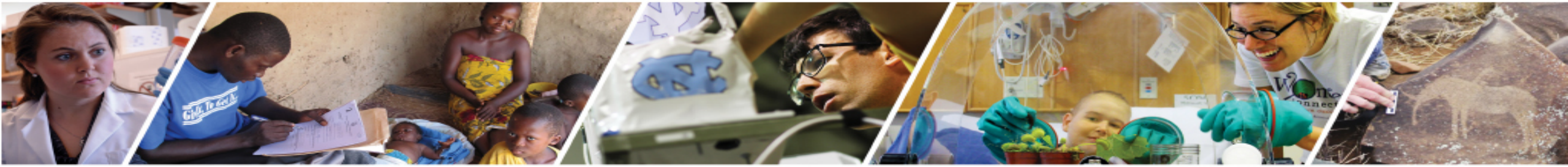
Why the Clinical Trial Agreement Matters



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UNC RESEARCH

Clinical Trial Agreement

Important Terms and Conditions for the Study Team:

- Publication
- Data Capture requirements (CRFs)
- Record Retention
- Adverse Events Reporting
- Audits & Monitoring
- Return/Destruction of Study Materials
- Biological samples
- Equipment
- Enrollment
- Subject Injury
- Budget/Payment Schedule Negotiation
- Billing and Invoicing Requirements

Publication

- Publication is required by the UNC Board of Governers policy, protection of our tax-exempt status, and Fundamental Research Exclusion under Export Control laws
- Allows the PI to develop expertise and reputation in their field
- Most journals require registration on clinicaltrials.gov for publication (ICMJE)
- Delay period – sponsor review, multi-center publication

Data Capture Requirements (CRFs)

4.3. Case Report Forms. For all Study Subjects, following an interaction/visit required under the Protocol, Institution or Investigator will promptly, in accordance with the timeframe described in the Protocol, but in any event, within ten (10) business days of the interaction/visit, complete and provide to Sponsor or its designee all case report forms required for that interaction/visit in the form and/or electronic medium supplied or specified by Sponsor or its designee (the "CRFs"). At the request of Sponsor or its designees, Institution or Investigator will promptly, in accordance with the timeframe described in the Protocol, but in any event within ten (10) business days of the request, correct any errors and/or omissions to the CRFs and will make available to Sponsor and/or its designees the corrected CRFs and supporting records for further verification.

- Pay attention for required timelines – check for feasibility

Record Retention

been communicated to PPD and Sponsor and as may be reasonably updated from time to time. Institution, at Sponsor's sole expense as provided for in the Budget in Exhibit A, will retain such records for twenty five (25) years after the final Clinical Study Report ("**CSR**") has been issued. Thereafter, Institution will destroy such records. Institution shall retain the records onsite for 1 year and then transfer the records an off-site storage facility for the remaining 24 years. During the record retention period, Sponsor shall notify Institution if the retention of the records is no longer required.

- Retention period
- Location
- Expenses related to record retention

Adverse Event Reporting

contemporaneously documented in accordance with established procedures. Institution and/or Investigator will, upon becoming aware, or as otherwise specified in the Protocol, notify Sponsor (a) within one (1) business day of any deviation from the Protocol, including any deviation necessary to protect the safety, rights or welfare of Study Subjects; (b) within one (1) business day of any serious adverse event or events involving Subject safety, (as those terms are defined in the Protocol) experienced by a Study Subject; or (c)

- Reporting timelines
- Sometimes in the contract, but can also be in the protocol

Return/Destruction of Study Materials

Upon completion or termination of the Study, the Site shall return or destroy, at Sponsor's option, the Investigational Product, comparator products, and materials and all Confidential Information (as defined below) at Sponsor's sole expense.

Institution and Investigator shall comply with all laws and regulations governing the disposition or destruction of Investigational Product and any instructions from Sponsor or Quintiles that are not inconsistent with such laws and regulations.

The Site shall return any equipment or materials provided by Sponsor for use in the Study unless Sponsor and Site have a written agreement for Site to acquire the equipment. If there are Site facility improvements provided by Quintiles or Sponsor in relation to the Study, then Site shall enter a separate written agreement with Quintiles or Sponsor with respect to such facility improvements.

