Developing and Maintaining A Profitable Research Center: Secrets of the Trade

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Learning Objectives

- Describe the infrastructure needed to ensure the profitability of the clinical research center
- Indentify effective methods of budget and contract negotiation/ review
- Understand how to select and train your study coordinator and other key clinical trial staff

The Contract and Budget Proposal: Initial Review

- Review the contract and budget for the overall offer
- Check Dun & Bradstreet Business Credit Report for new sponsor/CRO
- Send the contract to your research contract attorney for language review, indemnification, payment terms, study termination clause, hidden obligations and possible hidden financial cost

The Contract Proposal

- Identifies the Principal Investigator (PI), research center and sponsor/CRO
- Details the “scope of work” and “performance of study” and describes all aspects of the sponsor/CRO, PI and research center responsibilities

The Contract Proposal: Terms of Payment

- Terms of payment: data entry and case book completion, & monitoring visit
- Timelines and milestone payments (30, 45, 60 days)
- Terms of pro-rated payment for early terminated subjects and subjects who were consented but did not meet the inclusion/exclusion criteria
- End of study payment hold (10%)

The Contract Proposal

- Regulatory inspections and audits
- Publication rights
- Confidentiality
- Privacy and HIPPA
- Publicity and use of names
- Intellectual property rights
- Independent contractor relationship (CRO)
- Notice of debarment and disqualification

The Contract Proposal: Liability Insurance

♦ Liability insurance: **"check your research insurance coverage to the contract"**

"….comprehensive general liability insurance with liability limits of not less than $2,000,000 per occurrence and $4,000,000 in the aggregate; professional liability insurance including coverage for medical malpractice for the participation in and conducting of human clinical trials with liability limits of not less than $2,000,000 per occurrence and $4,000,000 in the aggregate…."

The Contract Proposal: Liability Insurance

♦….. "Institution and Principal Investigator shall maintain such coverage for the duration of the Agreement and for three **(3) years thereafter"….**

♦ Equipment liability supplied by the sponsor and "hidden purchase fee of equipment"

The Contract Proposal: Representation & Warranties

The Institution and Principal Investigator each represent and warrant that he/she:

"… will conduct the Study in strict accordance with the Protocol and this Agreement…"

Take the language out of the CTA for Strict/ complete

"**Strict"** adherence to the protocol

"**Complete"** adherence to the protocol

Clinical Trial Agreement (CTA) First Paragraph

- This Agreement is entered into by and between Dr Study, MD with a place of business at 8444 Winton Road, Cincinnati, Ohio 45231, hereinafter referred to as the "Institution," and Research Pharmaceuticals Corporation, a corporation with its principal office and place of business at 123 Fun City hereinafter referred to as "Pharmaceuticals," the Institution and Pharmaceuticals each being a "Party" and hereinafter collectively referred to as the "Parties."

CTA: "Party" (First Paragraph)

This Agreement is entered into by and between **Bernstein Clinical Research Center, LLC** **(do not use the PI name)** with a place of business at 8444 Winton Road, Cincinnati, Ohio 45231, hereinafter referred to as the "Institution," and Research Pharmaceuticals Corporation, a corporation with its principal office and place of business at 123 Fun City hereinafter referred to as "Pharmaceuticals," the Institution and Pharmaceuticals each being a "Party" and hereinafter collectively referred to as the "Parties."

Indemnification

Indemnification is making a party (indemnitee) "whole" by paying a loss suffered as a result of the indemnitor's actions or omissions.

Indemnification

- Is an agreement between two parties not to hold one of them liable for future **legal action or fines**
- Indemnification contracts for research **MUST** only work in one direction and not use reciprocal language

Reciprocal Indemnification: Void Malpractice

The research site exponentially increases Its potential liability if the language in the indemnification clause is:

- Mutual-indemnification
- Reciprocal-indemnification
- Cross–indemnification

Indemnification

Dr. Study, MD will indemnify, hold harmless and defend SPONSOR and its AFFILIATES, AGENTS, officers, directors, shareholders, and employees from and against any and all claims, liabilities, losses, expenses (including, without limitation, fines, forfeitures, reasonable attorneys' fees, disbursements and administrative or court costs), penalties or damages (collectively, the "LIABILITIES") from any third party claim arising from a breach of Dr. Study's privacy representations and warranties provided in Article 3.

