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- Olivera Vragovic, MBA
- Research Manager
- Obstetrics and Gynecology
- 85 E. Concord Street, 6th Floor
- Boston, MA 02118
- phone: 617-414-7304
- fax: 617-414-7300
- email: [ovragovi@bu.edu](mailto:ovragovi@bu.edu)
- <http://www.bu.edu/obgyn>

# Developing Budgets for Research Projects with a Focus on Phase III Clinical Trials



## Learning Objectives:

- **Develop budgets that make sense (sponsors & sites)**
  - **Justify budget positions to the other party**
- **Provide examples of different types of budgets**

# Elias Zerhouni, MD PhD



Dr. Zerhouni about the value of medical research and clinical trials.

- Without scientific knowledge it is hard to have a public policy that makes sense.
- Medical research is the search for cures to illness and disease. It has been one of the most important human activities throughout history and especially in the last 50 years with a development of modern medical science based on molecular biology that began with a discovery of structure of DNA in 1953. We realize that you don't get to a disease through just one cause or abnormality. There may be multiple, interacting ones. Medical research is like a detective story, always searching for new leads to follow. It is very important to sustain medical research.
- Since 1970, we have reduced the mortality rate from cardiovascular disease by 70 percent, at an average cost of \$4 per person a year for cardiovascular research. With cardiovascular disease, the results have been extraordinary.
- Clinical trials involve the testing of new ideas with people. There are essentially two kinds, observational and interventional. The trials have to be very rigorous, very objective. That is why in the 1940s and 1950s, NIH implemented the double-blind, randomized, prospective trial. It remains the gold standard today. When something is recommended to millions of people, it must be based on solid evidence.

# Clinical Trial



Clinical trials are conducted to collect data regarding the safety and efficacy of new drug and device development.