- Explicit instructions on how to destroy
- Return or destroy

Audits/Monitoring

(9) Monitoring and Audit Access: Lilly, Lilly-designated representatives, at mutually agreeable dates and times and during normal business hours, and domestic or foreign regulatory agencies may inspect the procedures, facilities and Study records (including portions of other pertinent records for all patients in the Study) and those procedures, facilities or Study records of any contractor, agent or Study Site(s) that is used in conducting the Study. Lilly and/or Lilly-designated representatives may inspect such Study-related procedures or facilities up to the time of regulatory approval or rejection after submission and review, or two (2) years after the completion or termination of the overall Study in the event Lilly does not submit for regulatory review. Inspections of Study records by Lilly and/or Lilly-designated representatives may occur until the end of the record retention period set forth in section I.B. Clinical Trial Materials and Record Retention of this Agreement. To the extent Lilly requires monitoring and/or auditing access to electronic medical records of the Study subjects, Lilly acknowledges that Institution requires the execution of Institution's Confidentiality Statement; provided that a copy of the Institution's Confidentiality Statement is provided in advance of such visit to allow Lilly and/or Lilly-designated representatives to review such. If

- Access to facilities, hard copies of study records, etc.
- Timelines

Biological samples

16.1.3 Institution and Principal Investigator shall not retain any portions or collect any additional Biological Samples from Subjects, except for Subject medical care, after administration of Product until six (6) months after last dosage of the Product without prior written consent from Company and an amendment to the applicable SA.

16.1.4 Additional Biological Samples. In the event Institution and Principal Investigator wish to collect Biological Samples from Subjects during the course of a Clinical Trial for its own internal, non-commercial research outside the Clinical Trial or for biobanking for future purposes including, but not limited to, future non-commercial research or provision to third parties, ("**Additional Biological Samples**") they shall submit a written request to Company.

- Leftover samples
- Additional research

Equipment

1.15 If necessary for purposes of conducting the Study, Sponsor may provide Institution with certain equipment. Any equipment provided by Sponsor hereunder is described in **Exhibit B** ("***Equipment***"), which is incorporated herein by reference. For any Equipment provided by Sponsor, Institution shall (i) promptly inspect the Equipment following receipt and notify Sponsor upon becoming aware that any Equipment is damaged or malfunctioning; (ii) use the Equipment in accordance with the user manual and/or other instructions provided with the Equipment; (iii) maintain the Equipment in a secure manner designed to protect such Equipment from unauthorized use, theft, or damage and exercise the same degree of care with respect to the Equipment that Institution exercises with respect to its own equipment of similar type and value. If, due to the negligence, recklessness, or intentional misconduct of Institution or any Institution Personnel, any of the Equipment is lost, stolen, or damaged, then Institution shall pay the reasonable cost of replacement or repair, as applicable, which shall not exceed the estimated value set forth in **Exhibit B**. At Sponsor's direction and expense, the Equipment shall be returned to a location specified by Sponsor at the end of the Study or earlier termination of this Agreement.

- Who is responsible for damages or replacement costs?
- Required storage conditions
- Required insurance
- Maintenance
- Return or keep?

Enrollment

1.7. Key Enrollment Date

The Site understands and agrees that if Site has not enrolled at least one (1) Study Subject by the Key Enrollment Date then Quintiles may terminate this Agreement in accordance with Section 15 "Term & Termination" Sponsor/Quintiles has the right to limit enrollment at any time upon written notice to Site.

1.8 Minimum Enrollment Goal

Site acknowledges that Site's minimum enrollment goal is 1 subjects and that Site will use best efforts to reach the enrollment goal within a reasonable time after commencement of the Study at Site. If Site fails to adhere to this principle Sponsor or Quintiles may reconsider Site's suitability to continue participation in the Study.

- Minimums/maximums
- Key enrollment dates

Subject Injury - Contract Language

Sponsor shall pay for reasonable and necessary medical expenses incurred by Subjects for any medical care, including hospitalization, in the diagnosis and treatment of an injury or illness experienced by a Study subject directly arising from the administration or use of the Study Drug or comparator drug or any clinical intervention or procedure provided for or required by the Protocol to which the Subjects would not have been exposed but- for their participation in the Study ("Subject Injury"). Sponsor shall have no responsibility for Subject Injury to the extent that the expenses are (i) attributable to the negligence or willful misconduct of any Institution; (ii) as a result of a pre-existing medical condition or natural progression of the Study subject's underlying disease.

- This language, or a variation that means the same thing, accepted MOST of the time
  - Exceptions: non-interventional clinical studies, IITs, EAPs/Single patient INDs

Subject Injury - ICF Language

Start with UNC template language

- Send draft to sponsor for approval
- If sponsor makes no changes, you can proceed with submission to the UNC IRB
- If submitting to an external IRB you will need an “official” email from OCT (we are working with OHRE to update their SOP)
- If sponsor makes changes to template, please send to Christine_nelson@unc.edu or OCT@unc.edu

Clinical Trial Budgets

The University has given departments the responsibility of negotiating their own budgets for clinical trial agreements.