Contract: Indemnification/ Liability

Sponsor agrees to indemnify, defend and hold harmless the Site, its employees, trustees, directors, owners, officers, sub-investigators, representatives or agents, and Investigator (the "Site Indemnitees") against any third party liability, loss, damage or expense (including reasonable attorneys' fees and expenses of litigation)

Contract: Indemnification/ Liability

….("Losses") resulting from any third party claims, actions or proceedings seeking compensation for bodily injury or death of any research Study Subject enrolled in the Study, to the extent that such injury or death was directly caused by the Study Drug or placebo provided by Sponsor and used in compliance with this Agreement, the Protocol, and the Informed Consent

Error or Omission (E & O) Insurance

- Professional indemnity liability insurance
- Helps protect professionals and companies from bearing the full cost of defending against a **negligence** claim made by a patient

Negligence involves harm caused by ***carelessness*, not intentional harm**

Contract: Indemnification/ Liability Language

Deviations from the protocol that may arise out of patient safety issues do not constitute a breach, negligence or willful misconduct provided that the indemnitee promptly provides notice to sponsor of any such deviations.

Budget Offer, Assessment and Negotiations

Budget Offer and Assessment

- The budget is usually sent with the CTA
- Budget outlines each visit payment
- "States" the **total** per patient payment or total cumulative study payment for all randomized subjects

Budget Offer and Assessment

- # subjects randomized
- Screen failure payment ratio
- Repeat screen failure allowance
- Unscheduled visit & early termination visit
- Subject stipend: reimbursement for patient time and travel

Budget Offer and Assessment

- Start-up fees
- Percent over head charge **(24%)**
- IRB and regulatory document budget
- Bonus payment for quick and timely document completion
- Data base search and payment (invoiced)

Budget Offer and Assessment

- Advertising budget
- Reimbursement for medication/ equipment required by the protocol: **(cost of medication) (rescue medication, Epi-pens, spacers)**
- Archive fee for document storage
- Directions and payment guidelines for invoices

The Budget Proposal

- Review the protocol for level of **protocol difficulty**, recruitment/ randomization, procedures and test
- Determine recruitment strategy and need to advertise
- Assess coordinator time and staffing requirements (hours, overtime and weekends)

The Budget Proposal

Prepare an excel spread sheet to **"cost out"** the study and compare "your" budget to the "sponsor's" proposed budget offer.

Budget Proposal from Schedule of Events

PROCEDURE	VISIT 1 (screening)	VISIT 2	VISIT 3	VISIT 4	VISIT 5 (ET)	TOTAL
Informed Consent	x					$0.00
Inclusion/Exclusion	x	x	x			$0.00
Medical/Disease History	x					$0.00
Concomitant Medication Review	x	x	x	x	x	$0.00
Physical Exam	x	x	X	x	x	$0.00
Vital Signs	x	x	8	8	8	$0.00
PFT	x	x	14 PFT's	14 PFT's	14 PFT's	$0.00
Reversibility	x					$0.00
Lab & PK samples	x	x	6	6	6	$0.00
Electrocardiogram	x		3	3	3	$0.00
Diary dispense/collect and review		x	x	x	x	$0.00
Review Medication Compliance		x	x	x	x	$0.00
AE/SAE assessment		x	x	x	x	$0.00
eNO measurement	x	x	x	x	x	$0.00
Investigator fee	x	x	x	x	x	$0.00
Coordinator Fee	x	x	x	x	x	$0.00
Subtotal	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Overhead 24%	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Stipend (patient)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Visit Total	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00

Negotiate the New Budget Proposal

- Complete the excel spreadsheet and email the new proposed budget to sponsor/CRO
- "Sell your site" in the email during the negotiations and revised budget submission
- Outline potential protocol challenges to substantiate "your" revised budget proposal
- Review the counter-offer from the sponsor/CRO or attorney representative

Negotiate the New Budget Proposal

Call the sponsor/CRO and discuss the new proposed budget and try to determine the **highest final offer** from the sponsor/CRO.

Sponsor/CRO Budget Counter-Offer

- Compare new proposed sponsor counter budget offer with "your" calculated budget
- Determine the profit
- Recalculate budget if sponsor/CRO budget is not accepted and continue to negotiate.

