

...advancing women's health through research

Clinical Trials Unit Process Manual

Presentation to TECT Fellows

February 2, 2011





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Center for Women's Health Research Clinical Trials Unit

...supporting industry sponsored and initiated clinical trials across all areas of women's health

November 17, 2010

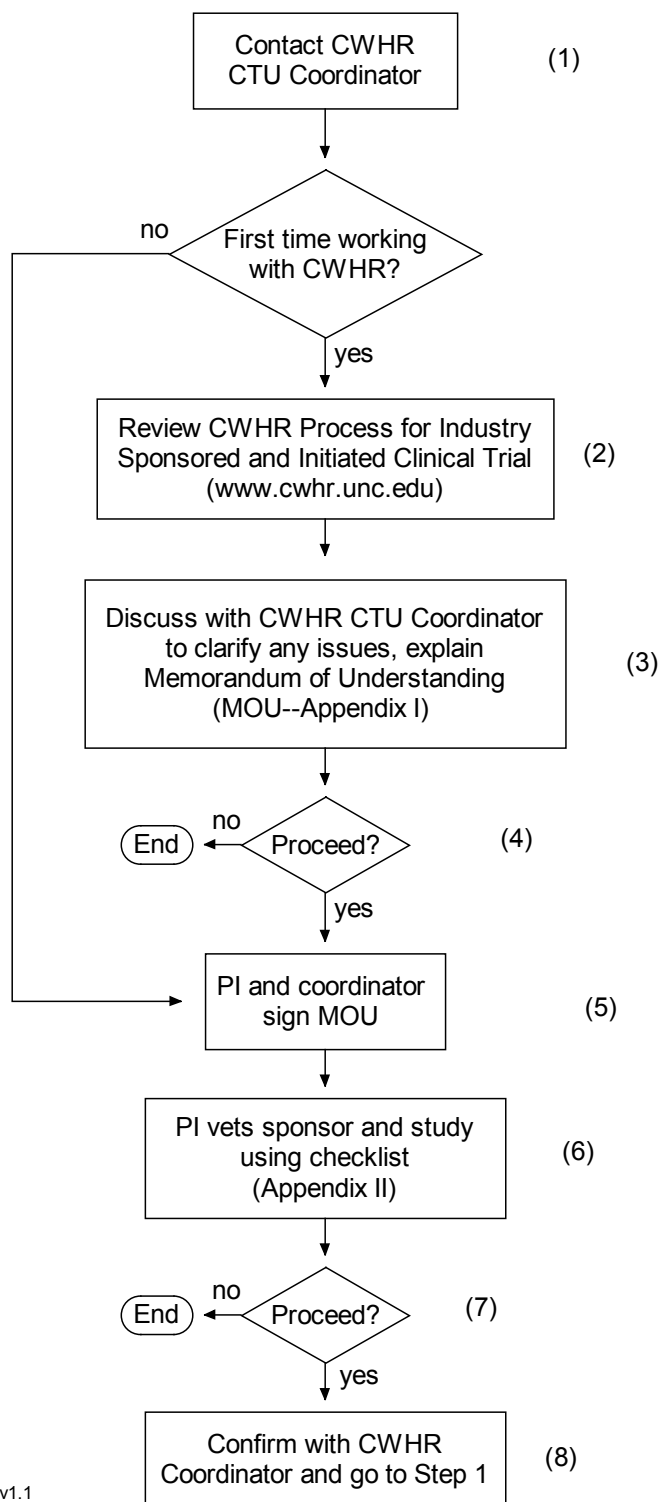
Dear Principal Investigator

The Center for Women's Health Research Clinical Trials Unit (CTU) is pleased to provide this manual describing our processes for starting industry sponsored and initiated clinical trials. We recognize that conducting trials of this nature is a business proposition; to that end we have established the CTU as a business unit of the Center for Women's Health Research. We intend to operate it as a business that must at least break even, and hopefully generate some surplus funds, which we propose will benefit both you and us. We have attempted to create a clear, easy-to-follow process to define who needs to do what, the role of the Office of Clinical Trials (OCT), and how we can/will assist you in carrying out the work involved in starting and conducting industry sponsored and initiated clinical trials. We welcome your feedback on the process as described in this manual and look forward to working with you.