Clinical Trial Budget

Items that must be included in industry sponsored or supported clinical trial budgets

- Correct IRB fees for initial and continuing reviews.
- Billing Compliance Fee
- IDS -Research Pharmacy set-up, maintenance and dispensing fees must be included in the budget if IDS needs to be involved in the study.
- UNC's 28% F&A/Indirect Cost will be charged to all budget items except for IRB , Billing Compliance fees, contracting and QA fees.
- OCT invoices for administrative fees

Clinical Trial Budget

	Industry Funded Studies using Central IRB	Industry Funded Studies using UNC's IRB
Initial IRB Review Fee	N/A	$3,000
Initial IRB Preparation Fee	$1,000	Included in the above
IRB Renewal Fee	N/A	$750
Contracting Fee including the ICF	$1,5000	$1,500
Contract Amendment Fee (when sponsor requested)	$500	$500
Billing Compliance Fee	$2,000	$2,000
Quality Assurance Fee	$2,000	$2,000

Clinical Trial Budget

- Take the time necessary to make sure that all costs associated with the trial (Medical Center, Physician, Department, etc.) are fully identified and included in the proposed budget.
- Underestimating costs leads to financial stress within your unit and inappropriate subsidization of industry.
- Overestimating costs can not only damage your reputation with sponsors, but in some cases could expose the institution to significant liability.

Payment terms

- Budget/Payment terms unique to each study
- Budget/Payment terms as Exhibits vs in the body of the CTA
- Budget terms consistent with mutually agreed upon rates
- Double check the final invoicing language
- Check for unacceptable payment term language
- Confirm approved budget is final included on the CTA

Payment terms

- Ideally payments should be made on a monthly basis if at all possible.
- The more you can standardize payment methods and schedules across sponsors, the easier it will be to follow-up, track, and reconcile payments from industry.
- If monthly payments are not possible, quarterly would be the second preference, with purely milestone based being the third preference unless the milestone based allow for more timely collection in a particular study.
- The contract should state that the sponsor must provide payment detail with each payment to facilitate reconciliation.
- Can accept payment on CRFs collected, but should try to include minimum frequency for monitoring visits (usually at least quarterly). If payment is tied to monitoring, include that if monitoring visits do not occur, sponsor will pay based upon CRFs received.

Best Practices for Industry Sponsored Clinical Trial Budgets

- IRB fees and Study start-up fees should be non-refundable and payable within 30 days of execution of contract, even if study is cancelled.
- Advanced payment, representing payment for a given number of completed patients, or a set amount is recommended. Advanced payment to be used until depleted; at that time, defined payment schedule starts. Advanced payment will be partially or fully refundable based on costs incurred (e.g., number of visits conducted, number of subjects completed).
- Advance payment should not apply to study start-up fees; these fees should be listed separately.
- If the study involves research related screening tests/exams, include in the payment for screen failures in the budget.
- If the sponsor includes a cap on the number of screen failure payments, it should be sufficient to cover the expected number of subjects that will fail screening.

Best Practices for Industry Sponsored Clinical Trial Budgets

- Payment schedules should be adequate to keep the study account from going into significant deficit during the course of the study.
- Should avoid time limits for invoicing and payment disputes. If required by the sponsor, should try to make the time period as long as possible and make it contingent upon the sponsor's final payment.
  - "**Within 30 days** of the last treatment visit of the final subject, institutions shall submit to Sponsor all invoices for costs related to subjects participating in the Study in accordance with the terms of this Agreement "
  - **Strive to negotiate that invoices are submitted within sixty (60) days**

Best Practices for Industry Sponsored Clinical Trial Budgets

- Avoid payment milestones based on resolution of data queries.
- OK to agree to invoice for certain costs. However, try and limit invoicing to those e.g. costs that are incurred on an “as needed” basis (consent translation, subject compensation for travel, etc.).
- Sponsor retention of final payment until after study is completed is acceptable. 10 - 20% of total budget is a customary withhold amount, but more than 20% of total budget is not acceptable.
- Should try to avoid sponsor not paying for ineligible subjects or subjects with protocol violations. If necessary, should limit nonpayment to the procedure that caused the protocol violation, or payment for the data that is now unusable due to the protocol violation. Always indicate that payment should be made for protocol violations approved in advance by the sponsor.
- Do not accept limiting the use of money received from sponsor only to the conduct of the study. Okay to agree to return refundable unearned funds to the sponsor at the end of the study, but do not agree to return unspent funds to the sponsor at the end of the study.

QUESTIONS