Clinical Trial Agreements: Understanding the Operational Requirements

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Hugh R. Anderson
Clinical Trials Financial Manager
Clinical Trials Office
Robert H. Lurie Comprehensive Cancer Center

Allison Siebold-Guzman, J.D.
Contracts Officer
Office for Sponsored Research

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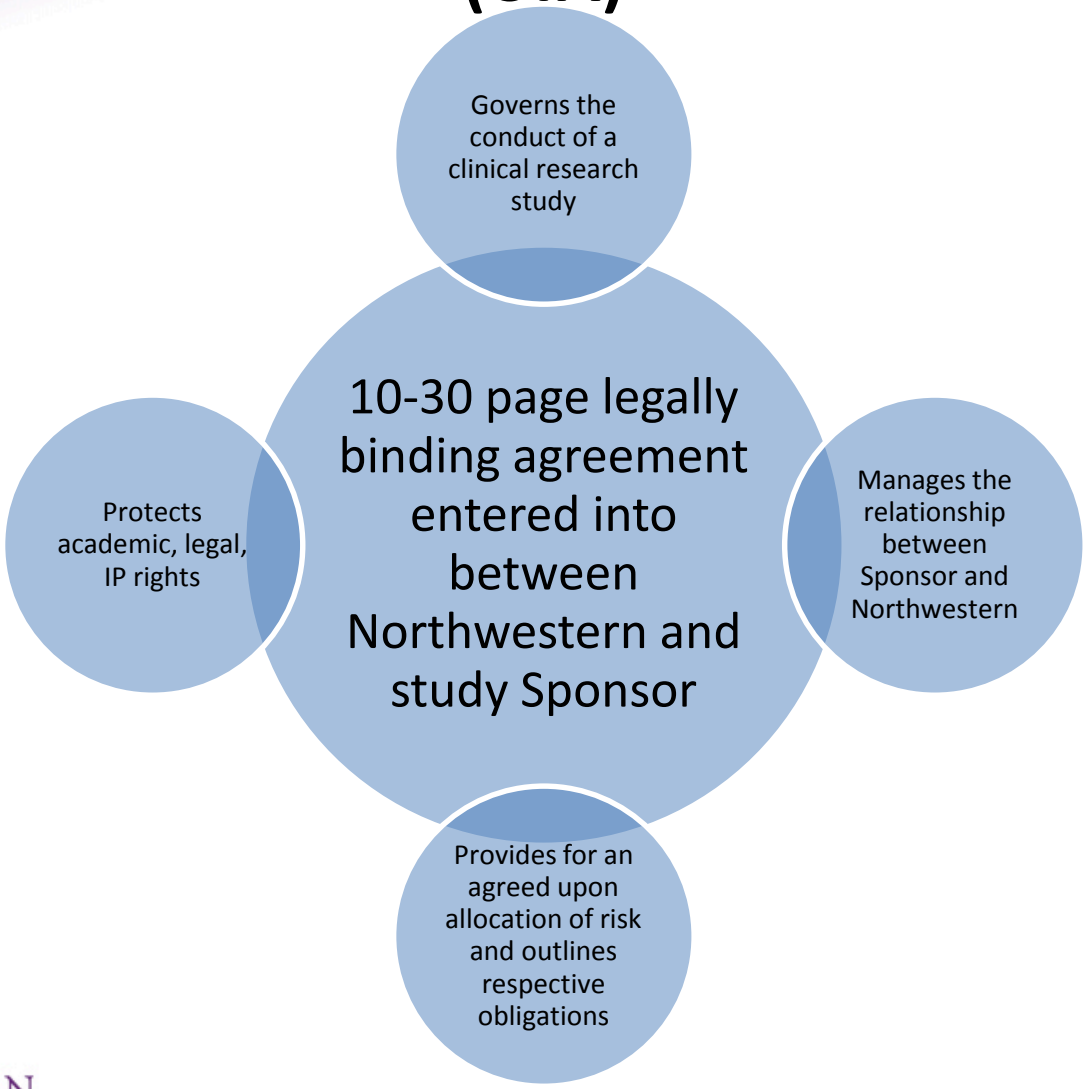
What is a Clinical Trial Agreement (CTA)



