Achieving Harmony Between the Clinical Trial Agreement and Site Operations

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Our Backgrounds

- Lurie Children's
  - Stand-alone pediatric hospital
  - Hospital policies universally applicable to studies

- Northwestern University
  - Office for Sponsored Research supports NU investigators in proposing and managing sponsored research
  - Departments conducting clinical trials focused on respective specialty

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Objectives

1. Identify and discuss CTA provisions that directly impact department and/or site operations
2. Tips and strategies for negotiating to avoid conflict and to ensure synergy between CTA and site operations
3. Tips for how to learn about department operations at your site

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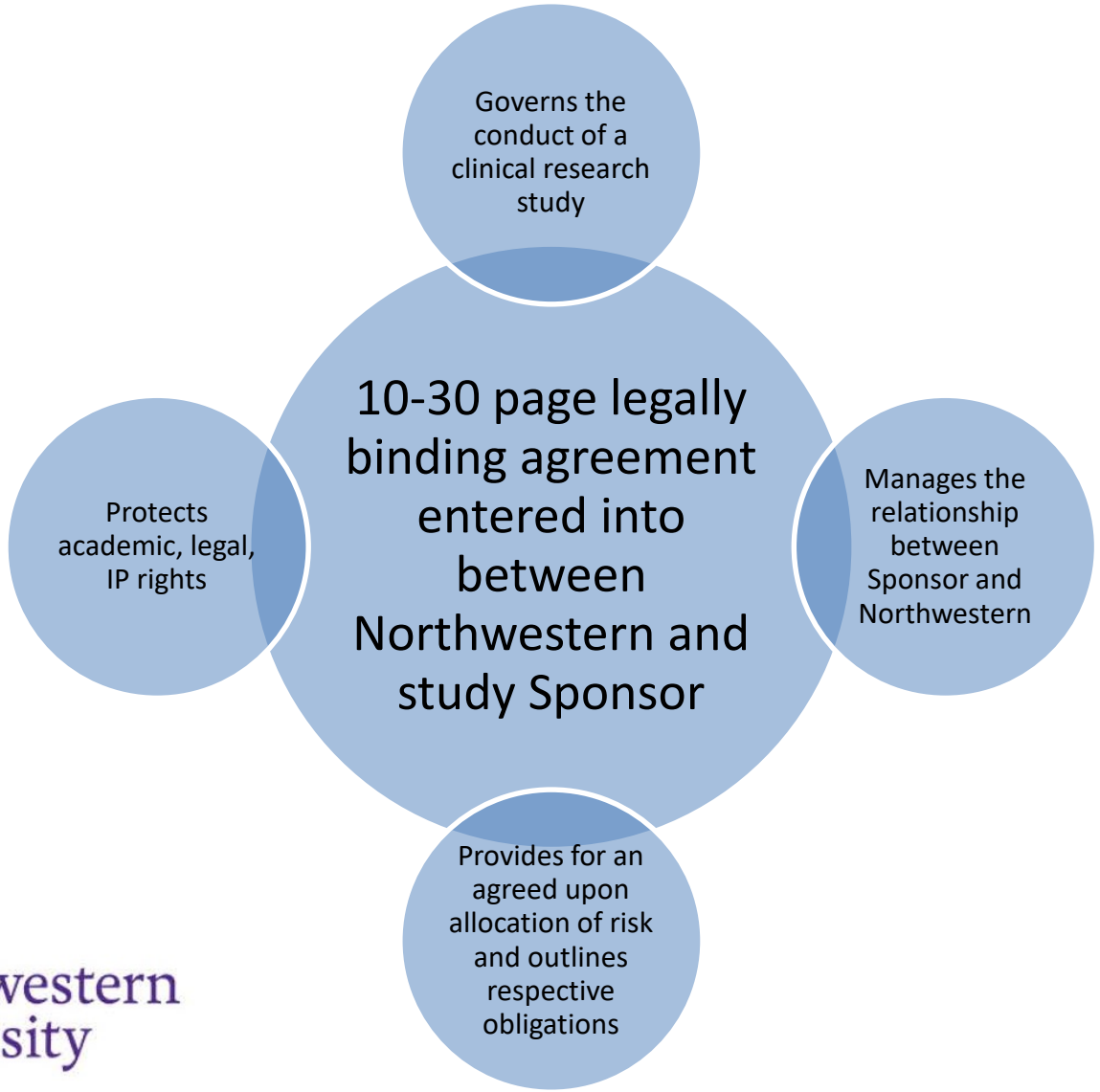
What is a Clinical Trial Agreement (CTA)



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Main Components of a CTA

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 CTA

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 CTA

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 operations?