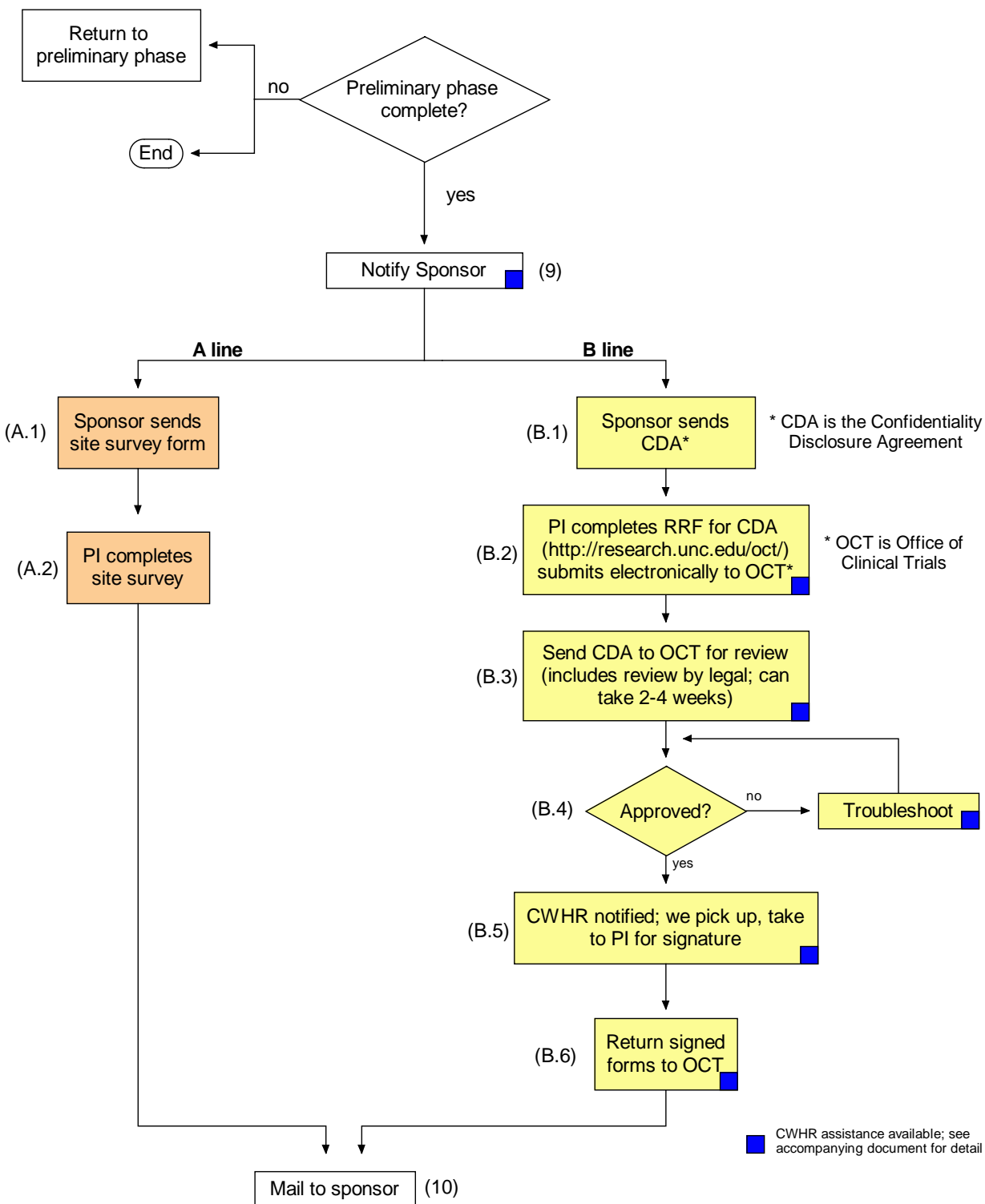
The current CWHR CTU Coordinator is Kim Andringa, PhD; please contact her at Kim_Andringa@unc.edu with comments, additional information, or to initiate a trial through the Center.