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Main Components of a Clinical Trial Agreement

SCOPE OF THE AGREEMENT	•Terms of CTA govern business/administrative matters; Protocol governs with respect to scientific matters •IRB Review / Approval •Applicable Laws
MONITORING/ AUDITING	•Identify specific timeframes for Sponsor visits • "Access is subject to reasonable safeguards to ensure patient and subject privacy and confidentiality and to protect the integrity of electronic medical records systems." •Provide Sponsors with NMHC written policy on access
CONFIDENTIALITY	•Definition of Confidential Information (exclude study data and results for publication) •Term of confidentiality •Standard exceptions

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Main Components of a Clinical Trial Agreement

DATA USE/OWNERSHIP	• Exclude medical records from definition of Data • Retain right to use for internal purposes (patient care, educational, non-commercial research purposes)
INVENTIONS	• Define: Pre-existing, Sponsor, Northwestern, Joint Inventions • License options
PUBLICATION	• Northwestern requires the independent right to publish the study results • Sponsor's right to review

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Main Components of a Clinical Trial Agreement

PAYMENT

- Budget/Payment options are unique to each study
- Budget/Payment terms as Exhibits vs in body of CTA
- Budget terms consistent with mutually agreed upon rates for the conduct of the study

INDEMNIFICATION

- Allocation of risk proportionate to the entity that controls the risk
- NU indemnifies for negligence and intentional misconduct

TERMINATION

- Termination rights
- "Payment for all funds earned in accordance with the budget, non-cancellable commitments and amounts to maintain subjects in the Study to the extent they cannot be safely withdrawn."

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24 HOURS

2 years

2 days

How do the terms of the CTA affect my department?

7 YEARS

Immediately

Promptly

30 DAYS

10 BUSINESS DAYS

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Operational Timelines

- OSR negotiates a variety of operational timelines within the CTA that directly impact research departments:
  - Replacement of Principal Investigator
  - Sponsor Monitoring Visits
  - IRB Communication / FDA Audit
  - Adverse Event Reporting
  - Subject Injury
  - CRF Completion
  - Record Retention
  - Drug destruction / return of study materials
  - Termination of Study
  - Payment, accounting, invoicing timelines

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REPLACEMENT PRINCIPAL INVESTIGATOR

- *"If for any reason, the Principal Investigator becomes unable to continue to serve as Principal Investigator for the study, Institution shall immediately notify the Sponsor, and shall use its reasonable best efforts to procure the replacement of the Principal Investigator within 30 days of the Principal Investigator becoming unavailable"*
- **OSR negotiates the language to ensure that the Sponsor is notified PROMPTLY and allows for the Principal Investigator to be replaced PROMPTLY**

- **"Promptly" = Quickly / Without unnecessary delay**
- **"Immediately" = Instantly**

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REPLACEMENT PRINCIPAL INVESTIGATOR

- NU will only initiate change in PI if the current PI is leaving the university (*employment termination*).
- We do not encourage PI change for any short-term leave. (Too many regulatory documents to change).
- We will accept a sponsor initiating a PI change at study start up.
- As OSR suggest, we would like to see “promptly” vs a hard time-frame for a change in PI.

SPONSOR MONITORING VISITS

- *"Sponsor and its respective appointed representatives shall have the right to inspect, audit and monitor the Study Site, Institution's facilities, and all Study Data and associated Source Documents."*

- **OSR will ensure that the following language is present in the monitoring section of the CTA: "*During the term of this Agreement, with reasonable advance notice, at mutually agreeable times, during normal business hours…*"**

- *DEPARTMENTAL CONSIDERATIONS: Scheduling visits and option to pay up front vs. at the end*

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IRB COMMUNICATION / FDA AUDIT

- *"Institution shall notify Sponsor in writing within 24-48 hours if the IRB withdraws approval of the Study."*
  - **Sponsors rarely agree to a longer timeframe or the insertion of "promptly" here.**

- *"Institution and/or Investigator will notify Sponsor no later than 24 hours after receiving notice of any impending inspection or audit (**related to the Study**) by the FDA or other governmental or regulatory authority."*

  - **OSR will negotiate the removal of a firm timeline, and the insertion of "*promptly*" for notice of FDA audit.**

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FDA AUDIT

NU becomes aware of FDA Audit

NU will notify sponsor within 24 hours of notification

Pay attention to other language and stipulation in the CTA – such as sponsor wanting daily FDA recap form for every day FDA auditor was here.