- Sponsor
- Site
  - Academic non profit
  - Private for profit CRO SMO

# Sponsored Research Source of Funding

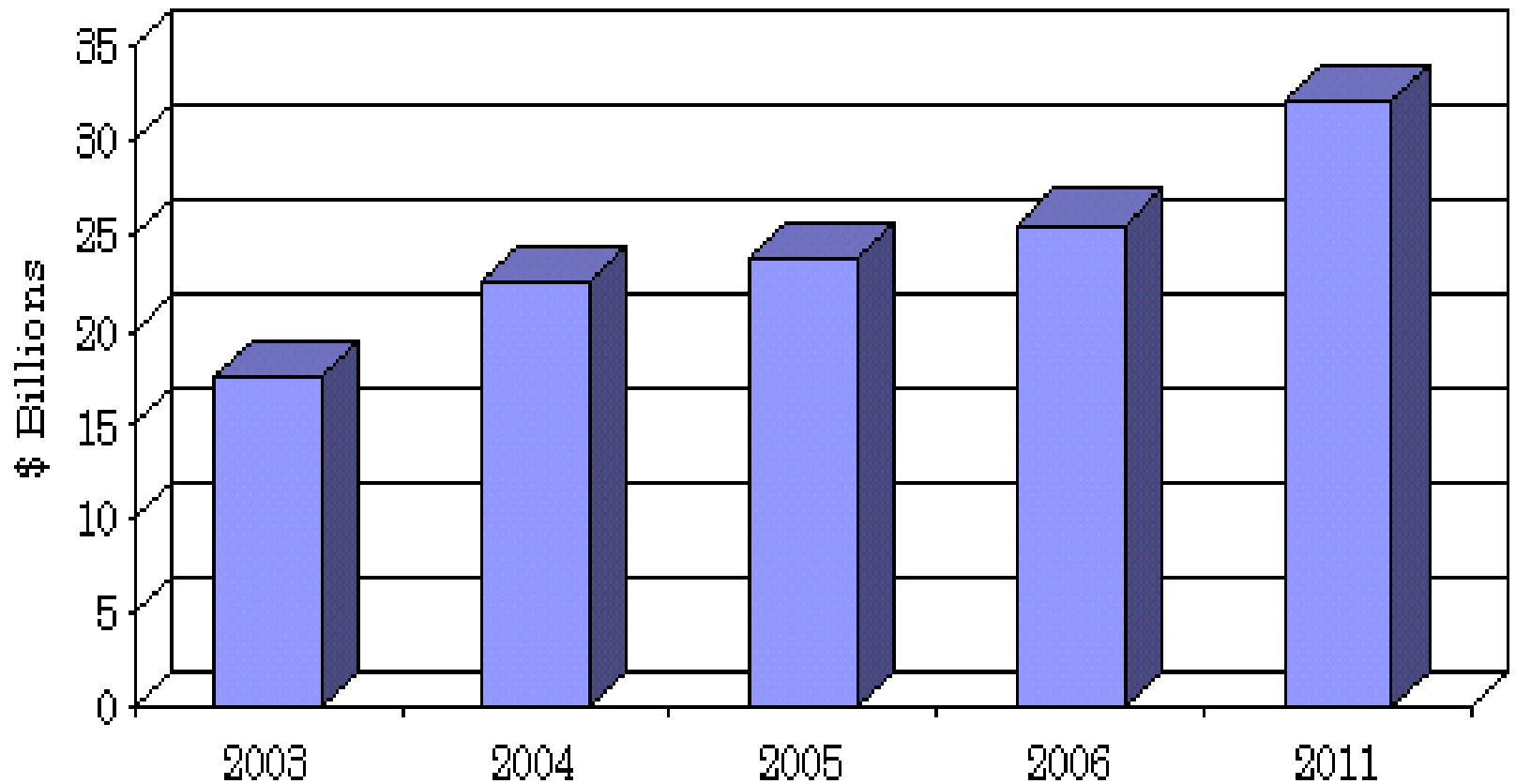


- **Industry** Mainly pharmaceutical and biotech companies
  - The phrase **Big Pharma** is often used to refer to companies with revenue in excess of \$3 billion, and/or **R&D** expenditure in excess of \$500 million. The annual investment in Clinical Trial is abt. \$26B.
- **Federal** National Institutes of Health, the Department of Defense, the Department of Veteran's Affairs
  - It is one of 12 Agencies among Department of Health and Human Services (DHHS) and it is comprised of 27 Institutes and Centers (IC). The primary federal agency for conducting and supporting medical research (\$28B total; 2.9B on clinical trials).
- **Medical Institutions**
- **Foundations**



# Industry Sponsored Clinical Trials

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# Industry Cont.



- Studies published in 2003 report an average pre-tax cost of approximately \$800 million to bring a new drug (i.e. a drug with a New Chemical Entity) to market.
- A study published in 2006 estimates that costs vary from around 500 million to 2,000 million dollars depending on the therapy or the developing firm.
- These figures relate only to new, innovative drugs (drugs with a New Chemical Entity NCE, also called New Active Substance NAS). Each year, worldwide, only about 26 such drugs enter the market (2005: 26, 2004: 24, 2003: 26, 2002: 28). The development cost of the thousands of other drugs are much smaller. The \$800 million quoted include the cost of all drug development which did not result in a new drug. It also includes some 400 million \$ of opportunity costs.
- 10 largest pharmaceutical and biotech companies ranked by market share. (Source: Wikipedia)

# Sponsored Research Forms of Funding



- **Grant** An arrangement under which there is a transfer of funds to the institution to assist in reaching a particular goal for public purpose
- **Contract** A mechanism for the procurement of the specific service that requires the contractor to produce some specific work product or service for the payer, often at a contract (current market) price.
- **Gift** Funds or goods that are given voluntarily to the institution with no reciprocal obligations. Absence of any quid pro quo expectations.