Sponsor/CRO Budget Counter-Offer

- Review the final contract and confirm the contract changes and final budget agreement before signing **(review contract margins)**

Send final version to attorney for final review and approval

The Clinical Research Team

- Principal investigator (PI) with experience in the disease study (must provide study oversight)
- Sub-investigators
- Clinical Research Coordinators

(detailed oriented, organized, honest, able to work independently, open minded, professional with a strong work ethic)

What Does the Sponsor/CRO Look For in a Clinical Research Center?

♦Principal Investigator's training, expertise & experience with clinical research

♦ Have properly trained and experienced clinical research Investigators & Coordinators knowledgeable in GCP/ICH guidelines

Certified Investigators and Coordinators

1. Association of Clinical Research Professionals (ACRP)
ACRP http://www.acrpnet.org/

2. Society of Clinical Research Associates (SoCRA)
http://www.socra.org/html/certific.htm

What does the Sponsor/CRO Look For in a Clinical Research Center?

- Experience with protocol specific patient population (data base)
- Track record for patient recruitment and randomization
  Reach Enrollment Goals
  Qualified, Compliant/Adherent patients
- Facility, equipment & infrastructure

What Does the Sponsor/CRO Look For in a Clinical Research Center?

- Standard Operating Procedures (SOP's) should reflect GCP/ICH guidelines and office procedures
- Complete the site feasibility questionnaire: accurately & completely (spelling & grammar)
  Be honest – do not accept a trial that your site cannot complete.
- Prompt turn around of regulatory documents

What does the Sponsor/CRO Look For in a Clinical Research Center?

- ♦ Prior FDA, sponsor, IRB audits and reports (FDA 483)
- ♦ Emergency room and hospital locations
- ♦ Site tour: friendly, knowledgeable & experienced CRC and PI to describe the research center & facility infrastructure

Summary: Profitable Research

- ■ Successfully negotiate the contract with a **profitable budget**
- ■ PI with clinical trial oversight
- ■ Talented and dedicated Clinical Research Coordinators
- ■ Proper facility, equipment & infrastructure
- ■ **Complete the enrollment and randomization according to the contract**. **(Meet study enrollment)**
- ■ Adhere to the protocol and follow ICH/GCP guidelines

Resources

- FDA Homepage
  http://www.fda.gov
- Office of Health Affairs
  http://www.fda.gov/oc/oha
- FDA Information Sheets
  http://www.fda.gov/oc/ohrt/irbs/
- Information for Health Professionals
  http://www.fda.gov/oc/oha/

Resources

- Center for Drug Evaluation & Research (CDER)
  http://www.fda.gov/CDER/
- International Council on Harmonization
  http://www.fda.gov/eder/guidance.html#InternationalonHarmonization

Resources

- National Human Research Protections
  www.ohrp.psophs.dhhs.gov
- Good Clinical Practices Monthly Bulletin Editor: (202) 739-9765, CLIN@thompson.com, www.thompson.com/alert

Developing and Maintaining A Profitable Research Center

Warner W. Carr, MD

Outline

- Personnel
- Coordinators
- Mentoring systems
- Investigator requirements
- How to get a study
- Marketing your site
- How to get a CRO / Sponsor to visit

Outline

- Site feasibility surveys
- Anatomy of getting the study
- Anatomy of doing the study
- Lost term obligations
- Survive an audit

Facilty: The Basics

- Adequate space for patients, monitors, coordinators and equipment
- Locking storage
  - Study drugs
  - Archiving study charts

Facility: The Basics

- Lab
  - Refrigeration -20 degree freezer
  - Centrifuge
  - Storage
  - CLIA waiver
  - IATA Certified staff: needed for shipping specimens every 2 years

Facility: The Basics

- 0_2, crash cart
- BP cuff, thermometers, scare, and stadiometer
- ECG machine
- Spirometer
- FeNO device
- All equipment for research must be calibrated on regular basis
  - daily to yearly

Facility: The Basics

Documentation is the key:

- Temperature logs:
  - Min and max
- All communications with:
  - Volunteers
  - Monitors
  - CRO
  - Sponsor

SOP's Are a Must

- SOP's
  - Everything you do and all your staff needs a SOP and description
  - These need to be reviewed by all study staff on a regular basis and updated as needed
  - Key SOP's are key areas of risk:
    - Delegation of responsibility
    - Consenting
    - Study visits
    - Reviewing study labs, etc.