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ADVERSE EVENT REPORTING

- Typically Sponsors require to be notified within 24 hours (or “immediately”) of Northwestern’s knowledge of any serious or unexpected adverse event.
  - ***“Unless otherwise specified in the protocol or required by applicable laws”*** **- OSR will ensure this language is included in the CTA. Allows for the terms of the protocol to govern and ensures that the terms of the CTA are not inconsistent with what is in the protocol or required by applicable laws.**

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ADVERSE EVENTS

Cancer Center has a 10 day data policy

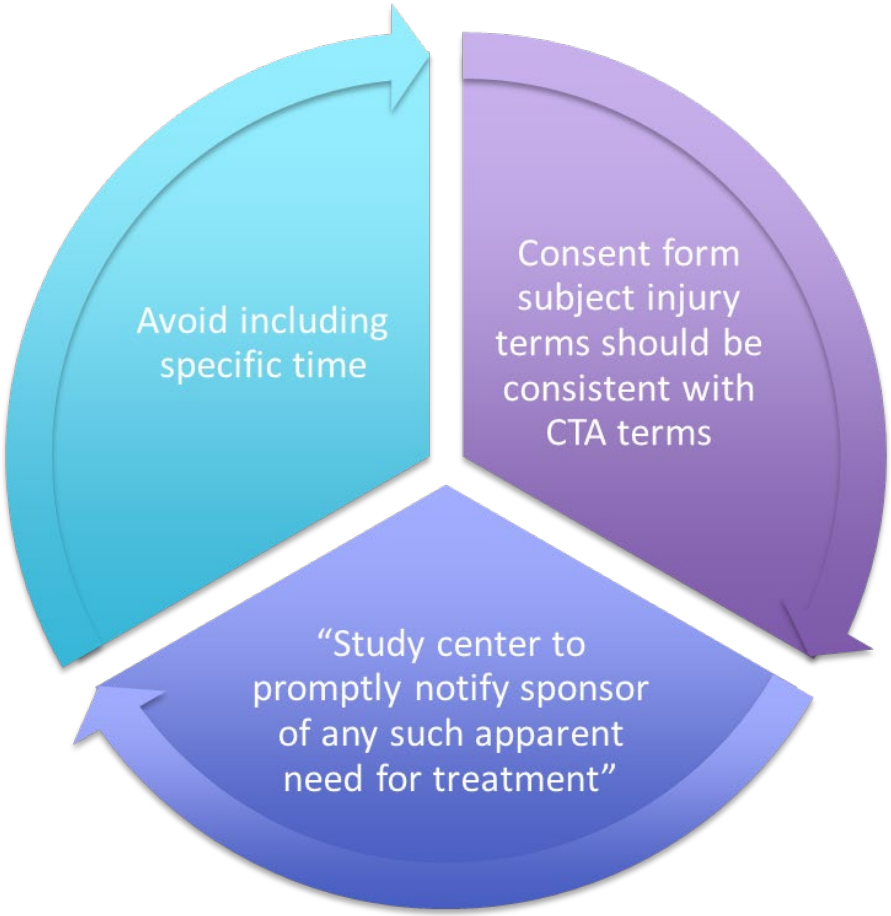
- Adverse events that are not considered serious or reportable to the IRB fall under this policy
- For Serious Adverse Events – are reported within 24 hours of PI becoming aware of event
- Cancer Center's preferred format for recording AE/SAE is adverse event log

SUBJECT INJURY

- *"If a Study subject suffers an adverse reaction, illness, or injury which, in the reasonable judgment of Institution, was directly caused by a Study Drug or Study Device or any properly performed procedures required by the Protocol, Sponsor shall reimburse for the reasonable and necessary costs of diagnosis and treatment of any Study subject injury, including hospitalization, but only to the extent such expenses are not attributable to (i) Institution's negligence or willful misconduct or (ii) the natural progression of an underlying or pre-existing condition or events, unless exacerbated by participating in the Study."*