# Types of Trials



- **Pre Clinical Studies (Basic Science / Animal Testing).** If the initial laboratory research is successful, researchers send the data to the Food and Drug Administration (FDA) for approval to continue research and testing in humans.
- **Human Clinical Trial Phases**
  - **Phase I – Safety of a drug or device \* Is it safe?**
  - **Phase II – Efficacy of a drug or device \* Does it work?**
    - 30% or about one-third of experimental drugs successfully complete both Phase I and Phase II studies.
  - **Phase III --- Large Scale Is it really safe/really works?**
    - 70-90% of studies that successfully complete it and request FDA Approval to market the drug
  - **Phase IV - Post Marketing Surveillance / Registries \* What Else Do We Need to Know? Are there rare side effects not yet discovered? Are there risks associated with long-term exposure?**
    - to compare a drug with other drugs already in the market
    - to monitor a drug's long-term effectiveness and impact on a patient's quality of life
    - to determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies. \* Phase IV studies can result in a drug or device being taken off the market or restrictions of use could be placed on the product depending on the findings in the study.



# Clinical Research Environment

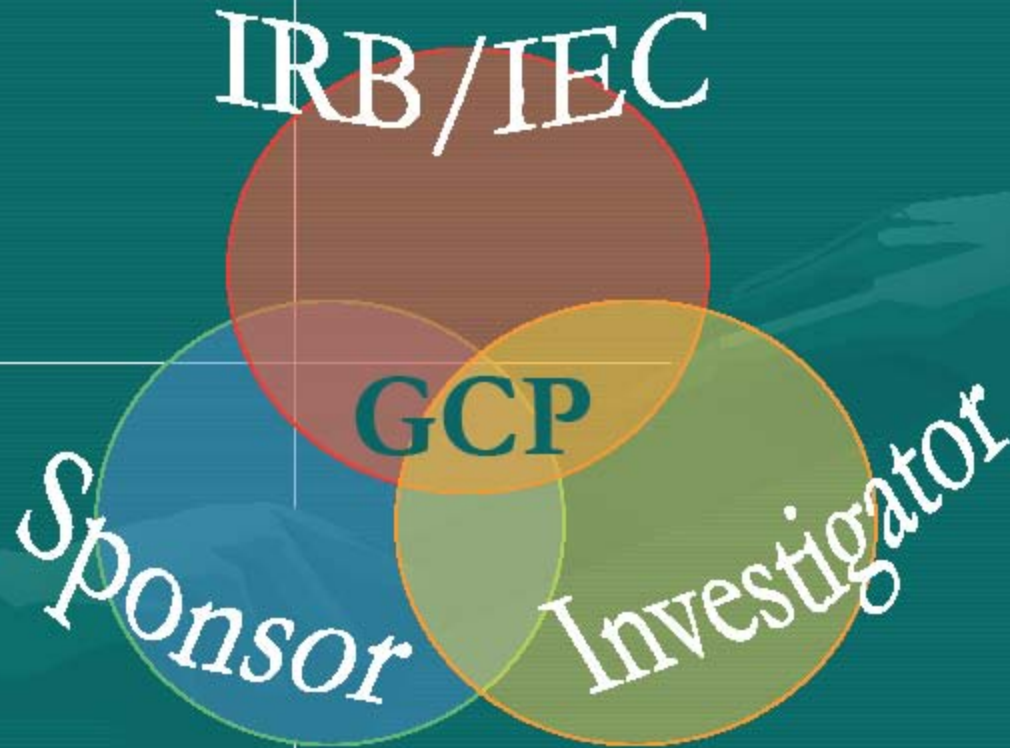
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Intense Regulatory and Compliance Scrutiny

- Legislative (HIPAA) VS. Guidance
- Guidance C.F.R.
  - **ICH GCP** International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Research Practices ICH GCRP E6 To harmonize the regulations and guidelines for drug development
  - **FDA** Food and Drug Administration (GCP 1978)
  - **OHRP** Office of Human Research Protection



# *Responsibilities*





# Before Start Questions

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- Does the protocol provide scientific value?
- Can I recruit subjects?
- Does the budget support the work to be performed?