CWHR Clinical Trials Unit

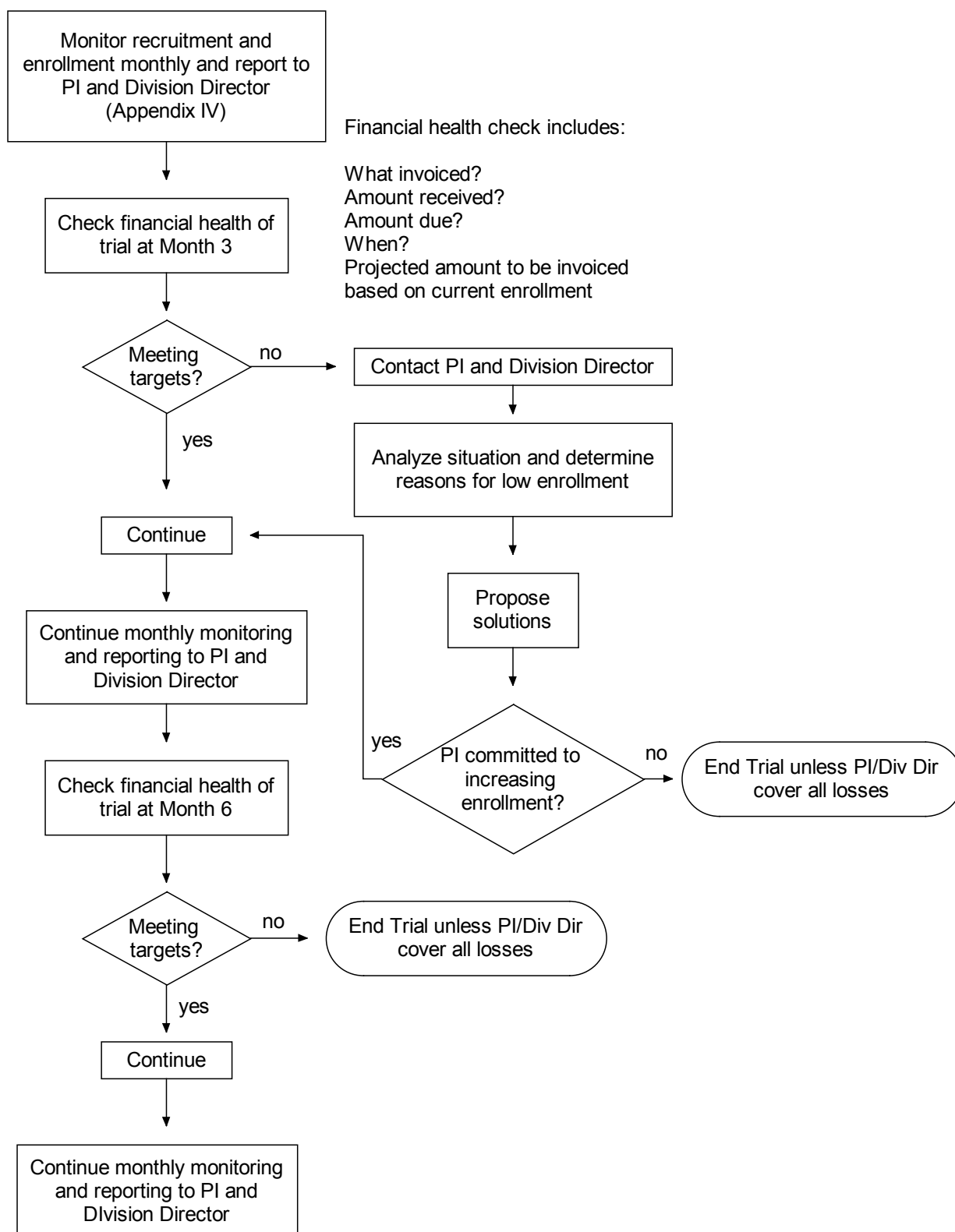
Preliminary phase of starting an Industry Sponsored and Initiated Clinical Trial through the CWHR Clinical Trials Unit