- **OSR avoids agreeing to specific timeframe in which a subject injury will be communicated to the Sponsor. It is in both parties' best interest that this information is communicated to the Sponsor as soon as possible.**

SUBJECT INJURY



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CASE REPORT FORM COMPLETION

- *"Institution shall complete Case Report Forms ("CRFs") accurately and submit these forms to the Sponsor within forty-eight (48) hours of obtaining the data."*

- **OSR will follow the timeline of the respective department's SOP, or ensure that "*pursuant to the protocol*" is inserted in place of the specific timeline.**

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CASE REPORT FORMS

CRF and Query Resolution Timelines		
Cancer Center Policy for CRF Completion	Cancer Center Policy for Query Resolution	Serious Adverse Events
10 Days	Ask for 10 days, but will accept 5-7	Reported within 24 hours of PI becoming Aware

Most sponsors agree to these timelines, but if you get pushback consider language such as “Institution will make every effort to complete the initial CRF forms within 7 business days.”
Written policy is very helpful in negotiations!

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Robert H. Lurie
Comprehensive Cancer Center
of Northwestern University

Policy Regarding Serious Adverse Event reporting/Data Entry Timelines

The Robert H. Lurie Comprehensive Cancer Center (RHLCCC) Clinical Trials Office (CTO) will process Serious Adverse Events per protocol specifications. Only those events meeting IRB reporting guidelines will be reported to the IRB of record.

The CTO will enter data within 10 working days of the study visit. If there is a request to turn-around data in a shorter timeframe, the CTO will consider the request on a case-by-case basis, and attempt to meet request if workload allows.

Gary Passaglia, MSRC, CCRP
Administrative Director
Clinical Trials Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University

RECORD RETENTION

- Standard record retention language as required by the FDA:

As applicable by law, Institution shall retain and preserve a copy of the Study records for the longer of:

a) two (2) years after a marketing authorization for Study Drug, or Study Device has been approved for the indication for which it was investigated or Sponsor has discontinued research on the Study Drug or Study Device;

b) such longer period as required by federal regulatory requirements; or

c) as requested by Sponsor at Sponsor's reasonable storage expense.

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RECORD RETENTION

- Per 21 CFR part 312.62
  - Investigator must retain records for 2 years following:
    - Marketing application approval for drug indication
    - Application approved for drug for indication investigated
    - If no application is filed, of if application not approved, following IND discontinuation

- **Cancer Center Policy**
  - Once study is terminated, trial master file is scanned and stored electronically indefinitely
  - Certified copy of originals kept electronically indefinitely

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TERM & TERMINATION

Standard term language: *"This Agreement shall commence on the Effective Date and shall continue in force until (in accordance with the protocol) the Study has been completed".*

Termination: *This Agreement may be terminated by Sponsor for any reason upon fifteen (15) days prior written notice to Institution.*

-OSR will strive to negotiate a minimum of 30 days prior written notice for cancellation or termination.

*Either party may terminate this agreement **immediately**, if necessary, in order to protect the health, safety or welfare of Study subjects with written notice to the other Party.*

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TERMINATION

- STUDY CLOSE-OUT LETTER / STUDY WIND-DOWN PROCESS

- Considerations
  - Sponsors may request study drug, materials, etc…be returned within 30-60 days of termination effective date
  - Usually changed to 90 days

DRUG DESTRUCTION /RETURN OF STUDY MATERIALS

- *"Upon termination or completion of the Study, termination or expiration of this Agreement, or upon any earlier request by Sponsor, any unused Study drug and all Sponsor property shall promptly be returned to Sponsor at Sponsor's expense."*

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DRUG DESTRUCTION / RETURN OF STUDY DRUG

Investigational Pharmacy's Policy (NMH)

- After study is terminated, any unused drugs will be destroyed
- Sponsor requests for pharmacy to store drug until the sponsor's monitor visit
  - Incur additional charge of $1,000/year, and the saving period shall be no longer than 30 days once the drug is returned to pharmacy.
- Requests for documents by email or fax only apply to those studies that request monthly inventory record (very few studies request this).
- There are certain types of returns package not acceptable by pharmacy
  - Example: blister packs, anything injectable /punctured vials, Syringes in injectable form (high risk), topical cream that has to be weighed (aerosol/liquid). Once the recording is done, they are destroyed immediately and are not kept until monitor is here.