If you can not answer yes to each of these questions – then decline the trial



# Budget Purpose Site Obligation

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- The budget serves to map out the assumed costs associated with conducting a clinical trial, directly & indirectly
- Typically includes the “estimated” per subject cost as well as the total cost for the completion of the study
- Site Obligations
  - Regulatory compliance
  - Data collection
  - Record retention
  - Adverse event reporting
  - Financial disclosure of key personnel (PI, Co-Inv, CRC)
  - IRB and informed consent
  - HIPAA
  - Inspections



# Tools and Processes for Developing Budgets

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## ■ **Benchmarking Tools**

- Internal databanks
- Industry databases
- Previous negotiations
- Ongoing communication
- Budget template
  - Clearly indicate costs on a unitized basis
  - Have full transparency to financial auditors
  - Easy to understand by clinical/non-clinical (finance) staff
  - Accurately represent work performed



# Site Perspective Golden Rules

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- Analyze protocol
- Study Case Report Form (CRF)
- Know your costs and overhead
- Reconcile schedule of events with budget
- Communicate with the study team
- ***Balance enthusiasm with facts***

# Fair Market Value



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- Fair Market Value Vs. Reasonable Costs

“Payments for research services should be fair market value for legitimate, reasonable, and necessary services.” (HHS OIG, 2003 *Notices*) Promoting Objectivity in Research (CFR, Title 42)

- Definition:

“The fair market value is the price at which the property would change hands between a willing buyer and a willing seller, neither being under any compulsion to buy or to sell and both having reasonable knowledge of relevant facts.” (CFR, Title 26)

\*Even though it is required it is not easy to know what it really is. There is NO simple answer to what the ‘fair market value’ is





# Budget Preparation and Negotiation

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- STEP 1: Preparation Phase
  - Analyze the Protocol / Determine expected enrollment & estimated number of treatment cycles
  
- STEP 2: Development of Budget
  - The budget must total the estimated per subject costs plus all one time allowable fees
  
- STEP 3: Negotiate the Budget and Budget Terms / Clinical Trial Agreement
  
- STEP 4: Monitor expenditures during the trial / Check if they are in synch with budget

# STEP 1

## Budget Background



- **Before you Start**
  - Obtain final protocol
  - Request copy of CRF
  - Be aware of research related standardized pricing
  - Research vs. 'Standard of Care' – Medicare Compensation
    - Myth: Medicare pays for standard of care during research studies
    - Reality: Medicare pays for "routine costs" during "qualifying clinical trials "  
(Reasonable /customary costs and the reimbursement varies across states)
  
- **Consider Personnel / Costs**
  - Research team
    - Availability of Investigators – Also, account for PIs percent of effort spent on dealing with different aspects of the trial
    - Study Coordinator Vs. Research Assistant
  
- **Hidden Costs**
  - Services/items not listed in the protocol: Storage fees, Close out costs and eventually Inspection / Audits ...

# STEP 2

## Develop Overall Study Budget

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The parts of a study budget:

- Upfront/Start Up Costs
- Per-Subject Costs (one single, completed subject)
- Pass through costs (per invoice, WIRB fees, etc.)
- Additional Costs – (event that may or may not occur during the study but has to be in the budget: Screen Failure, Unscheduled Visits, Queries, also SAE if many are expected)



\*Budget Footnotes -Provides clarifications on budgets

# STEP 2: Cont.

## Start Up Costs

- **Start Up Costs**

- Funds that are needed before enrolling the first subject. Separate from the per subject costs and non-refundable regardless if trial enrolls subjects or not:
  - Preparing and submitting regulatory package
    - To the IRB and to the Sponsor
  - Budget preparation and negotiation /Review and execution of CTA
  - Staff training for specific protocol (not cost of doing business)
  - Pre-study meetings
  - Pre-study chart reviews
  - Preparing source document, roster and other forms
  - Unpacking study drug and supplies
  - Ordering any special supplies needed for study (dry ice)
  - Setting up any possible procedures (e.g. chest x-rays, etc.)
  - Screening potential subjects
  - Medicare Coverage Analysis



# STEP 2: Cont.

## Medicare Coverage Analysis

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- Does the study “qualify” for coverage?
    - Categorization is based on CMS guidelines National Coverage Determination (NCD) sect 310.1 definitions of routine care for clinical trials
  - What items and services are “routine costs”?
  - Do Medicare rules allow coverage of specific “routine costs” within a research study?
- 
- The study must enroll patients with diagnosed disease
  - The study must have therapeutic intent
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- What is paid for by the sponsor?
    - Test result that is routinely done may be used for research
    - Insurance can not be billed if already paid by the sponsor
  - Be aware what is promised to be free in informed consent!