INDUSTRY SPONSORED AND INITIATED CLINICAL TRIALS Step 1



Monitoring Financial Health of Trials



NARRATIVE FOR INDUSTRY SPONSORED AND INITIATED CLINICAL TRIALS CWHR Clinical Trials Unit

PRELIMINARY PHASE

If you wish to pursue a clinical trial through the CWHR Clinical Trials Unit, please contact the CTU Coordinator (1). CWHR has a clinical trials unit Coordinator, a Finance Administrator, Administrative Assistant, and possibly a Research Assistant (depending on current workloads) to work on the tasks that make up this process; the numbers below correspond to the numbers on the flow charts on the preceding pages. Of course, a PI is welcome to do any given part of the process him or herself, or have someone in their office complete the task. However, if CWHR is to be the funds administrator, please notify us immediately so we can work with you to ensure maximum probability of a successful trial.

Once you have notified us, if this is your first time working with us, please go to our website at www.cwhr.unc.edu and review the Clinical Trials Process documents (2). CWHR's CTU Coordinator will contact you for a brief meeting to review the process with you, answer any questions, clarify who is doing what and when they will do it, and explain our Memorandum of Understanding (3—[Appendix I](#)). Assuming you decide to move ahead with pursuing the trial (4), the coordinator will ask for you to sign the MOU (5). If you have worked with the Center using these processes before, you can simply sign a new MOU and move forward.

After the formal agreement is in place, we strongly advise you, your Division Director, and others from your department/division to carefully examine the sponsor and the study (6) and have at least one discussion prior to moving forward. The checklist in [Appendix II](#) should be used as a guide to the discussions with your colleagues (first set of questions) and with a representative from the sponsor organization (second set of questions/statements). Key issues to examine/discuss include:

- ❖ Is recruitment already open? If so, you should not join unless the sponsor is willing to hold a set number of slots for participants from your site. If the window is not currently open, how long before it opens, and how long does the sponsor anticipate it being open? Keep in mind that our internal approval process is quite lengthy (can be as long as six months) and the recruitment window could close before you even get approval.
- ❖ Is this a capitated study with financial success dependent on your ability to recruit and enroll patients? And if so, does UNC have an adequate patient population to support the study?
- ❖ Does the study seem to have significant clinical importance, at least from what you can see presently?
- ❖ Is it a Pharma Company or a Contract Research Organization (CRO) you would be dealing with? Either type of organization will attempt to minimize the budget but CROs in particular have a vested interest in keeping their costs down to maximize their profits since they are the ones dealing directly with the Pharma Company.
- ❖ Has anyone else in your department worked with the Pharma Company or CRO with whom you are proposing to work? If so, ask about the following:
 - What was your overall experience in working with them?
 - How did the budget negotiation process go?
 - How quickly did they pay once they were invoiced?
 - If the sponsor company ended the study early, were they fair to you (and the university) in their settlement?

This last question is particularly important, as we have had at least one company that abruptly ended a study and we lost about \$30,000 on it; they covered none of the loss. **It is extremely important that you know your potential partner.** If no one here has worked with them before, perhaps you could ask other investigators from outside UNC if they have any experience with them; you may also want to ask for names of other organizations with whom they have worked as references. If you cannot find anyone who has worked with them, please proceed with caution. If there are others who should be involved in the decision to pursue a clinical trial (e.g. CWHR, Division Chief, Department Chair, colleagues), contact them as you are making the decision about whether or not to proceed.

The set of questions/statements that should be discussed with the sponsor (see [Appendix II](#)) represents the Center's beginning point for negotiation of a budget; if the sponsor does not understand or agree with these, the Center is not willing to support the trial.

Assuming you have now decided to pursue a given trial (7), please confirm with the CWHR Coordinator and proceed to Step 1 (8).

