Direct cost basis more common
 - Determined by Institution
 - Average 20-30% Total Direct Costs

Per Subject Costs

- Every study different
 - Protocol driven
 - Make flow chart if not provided
- Know which tests sponsor will cover
 - Research – study budget
 - Usual Care – subject or insurance

Billable Items

- FDA approval to charge test article
 - Revisiting charges for 3rd party comparator drugs
- Procedures/tests absent the study
 - Usual care
- Medicare has special rules
 - Old rules
 - Device rules
 - National Coverage Determination
- Medicaid?

Per Subject Budgeting

- Facility charges
 - Inpatient vs outpatient
 - Room not available for revenue patients during study
 - Cost of space may vary within institution
- Pharmacy charges
 - Drug compounding (onsite mixing)
 - Drug dispensing and disposal
 - QA testing (new JCAHO requirement)

Per Subject Budgeting

- Age related impacts/considerations
 - Infants/small children or the elderly
- Equipment use
- Usual care billed to study (sponsor pays)
- Test interpretation (X-ray, ECG, etc)
 - Onsite - Staff time or FMV (professional fee)
 - Off-site - Institution may require even if results sent to central facility – liability issue

Per Subject Budgeting

- Subject stipend
- Specimen preparation
 - Centrifuge, separate components
 - Tissue preparation
 - » Fixing, staining, mounting, sections
 - » Extra blocks, frozen sections
 - Complete specimen related CRFs

Per Subject Budgeting

- Packaging and Packing
 - Documents vs Specimens
 - Hazardous Materials
 - » Dry ice (49 CFR 172.101)
 - » Potentially infectious tissues or fluids (42 CFR 72)
 - » Special training needed
- Shipping charge if not prepaid

Contingent Budgeting

- Contingencies
 - Negotiated with budget, but not in the budget
 - Specified in contract; invoiced only if occur
- Can be bargaining chips
- Can be hard to track

Contingent Budgeting

- IRB & Consent related changes
 - Annual review (preparation and review fee)
 - Consent form change without an amendment
 - Language translation
 - » Consent, subject materials
 - » Certified translation required?
- Protocol amendment
 - Pharmacy, laboratory review
 - Re-consent subjects?
 - » PI and/or coordinator time
 - » Facility charge (e.g., room)
 - Retraining staff?

Contingent Budgeting

- Onsite Serious Adverse Events
 - PI and/or Coordinator time
 - » Evaluation beyond medical management
 - » CRF completion
 - Sponsor notification - Phone, fax, time
 - IRB report prep (and presentation?)
- Direct costs of treatment
 - Subject or sponsor paying?

Contingent Budgeting

- Additional Monitoring visits
 - Negotiate a base number (2-4/yr)
 - If a payment milestone, may want more for rapidly enrolling studies
- Advertising
 - Pass-through cost?
 - Administrative fee?

Contingent Budgeting

- Sponsor adds or changes CRO
- Sponsor induced delays
 - Shortage of test article
 - Suspended enrollment for statistical analysis
- Staff may need retraining if long delay

Contingent Budgeting

- Unplanned study related visits
- Screen failures
- Reopen budget negotiation if study active >2 years
- Cancellation fee
 - Sponsor ends study shortly after initiation

Negotiation is All About Achieving Goals

- Sponsor's goals
 - » Most favorable budget (lowest)
 - » Fast negotiation (minimum delay to project)
 - » Most favorable (back load payments)
- Site's goals
 - » Most favorable budget (highest)
 - » Fast negotiation (minimum delay to project)
 - » Most favorable (front load payments)

Challenges

- Most negotiations by email or telephone
 - Not face to face (no body language)
 - Difficult to assess 'level of interest'
- Often negotiator not final arbiter
 - Sponsor's negotiator has limited authority
 - » Where else is this common? Why?
 - Site's negotiator has limited flexibility

Strengths in Bargaining

- Sponsor/CRO
 - Knows project budget and timeline
 - May know site's study history
- Site
 - Knows costs of conducting study
 - Knows site's history (?)
 - Delays cost the sponsor money

Submitting the Budget

- Single numbers for Start-up, Per Subject and Close Out costs
- Itemized list if asked
 - Categories, if possible
 - No individual costs
 - Be prepared to provide justification
- Events and itemized contingent charges

Best Practices

- Know your story
- Funding needs to do the study
 - Ideal budget and ‘drop dead’ limit
 - Final should be somewhere between
- History
 - Previous work for sponsor
 - » Number of prior studies
 - » Percent of enrollment completed and time required
 - » Time from protocol receipt to first subject enrolled

Best Practices

- Treat phone negotiation the same as in person
- Schedule negotiation calls if possible
 - Both parties can be prepared
 - Fewer interruptions
 - » Don't read email during the negotiation
 - » Close your door
- Listen carefully, it's your only feedback

Best Practices

- Document progress (who, when, how much)
- Send confirmatory emails or faxes
 - complex issues, preliminary agreements
- Leave messages and follow-up
 - Keep a phone log
- Go around gatekeeper if needed to keep negotiations moving
 - But be careful not to offend the gatekeeper

Best Practices

- Keep email negotiations on track
 - Be brief, stay on topic
 - Avoid side opinions
 - Remain professional
 - Avoid IM abbreviations
- Be aware of 'Reply' vs 'Reply to All'
- Blind copy (bcc) to keep your team informed

Best Practices

- Re-read email before sending
- Track versions of documents
 - Date (and time if needed)
 - ‘Track Changes’ function (who, when)
 - ‘Comments’ to explain need for changes
- Use ‘priority’ email flag, if needed
- If email negotiation stalls, grab the phone

FDA Initiatives

- ‘Critical Path’ Initiative
 - Improve product development process
 - www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
- Phase ‘0’ IND
 - Very small, very fast
- Reevaluate charging for investigational drugs
- ‘Adaptive Trials’

Charges for Drugs

- Charging for investigational drugs
 - Common request by sponsor
 - » Trial for new indication done by 3rd party
 - » Study drug obtained from another company
- FDA “May be appropriate in some cases”
- Criteria for evaluation not clear in regulations or guidance

Adaptive Trials

- Sponsor may change protocol ‘on-the-fly’
 - Outcomes used to adjust allocation of subjects
 - Improve expected outcomes during study
 - Ethical and cost advantages over fixed studies
 - “Contingent” budgeting opportunity?
- Critical Path Institute (www.c-path.org)
- Very new concept - FDA moving slowly
- Could have serious effects at sites