# STEP 2: Cont.

## Per Subject Costs

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### Per Subject Costs

- IC Process
- Physical exam (PE)
- Labs
- Types and Number of Procedures
- Dispensing of Drug
- All Clinical Visits
- Unscheduled Visits

List events from analysis of protocol by study visit include:

- Research staff/ Personnel time – salary and fringe (NIH has a cap \$196700)
- Professional, Hospital and Clinic charges (technical and professional fees)

# STEP 2: Cont.

## Points to Remember

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- Budget appropriately for research related cost of tests and procedures
  - Ensure that your budget has sufficient funds to cover the costs of procedures and tests performed for research.
  - The research rates for clinical trials have been regularly updated to reflect BMC current federal rate agreement as well as updated charge list. Detailed information: <http://internal.bmc.org/grants/ClinicalTrials.html> Click on "Hospital Ancillary Rate Sheet" for research related costs. BMC Contact Alexandria Hui at 617-414-5110
  - Laboratory Fees - Mary Willis 617-638-7800
- Subjects' Honoraria (e.g., travel, parking)
- Supplies if needed





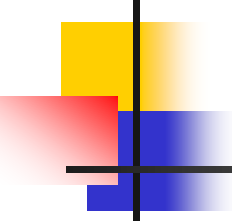
# STEP 2: Cont.

## Labor Cost

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- How many people? How much time?
- Covering labor costs should include the following: The projected amount of time in minutes / hours it takes to complete a task that is required by the protocol and the amount of time it takes to follow up with the task if required
- Costs that are not properly allocated to labor costs will end up using money out of your trial budgets. This could cause your office financial burdens over the length of the trial
- Actual costs are costs that the institution pays monthly to keep the staff member employed if it is FT employee (salary or wage, fringe benefits cost, vacation and sick days)





# STEP 2: Cont.

## Labor Cost

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Helpful hints:

Require that staff complete a form to:

- document and keep track of extra work required out of the usual realm of things such as SAE or
- if extra time is required for collection of new data points from the sponsor that were not requested in the initial protocol

\* This information will help you determine what labor is actually being provided– that was not accounted for in the initial budget and help in addressing this problem as well as determine the next study budget costs more accurately.

\* Remedy for underestimated labor costs: re-negotiate the budget as the sponsor may cover extra costs upon request if there is documentation to support the request.



# STEP 2: Cont.

## Pass Through Costs

### Pass Through (One Time) Costs

- IRB Review Fee
  - BU IRB has one time charge per project only
  - WIRB charges: Review and Continuing Review, Amendment Review etc. (Per WIRB Price list)
- Investigational Drug Pharmacy fee is a flat rate per year charged for the service provided by the Research Pharmacy
- Advertising for Recruitment (e.g. 2\*3 at \$265 Boston Metro (current price w/academic discount))
- Archive document storage fee \$\$ / year \* X years (EUR-15 yrs, CAN 20 yrs...) off site recommended



## STEP 2: Cont. Additional Costs

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- **Additional Costs** event that may or may not occur during the study but has to be in the budget:
  - Screen Failure
  - Unscheduled Visits
  - Queries
  - AEs and SAEs - if many are expected such as in geriatric studies
  - Protocol Amendment(s)

# STEP 2: Cont.

## Indirect Cost

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- All industry sponsored expenses are subject to F&A (Facilities and Administrative Costs) or Indirect Costs – (Overhead)

### **BU Indirect Cost 30%**

- Contact person for BU ORA Emily Campbell at 617-414-5110

\* Industry sponsored clinical trials must use the Indirect rate of 30% at BU. Federally sponsored clinical trials indirect rate is 65%. There are no indirect costs on patient care costs (equipment and subcontracts) in Federally sponsored trial budgets.