STEP 1

Notify the sponsor of your interest. They will get some information from you and from this point there are two lines of the process that happen simultaneously (see flow chart)—the A line (tan) for the site survey and the B line (yellow) for the CDA. On the B line, (B.1) the sponsor will send you a confidentiality agreement (CDA) for signature; **you are not**

authorized to sign the CDA on behalf of the university (see PI Overall Responsibilities OSR Policy 200.4 and Departmental Administrator Responsibilities OSR Policy 200.5 at http://unc.edu/n/CCM1_030787). The CDA must be reviewed and approved by the Office of Clinical Trials (OCT <http://research.unc.edu/oct/>) before you can sign it. Complete the Review Request Form for CDAs (RRF-CDA) which can be found on the OCT website and submit it electronically (B.2). Send the CDA (B.3), electronically or delivered in hard copy, to the OCT (1109A Bioinformatics Building, 130 Mason Farm Road, CB 1651, Chapel Hill, NC 27599-1651; phone 843-2698 Fax 843-2399). OCT will review it (includes a review by Legal), and troubleshoot any areas that they disagree with (B.4). Once approved, OCT will notify CWHR (B.5). We will pick up the approved CDA and bring it to you for your signature. Once you sign, (B.6) we return the document to OCT and (10) they will send it to the sponsor. **Please allow 2 to 4 weeks for completion of the B line of the process.**

On the A line, in parallel with the CDA approval, the sponsor will send you a site survey (A.1) which you need to complete (A.2) and return directly to the sponsor (10).

STEP 2

Once the sponsor has the site survey and the signed CDA, (11) they will send you a packet of regulatory documents; the packet will contain the protocol, a draft contract agreement, draft consent form, and possibly other regulatory forms or documents. From this point, there are three lines to the process; the A line (tan) for the IRB, the B line (blue/yellow) for assessing feasibility, conducting the protocol review and budgeting, and the C line (green) for contract negotiations.

Your initial actions should be focused on tasks in the blue components of the B line, starting at (B.7). The PI and his/her Division Director (and others as appropriate) assess the value of the protocol and its feasibility. One component of the feasibility evaluation should be consideration of the personnel needs associated with the trial such as number of people, qualifications, shifts that must be covered, can you recruit the required number of participants in the time allotted, etc. The CTU Coordinator or designee will be available to discuss staffing and potential time frames. See [Appendix III](#) for a list of other questions/areas you should consider; you can either use this form, or use your own process for this step. Following discussions, the PI and others involved (B.8) make a decision on whether or not to proceed. If the decision is not to move ahead (B.8.1), the process ends here. If the decision is to move forward and CWHR is the fund administrator, your Division Director will be formally notified of the decision to proceed (B.8.2).

The process then moves in three directions; the PI needs to focus on tasks on two of the lines: the C Line (green) and to continue with the tasks on the B Line (yellow). The PI (C.1) keeps a copy of the contract, completes and submits electronically the RRF for a new clinical trial (<http://research.unc.edu/oct/>), and (C.2) sends the original draft contract agreement and other documents to OCT. (C.3) OCT and Legal will review the contract and negotiate any points of difference with the sponsor. (C.3.1) The PI and others such as CWHR personnel, Division Director, Department Chair, and/or colleagues should read the contract and provide OCT with any points they want to make sure are included. The contract spells out **only the legal arrangement of the partnership** with the sponsor, indicates what triggers payment, and defines a payment schedule among other items; **contract negotiation does not include the budget**. Contract negotiations can take from several weeks to several months to complete, depending on the work load of OCT, the complexity of the contract, how easy the company is to deal with, and a multitude of other factors. **OCT negotiates the contract with the sponsor (C.4)**. The approved contract is the first document in the Final Compilation Package.

While contract negotiations are going on, (B.9) the PI (or designee) breaks the protocol into its component parts and obtains a cost for each component. Costs are totaled to arrive at a per-patient cost to do the study. Staff salaries, start up dollars, and IRB/protocol change fees, etc. must be added to the budget as well as F&A; CWHR will assist with the total costing and budgeting process. If we do not already have the sponsor's proposed budget (what the sponsor proposes paying a site to do the study), (B.10) the PI (or CWHR) gets a copy of it from the sponsor, and compares to our estimated costs. **Very seldom does the proposed sponsor budget cover our actual costs of doing the study; (B.11) therefore a period of negotiation follows.** CWHR will assist with budget negotiations, or will conduct them on your behalf, always with your input and agreement. If a satisfactory budget agreement between the site and the sponsor cannot be reached, we (the site) reserve the right to terminate negotiations and end the process. (B.12.1) If this happens, notify OCT and CWHR of your decision (B.12.1).