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PAYMENT TERMS

- Can be included in the body of the CTA or attached as an exhibit.

SUBMISSION OF INVOICES

- *"Within thirty (30) days of the last treatment visit of the final Subject, Institution shall submit to Sponsor all invoices for costs related to subjects participating in the Study in accordance with the terms of this Agreement."*
- **OSR will strive to negotiate that invoices are submitted within a minimum of sixty (60) days.**

PAYMENT TO NORTHWESTERN

- *"Sponsor shall pay Institution for invoiced costs within ninety (90) days of receipt of an invoice."*
- **OSR will attempt to negotiate invoices are paid within thirty (30) days.**

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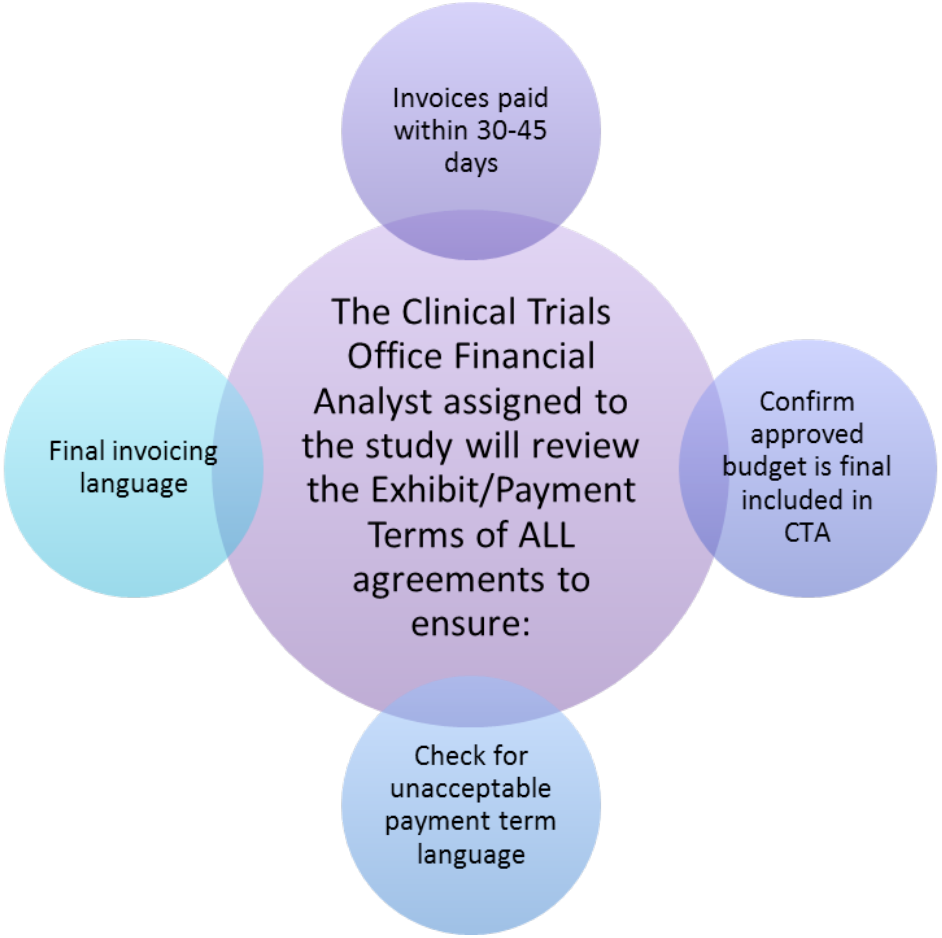
PAYMENT TERMS



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Thank You

Contact Information

Allison Siebold-Guzman, J.D.
Contracts Officer
Office for Sponsored Research
Allison.Siebold-Guzman@northwestern.edu
312.503.0884

Hugh R. Anderson
Clinical Trials Financial Manager
Clinical Trials Office
Hugh.Anderson@northwestern.edu
312.926.6476

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