## STEP 3: Negotiation

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*Grant me the ability to accept the funding I cannot change, the courage to change the funding I can, and the wisdom to know the difference.*



# STEP 3: Negotiate Payment Terms



## *Payment Dynamic Considerations*

- Initial Payment upon the full execution of CTA
- **Advance Payment:** Not the same as Initial/Start-up Payment. It is designed to cover the cash-flow gap prior to enrollment - usually equal to 1-2 completed subjects or a percentage of total study budget. This payment is a "credit" against future enrollment and it is typically fully refundable to sponsor if tied to enrollment that doesn't occur
- During the course of the trial payment - Criteria or time points for payment usually based on achieving a milestone of enrollment (CRFs)
- Reimbursement for unscheduled visits / events
  - Payments should be prorated based on visits completed up to the point of study discontinuation
- Screen failure (ratio)
- For multi-year trials, consider adding an inflation rate of **3%** to the per-completed-subject cost.
- **Final payment:** Defined as flat amount paid upon completion of requests for information and all close-out activities defined in the Protocol. Holds back approximately 10-20% of the subject fee (w/out stipends. \*\*\* > 20% is not reasonable.

## STEP 3: Negotiation Sponsors' Perspective

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- Conducting successful, compliant trials
  - Meeting recruitment targets
  - Addressing site needs
  - Covering reasonable costs
  - Willing to pay for quality and success
  - Facilitating effective negotiations
- The bottom line is to help people!

# STEP 3: Continued Negotiation Win-Win Outcome



## Critical to successful Win-Win Outcome

- Understanding the Sponsor's goals, issues, priorities
- Build in honesty and transparency
- Trust – Building Using and Sustaining
- Active Listening
- Requires skill in Active Listening / Questioning / In getting your point across and maintaining or improving the relationship
- Understand the impact of culture
- Start with a reasonable budget – to cover cost and 20% margin
- **Provide detailed**, line-item cost for each activity
- Know your bargaining power and importance of study
  - Be aware of intangibles (the Role of PI - expert in the area)
  - List possible solutions, settlements and concessions
  - Plan the preferred agenda and sequence before the meeting
- Never be afraid to ask for more money but document why
- Be prepared to say "no"



## STEP 3: Continued

### Principles of Successful Negotiation



- Our **relationship is ongoing**
- We are **always negotiating Win-Win**
- We must address **underlying needs and interests** Vs. positions
- We are engaged in a **problem solving process**
- The other person always believes they are right – Find out why

# STEP 3: Continued

## The Importance of TRUST

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- **Consequences (Benefits) of High Trust**
  - Trust provides open exchange of ideas and information – critical for accurate tracking and problem solving
  - Trust creates a reservoir of good will
  - People who trust each other provide relevant, comprehensive, accurate, and timely information, contribute realistic data, have less fear and are receptive to influence from other party, therefore, they are more likely to communicate relevant ideas and findings
  - Less or no need to monitor your counterpart's behavior
  - Trusted partners will “go the extra mile”
  - Trust enables “tougher” negotiating positions
  - Define problems more clearly and search more extensively for solutions - Practice collaborative problem solving

*Trust is dependent on the extent commitments are met and honored*



# WIN - WIN Negotiation

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## *Relationship*

Low Trust



High Trust

## *Content*

My Gain/  
Your Loss



Mutual Gain/  
Both Win

## *Process*

Position  
Bargaining



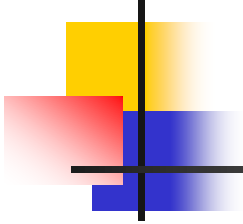
Needs and Interests  
Bargaining



# Summary

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- Make informed decisions on trial participation
- Analyze protocol and consider all costs
- Budget should be reasonable and consistent with 'fair market value' if at all possible
- Create a positive relationship between site and sponsor – establish trust by developing frequent communication, active listening, transparency, follow up with action on all promises