Personnel

- Investigator
  - PI and Sub-I
- Regulatory
- Contract and budget
- Coordinator
- Recruiters

The PI

- Responsible for conduct of all aspects of the study
  - Signs the 1572
  - Delegates all aspects of the study to qualified staff or does it themselves
  - Ensures proper consent and conduct of study in appropriate volunteer population
- Typically an MD or DO
- Familiar with disease or drug under study
- Expert in GCP, ICH
- Promptly reports all AE's and SAE's
- Conducts the protocol as written and approved by IRB / Regulatory authority

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FDA form 1572

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

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FDA form 1572

- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

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The Sub-I

- Knowledge of the disease or drug being studied
- Typically a MD, DO, PA, NP
- Expert in GCP, ICH
- Ensures AE, SAE's reported promptly and PI closely informed

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Manager: Contracts / Regulatory

- Completes feasibility questionnaire in a honest way
- Negotiates contracts and budgets
- Ensures all IRB submissions are completed appropriately
- Ensures 1572 completed and maintains up-to-date regulatory documents
- Coordinates pre-site and site visits
- Maintains and updates all SOP's
- Responsible for all coordinators

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Coordinator

- NOT an entry level job
- Minimum 6-12 months of training involved
- Multi-task, detail oriented person
- Must have some medical knowledge
- GCP and ICH expert
- Ability to understand and follow the protocol
- Must be:
  - Proficient in all equipment
  - Proficient in phlebotomy
- Completes all study specific training, electronic data capture, and study queries

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Anatomy of Clinical Trials

Initial contact	Complete Feasibility questionnaire	Initial visit to site	budget negotiations
• PI maintains relationships with pharma and CRO's	• This is an honest response to questions. Lie and you will likely not do any studies.	• CRO or Sponsor representative will visit site and evaluate if you are capable of conducting study. • Are you and expert • Do you have the population • Are you and your staff qualified and competent	• This is an ongoing process. The sooner you can get a CDA, a copy of the protocol, and start the better off you will be. • CRO will always "low ball you" • Fight for your overhead • A lot of work is done early on that is not paid for.

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Anatomy of Clinical Trials (con't)

Investigator meeting

- PI or Sub-I plus coordinator must attend
- Typically not a paid meeting
- Review all aspects of study and provide feedback to sponsor
- Study specific GCP training
- Great place to network
- Make sure you know the study

Final Budget

- You put in a lot of work before the final budget many of which is not compensated
- Pre-screen patients
- File IRB and regulatory documents
- Several meetings with sponsor and CRO

Site visit

- CRO or Sponsor representative will visit site and ensure you understand all aspects of study and any amendments
- Ensure that you understand all of you responsibilities

Start screening

- You should have a database of all your research and clinic patients
- Have affective marketing
- Ensure all source documents are available and completed
- Ensure

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Anatomy of Clinical Trials (con't)

Conduct the study per protocol

- Follow the protocol. Period
- Deviations must be reported and documented
- All consents must be appropriate
- Ensure all study visits are completed
- Follow all GCP, ICH, HIPPA guidelines
- Maintain and store all records, and study related materials.

Monitoring visits

- Have a good place for your monitor to site and review all study related materials.
- Correct any deficiencies per protocol
- Update SOP's a needed

Close out visit

- Ensure all patients have completed
- Ensure all documents and data queries have been addressed
- Sign all forms and review all electronic data
- Understand your responsibilities ongoing after completion of the study.

Long term storage

- Include these costs in your budget
- Keep records 2-12 years or longer depending on the drug or drug product
- Notify sponsor or any changes
- Notify sponsor of any audits

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Survive an Audit

- Follow the protocol
- Complete all forms at the time of the visit
- Prepare for and respond immediately to your monitoring visits
- Do honest work
- Be open and have full disclosure
- Mistakes happen
  - Learn from them

GET YOUR PRACTICE IN TUNE AT THE PRACTICE MANAGEMENT WORKSHOP

Bottom Line

- Research is not a big money maker
- Research is hard
- Make sure you know what you are doing
- Get certified through ACRP, do the NIH course for a brief refresher
- Ensure your coordinators are certified
- Review everything and document everything
- Learn and understand the entire clinical development process and the CFR that govern them

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Questions

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