Assuming an agreement on the budget is reached, (B.12) the PI must then get final approval from their Division Director. If the PI has involved the Division Director all along, this step will be quite simple (B.13). If the Division Director does not agree, that can either end the process (B.12.1), or the PI (or CWHR) can re-negotiate points of difference with the sponsor (B.11). Once all parties have agreed, put the agreement in writing and get it acknowledged by the sponsor, the Division Director, and the fund administrator (B.14). **The final agreed-upon budget is appended to and becomes part of the contract at this point**, and is included in the Final Compilation Package (12). The budget negotiation process can take from several weeks to several months, depending on the size of the initial gap between the proposed budget and our estimated costs, how flexible the sponsor is and how accessible they are.

On the A line for the IRB, (A.3) when the PI knows enough about the protocol and has determined that the sponsor budget seems reasonable, or budget negotiations are progressing well, he/she (or designee) completes all IRB documents, submits them for approval and (A.4) works with the IRB to resolve any issues that arise. The IRB approval process can take from several weeks to several months, depending on the timing of IRB meetings, how many issues they have with the protocol, and how well and quickly the PI (or designee) responds to the issues. **The completed IRB is the third document in the Final Compilation Package (12).**

The Final Compilation of all approved documents (12) is done at CWHR. The entire package is entered into Ramses and routed for approvals. (13) After the study has been approved in Ramses by all parties concerned and the PI is notified, (14) the final contract is executed and recruitment may begin (pending staffing availability- thus staff recruitment and hiring need to be considered during this process).

MONITORING THE FINANCIAL HEALTH OF TRIALS

Once the contract is executed, the trial is underway, and you are recruiting and enrolling participants, CWHR will monitor recruitment and enrollment numbers (see [Appendix IV](#)), and send monthly reports to the PI and the Division Director.

Recruitment and enrollment is absolutely crucial to the success of clinical trials; if we do not enroll, we do not get paid beyond start-up dollars. At the three month point we will conduct an in-depth check of the financial health of your study. We will review current recruitment and enrollment numbers, project amounts that can be billed, review what has been invoiced, what has been paid, and when additional payments are anticipated. If the study is not healthy from a financial perspective, we will work with you to remediate the situation, and you will have an additional three months to see whether the financial health improves. In the interim, the Division is responsible for covering the costs of study and administrative personnel to keep the trial running. At the end of six months, if the trial is not financially healthy, we will end our involvement in the study unless you and your Department Chair and/or Division Director agree to cover all losses, including the time required for administering the trial funds (CWHR expenses).

Once a contract is executed, the Division is responsible for any losses incurred. For example, if there is a delay before the start of recruitment and enrollment, and bridge funding is required to cover the expenses of the trial until recruitment begins, the PI and his/her Division are responsible for covering the expenses of study personnel and Center personnel to administer the funds.

CWHR assistance available to support industry sponsored and initiated clinical trials (Pre-Award)

Step 1

A two step process with specific tasks is available on the CWHR website www.cwhr.unc.edu; it includes the process and a narrative that explains it, identifies points where CWHR can assist you, and has checklists for your use.

(9) Once the Preliminary Phase has been completed, we have a formalized agreement and have decided to proceed, we will be happy to notify the sponsor of your interest and initiate the next steps. This also gets your proposed trial in our work queue. From this point, the process follows two parallel lines.

Step 1

On the B line, once you get the CDA, the CTU Coordinator will review it and coordinate with you what pre-award tasks you want the Center to do and which you will handle yourself. Center personnel are available to submit requests to OCT, track proposals through the process, troubleshooting as needed, and keep you informed of progress and/or sticking points. While there is a significant amount of work that the Center can assist you with, as PI you are ultimately responsible for the study as outlined in OSR Policy 200.4 (research.unc.edu/n/CCM1_030787). Please discuss roles with the Coordinator and come to an agreement regarding your/your division's involvement with the process.