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<u>Item</u>	<u>Unit Cost</u>	<u>Visit 1</u>
Samples (serum, plasma, urine)	35	35
Patient Stipend	25	25
Study Coordinator effort	25.2	151.2
Principal Investigator effort	135.3	101.475
Subtotal	220.5	312.675
Overhead (30%)	66.15	93.8025
Total per patient	286.65	406.4775

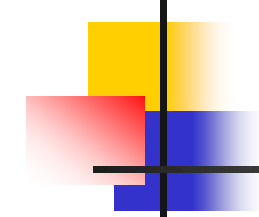


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**EXHIBIT A: FEE STRUCTURE    BUMC**

Diagnosis of Preeclampsia by means of the Elecsys Assays for sFlt-1 and PlGF

<b>Start Up Cost</b>	\$2,500
Miscellaneous expenses (Storage fees, etc)	\$2,500
<b>IRB Fees</b>	\$5,000
<b>30% overhead</b>	\$3,000
Total with 30% Overhead	\$13,000.00



	\$100	\$200	\$200	\$75	\$225	\$45	\$45	\$60		\$25		30%		15%	
	Informed Consent, Demographics and Baseline Characteristics	Medical / Surgical, Gynecological, Menstrual and Medication History	Physical Exam including Vital signs and Weight <sup>1</sup>	Gynecological Exam including Breast Palpation <sup>2</sup> and Pap Smear <sup>3</sup>	Transvaginal Ultrasound	One Random Serum Sample for LGN/SHBG	Safety Lab Draw Fees, Collection and Sample Processing	Coordinator Fee	Investigator Fee <sup>4</sup>	Subject Honorarium	SubTotal	Overhead	Total	Holdback	Amount <sup>5</sup>
- Screening	\$100	\$200	\$200	\$100	\$225		\$45	\$100	\$100	\$100	\$1,170	\$351	\$1,521	\$228	\$1,293
2 - Baseline				\$75	\$225			\$75	\$150	\$50	\$575	\$173	\$748	\$112	\$635
3 - Month 3				\$75	\$225			\$75	\$100	\$50	\$525	\$158	\$683	\$102	\$580
4 - Month 6				\$75	\$225			\$75	\$100	\$50	\$525	\$158	\$683	\$102	\$580
5 - Month 9				\$75	\$225			\$75	\$100	\$50	\$525	\$158	\$683	\$102	\$580
6 - Month 12			\$25	\$75	\$225			\$75	\$100	\$50	\$550	\$165	\$715	\$107	\$608
7 - Month 18				\$75	\$225			\$75	\$100	\$50	\$525	\$158	\$683	\$102	\$580
8 - Month 24			\$25	\$75	\$225			\$75	\$100	\$50	\$550	\$165	\$715	\$107	\$608
9 - Month 30				\$75	\$225			\$75	\$100	\$50	\$525	\$158	\$683	\$102	\$580
10 - Month 36			\$200	\$100	\$225		\$45	\$100	\$150	\$50	\$870	\$261	\$1,131	\$170	\$961
11 - PK Sample						\$45					\$45	\$14	\$59	\$9	\$50
										<b>Total</b>	<b>\$6,385</b>	<b>\$1,916</b>	<b>\$8,301</b>	<b>\$1,245</b>	<b>\$7,055</b>



# Sample Budget # 2

## NOTES

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### General Notes:

- Start-up costs will equal 50% of one completed patient costs as determined above and will be paid with the Advance Payment.
- Screen failure and unscheduled Visits will be prorated based on the costs detailed in this budget.
- IRB Fees will be paid as per invoice and will not be included in the general budget.
- Pharmacy Fee - An initial pharmacy fee of \$2,080 will be paid upon execution of Agreement. Any additional pharmacy fees of \$2,080 will be paid upon receipt on invoice by Sponsor.
- Advertising - Sponsor will reimburse Institution for any advertising fees upon receipt of invoice.
- Fifteen % holdback will be paid when the patient completes the study.
  