On the A line, someone will need to complete the site survey form; this is best done either by the PI or by someone in his/her department/division as you will have the best view of the information requested. We will be happy to support your efforts in completing this task; however, you should be prepared to take prime ownership. We are available to assist on the B line as follows:

- (B.2) CWHR can complete the RRF Request for Review Form) and submit it to the Office of Clinical Trials (OCT).
- (B.3) CWHR can send the CDA to OCT, keeping a copy for review by you and others you deem appropriate.
- (B.4) Assuming CWHR is the contact for OCT, if there are issues with the CDA, CWHR will be notified and will attempt to resolve them; it may necessitate bringing you into the discussion; however if CWHR can troubleshoot the issue(s) without having to involve you, we will, unless you indicate otherwise.
- (B.5) Once OCT has approved the CDA, they will notify CWHR. We will pick up the document from OCT and bring it to you for your signature; we will keep a copy of the signed CDA on file.
- (B.6) We will return the signed original to OCT, who in turn will mail it to the sponsor (10).

Step 2

Note that the three lines of the process happen in parallel; the CTU Coordinator will oversee activities on all three lines and ensure that everything comes together as required for the submission.

- (B.7) CWHR can assist with reviewing staffing needs, identify potential sources for personnel, and work with you to understand the hiring process, should that be required.
- (B.8.2) Once you notify us of your intent to proceed, CWHR will notify your Division Director of the pending clinical trial. Bring or send the entire packet to the CTU Coordinator.

- (C.1) CWHR will keep a copy of the contract and ensure you have a copy; we will complete the RRF and submit it to OCT.
- (C.2) CWHR will send the original contract to OCT.
- (B.9) CWHR will work with you to deconstruct the protocol and determine the REAL COST of each element and will draft a budget to include these costs as well as staff and recruitment costs, indirects, and overhead to cover a portion of items such as clinic space, computers, telephones, and anything else not included in indirects.
- (B.11) CWHR will work with you to negotiate the budget with the sponsor organization.
- (A.3) If you choose, CWHR will develop the IRB submission, have you review it, make corrections, and submit it to the IRB. We will continue to follow up with the IRB to resolve any issues they might have with the submission, always with your involvement as needed.
- (12) CWHR will do the final compilation of the documents; this will include at a minimum the approved contract, the budget, and the IRB approval.
- (13/14) CWHR will enter the information into Ramses where it will be routed for approval. We will follow it and re-work, re-negotiate, and re-submit as needed, with your involvement as indicated, until final approval is obtained.

Throughout Steps 1 and 2 of this process, CWHR will monitor progress, facilitate actions to keep things moving, and keep you informed. The CTU Coordinator will discuss with you staffing needs, sources of staff, and work with you to fill staff needs. It is possible that CWHR will have some Research Assistant time available; please check with the CTU Coordinator.

Appendix I Memorandum of Understanding

Memorandum of Understanding for Industry Initiated and Sponsored Clinical Trials

The purpose of this agreement is the establishment of a mutually beneficial arrangement for the administration of an industry initiated and sponsored clinical trial. The specific elements of the agreement, and the budgetary requirements that the Center for Women's Health Research has established for clinical trials reflect our past experience with a wide variety of trials and sponsors. We have formalized the process in order to protect both parties (CWHR and PI/Division), and affirm that if the trial adheres to this process it should generate income, or at minimum be revenue neutral. At the end of the study, any "profit" or surplus of funds, not including start-up funds, will be divided equally (50/50) between CWHR and the PI's division. The PI's division is responsible for any financial loss after execution of the contract. Please initial or check the boxes below to indicate your understanding and acceptance of each item, and sign at the bottom.

- CWHR will be the administrator of the trial, and as such will provide assistance with the following:
 - Budget creation, negotiation with sponsor, and ongoing management
 - Study personnel recruitment
 - IRB preparation and submission
 - Submissions to and follow-up with Office of Clinical Trials (OCT)
 - Ongoing oversight of recruitment and enrollment, with reports provided monthly to PI and Division Director
 - Reports to PI and Division Director at 3 and 6 month points for assessment of viability

- PI will be responsible for hiring the study manager and any other study personnel, and they will be employed through PI's home department (unless personnel are shared with another study and are employed through the home department for that study).

- After execution of the contract, the PI's division will be responsible for covering study costs incurred by a delay in start time (often referred to as bridge funding), including time for CWHR administrative personnel.

- CWHR will examine study recruitment and enrollment monthly using reports completed by the study manager (Appendix IV), and will provide feedback to the study manager, PI and Division Director regarding financial viability of the study.