- The above budget is calculated assuming that a central lab is being used. Any STAT labs will be paid as per invoice.
- A visit is completed once the CRA has monitored it and corrections have been completed and it is recorded in the IVRS.
- All amounts in US dollars and rounded to the nearest full dollar amount.





# Sample Budget # 3

<b>Clinical Procedures</b>				
a.	Complete Physical w/History			
b.	Brief Physical Exam (incl. Vital Signs and Body Weight)			
c.	Vital Signs and Body Weight			
d.	Gynecological examination			
e.	3-month follow-up call			
<b>Clinical Laboratory Tests</b>				
	<i>(Central Lab testing costs paid directly by B</i>			
a.	Urine Pregnancy Test (Local Lab)			
b.	Safety Laboratory (Central Lab)			
c.	Specimen collection/handling (Central & Loc			
<b>Patient Reimbursement and Recruitment Costs</b>				
a.	Patient Stipend			
<b>Administrative Costs</b>				
a.	Study Coordinator \ Research Nurse			
b.	Data Entry Person for CRF			
c.	Pharmacy Admin (Storage & Dispensing)			
d.	Diary Cards Dispensed/Checked			

**Direct Costs\***

a.	IRB Pass-Through Fees up to \$3,000/Site <sup>a</sup>								3,000.00	
b.	Administrative Fees @ \$2,000/Site <sup>b</sup>								2,000.00	
c.	Pharmacy Set-Up Fees up to \$1,000/Site <sup>c</sup>								1,000.00	
d.	Screening Failure Costs @ \$981/pt at a ratio of 1 screened : 6 enrolled <sup>d</sup> (Maximum of 6 screen failure patients)								#REF!	
e.	Advertising Fees @ \$3,000/Site <sup>e</sup>								3,000.00	
									<b>Total Direct Costs:</b>	#REF!

**\*Budget Notes:**

*Expenses beyond the amounts specified in the budget are the responsibility of the site unless otherwise agreed to in writing prior to incurring such costs. Sponsor reserves the right to require adequate supporting detail for verification of costs to be reimbursed.*

- a. Reimbursement for IRB pass-through fees will be issued on presentation of an invoice to Sponsor documenting the pass-through cost actually paid.
- b. Reimbursement for Administrative Fees will be paid and released with the Initial Payment.
- c. Pharmacy Set-Up Fees will be issued on presentation of an invoice to Sponsor documenting the pass-through cost actually paid, this is an annual fee.
- d. Screening Failure Cost allowances are pro-rated on the following basis:  
 \$981 per patient for screening activities at a ratio of 1 patient screened to 6 patients enrolled, for a total allowance of \$5,886/site. Allowance provides for a maximum total of 6 screen failure patients.  
 Do not submit invoices; Payments will be based on periodic review of screening data as entered into the EDC system and verified by Site Monitor.
- e. Reimbursement for Advertising Fees will be issued on presentation of an invoice to Sponsor documenting the cost actually paid, up to the \$3,000 site limit.



## STEP 4: Cont.

### During the Trial

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- Closely monitor earned income and actual trial expenditures
- Be aware of patient enrollment and the timeliness of case reporting
- Make adjustments to the project expenses if/when patient enrollments / expenditures vary significantly from the budget, i.e. reduce expenses, if supporting revenue does not develop

# Intersection of Budgets and Compliance

From the Office of Inspector General

- Inappropriate clinical trial billing (special considerations for Medicare billing)
- Double Dipping
- Improper waiver of co-payments or deductibles
- Residual funding
- Kick-backs
- Recruitment fees
- False Claims





# Contact Information at BUMC

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- Alexandria Hui at 617-414-5110 Procedure Costs - BMC Contact  
<http://internal.bmc.org/grants/ClinicalTrials.html>  
Click on "Hospital Ancillary Rate Sheet" for research related costs.
- HyeSeon Hong 617-638-6779 Research Pharmacy
- Mary Willis 617-638-7800 Research Laboratory
- Emily Campbell at 617-414-5110 - Contact person for BU ORA