- CWHR reserves the right to discontinue our participation in any given study after 6 months if the enrollment data suggest that the study will not be financially self-sustaining (via capitated payments from sponsor for recruitment/enrollment/completion) beyond the period of time covered by start-up funds. If the PI chooses to continue the study beyond this point, s/he and/or the PI's home department agree to take financial responsibility for any losses incurred, including CWHR administrative costs if we continue to be the funds administrator.

PI

Date

CWHR Administrator

Date

Appendix II Checklist to Vet Sponsor and Study

**Checklist for use in Industry Initiated and Sponsored Clinical Trials
CWHR Clinical Trials Unit**

ITEM	YES	NO	Comments
For discussion in your Division			
Is this sponsor reputable—easy to work with, pays on time, fair?			
Does the study have clinical significance?			
Is the recruitment window currently open?*			
For discussion with the sponsor			
Does the sponsor understand and agree to the following?***			
1. Our start up fee is a <u>minimum</u> of \$8000, to be paid at the time of the executed contract agreement, is non-refundable, and is not associated with recruitment of any subjects.			
2. There is an Investigational Drug Service (IDS) fee that is separate from the start-up; it is determined by IDS and consists of a set amount for start up and a calculated amount each month.			
3. There is a separate IRB filing fee of \$2000 or the current rate which is due at start-up and is non-refundable.			
4. Indirect rate must be 28% or higher.			
5. Sponsor organization may only withhold 10%.			
6. Additional overhead to cover cost of rent for facilities, record storage after completion, etc. will be added			
7. Budget must include costs of coordinators, research assistants, administrative personnel, nurses, lab techs, physicians and any other personnel required to carry out the protocol effectively.			

*If recruitment is currently open, you should not join the trial unless the sponsor will reserve a set number of slots for participants from your site to ensure that we will break even on the study.

***If the response to any of the seven questions is “No”, CWHR is not willing to support the trial.

Appendix III Protocol Assessment

CWHR Clinical Trials Unit Protocol Evaluation

General Information

Protocol Name _____ CTU Name for Study _____
 Sponsor _____ Anticipated study dates _____ Projected start date _____
 Health status of study population: Healthy Acute Chronic Age of study population: Adult Minor
 Other characteristics: Non-English speaking Pregnant Other (specify) _____
 Other relevant details _____

This form is intended to stimulate discussion; questions like these should be included as part of a discussion in your division as you consider a given opportunity..	Rating		
	High	Medium	Low
"Desirability" as a study population			
Frequency of observations/procedures			
Flexibility of visit schedule			
Number of follow up visits			
Difficulty of procedures/assessments			
Benefit to our patient population			
Desirability of study from a scientific viewpoint			
Protocol fit with current protocol(s) and work demands			
Financial soundness (Make sense for us to do financially)			
General hassle factor			
These questions should help you answer whether you can meet the enrollment targets in a timely manner.	Very realistic	Realistic	Not at all realistic
How realistic is the number of patients to be enrolled?			
How realistic is the enrollment period?			
How realistic are the inclusion/exclusion criteria ?			
	Yes	Maybe	No
Is specialist involvement needed?			
Is current staffing adequate?			
Do you believe you can meet the enrollment numbers in the window provided?			

Appendix IV Recruitment/Enrollment Tracking

**Weekly Recruitment and Enrollment Record
CWHR Clinical Trials Unit**

Study name _____ PI _____

Week of _____ Recruiter _____

What are your recruitment goals for this week?

Active/in-person recruitment

What clinics did you recruit in this week?

Where else did you recruit (e.g. hospital, L&D, private doctor's offices)

Passive recruitment

What recruitment techniques did you use?

- Flyers/brochures/posters
 Radio or TV ads
 Newspaper ads
 Website
 Other (list)
-

	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Finding potential participants							
# clinic schedules reviewed							
# potential participants from clinic schedules							
# charts reviewed							
# potential participants from charts							
Contact							
# potential participants you approached in person							
# potential participants you approached via phone							
# potential participants who contacted you							
Screening							
# potential participants interested							
# potential participants screened for eligibility							
# eligible							
Enrollment							
# participants enrolled							
TOTALS							