7 YEARS

Immediately

Promptly

30 DAYS

10 BUSINESS DAYS

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Question of Timing

- The CTA contains many provisions that dictate timeframes in which departments must act, respond, notify, retain, etc.
- Not always driven by statute or law, but also by policy and preference
- What is an appropriate amount of time for the site to respond/act?
- Under what circumstances is it appropriate to act "immediately"?

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Question of Underlying Obligation

- Replacement of Principal Investigator
- Monitoring Visits
- IRB Communication/ FDA Audit
- Adverse Event Reporting
- Subject Injury
- Use of Equipment
- Enrollment
- CRF Completion
- Record Retention
- Publication
- Termination of Study
  - Final Study Report
  - Drug Destruction/ Return of Study Materials
- Payments/ Invoices
- Subcontracts/Vendors
- Investigator-Initiated Study
- Insurance

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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.

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REPLACEMENT PRINCIPAL INVESTIGATOR

Preferred Contract Provision:

"If for any reason, the Principal Investigator becomes unable to continue to serve as Principal Investigator for the study, Institution shall promptly 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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SPONSOR MONITORING VISITS

Common challenges for sites regarding monitoring visits:

- *Scheduling, timing and duration*
- *Frequency/ Necessity*
- *Inexperienced monitor, change in monitor (can result in extra visits)*

Typical Clause: "Sponsor and its respective appointed representatives shall have the right [upon advance notice] *to inspect, audit and monitor the Study Site, Institution's facilities, and all Study Data and associated Source Documents."*

- *Leaves sponsor a lot of discretion for visit frequency, scheduling, etc with limited recourse for the site*

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SPONSOR MONITORING VISITS

Better CTA provision: Monitoring visits should be held "upon mutually agreed upon dates and times during regular business hours"

- *Means the visit needs to be scheduled jointly*
- *Needs to happen during normal business hours*
- *This language better protects the site if issues arise re: frequency, duration, start/end time, access*
- *Protect your site: Ask sponsor for its monitoring plan and address monitoring in the study budget*
  - *NU Approach: Scheduling visits and option to pay up front vs. at the end*
  - *Lurie Children's: Negotiate a fee for each day of monitoring*

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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.**
  - **Lurie Children's will carve out exception to notify for confidential audit**
  - **Obligation to notify sponsor extends to audits related to their study**
  - **Limit conditional/speculative language such as "could relate to"**

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IRB COMMUNICATION / FDA AUDIT

- Can the sponsor help prepare for or attend the audit?
  - NU: Yes. NU feels that the Sponsor can provide valuable assistance with these audits
  - Lurie Children's: Lurie has permitted this.

- Can the sponsor comment on Site's responses to FDA or other agency?
  - NU: Yes, if time permits
  - Lurie Children's: Yes, if time permits.

- Sponsor should not be granted the right to "approve" responses

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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

Northwestern's Cancer Center has a 10 day data policy

- Adverse events that are not considered serious or reportable to the IRB fall under this 10 day 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

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SUBJECT INJURY - NU

"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.**

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Subject Injury – Lurie Children's

"Sponsor shall pay actual and reasonable medical expenses incurred in the diagnosis and treatment of any injury or illness to a Subject that, in the Principal Investigator's reasonable determination, is directly related to the administration of the Drug or the performance of any procedure in accordance with the Protocol, each in accordance with the Protocol and the Sponsor's written instructions to the Institution."

Lurie will also accept the following in addition to the above:

Sponsor is not required under this Section to provide compensation for

- (a) other injury-or illness-related costs (such as lost wages),
- (b) medical expenses that are paid for by a third party, provided that neither the Institution nor the Subject shall be obligated to seek reimbursement from a third party insurer, and
- (c) medical expenses that are incurred as the result of a violation of the Protocol or other misconduct or negligence by an employee or agent of Institution.

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Subject Injury - Continued

- Avoid coverage limited to "immediate" treatment
- Include both injuries caused by study drug/device AND procedures required by protocol
- Also avoid time limitations on the sponsor's obligation to cover injury such as "until 2 years from the close of the Study"
- Lurie Children's does not accept a carve out for injuries that result from a subject's failure to follow instructions, or that obligate Lurie to bill a third party payor first
- Lurie Children's does not agree to use a fee schedule (i.e. Medicare) for billing subject injury costs that is different from the schedule applied to the study
- Specify that subject is not required to seek care at Study Site

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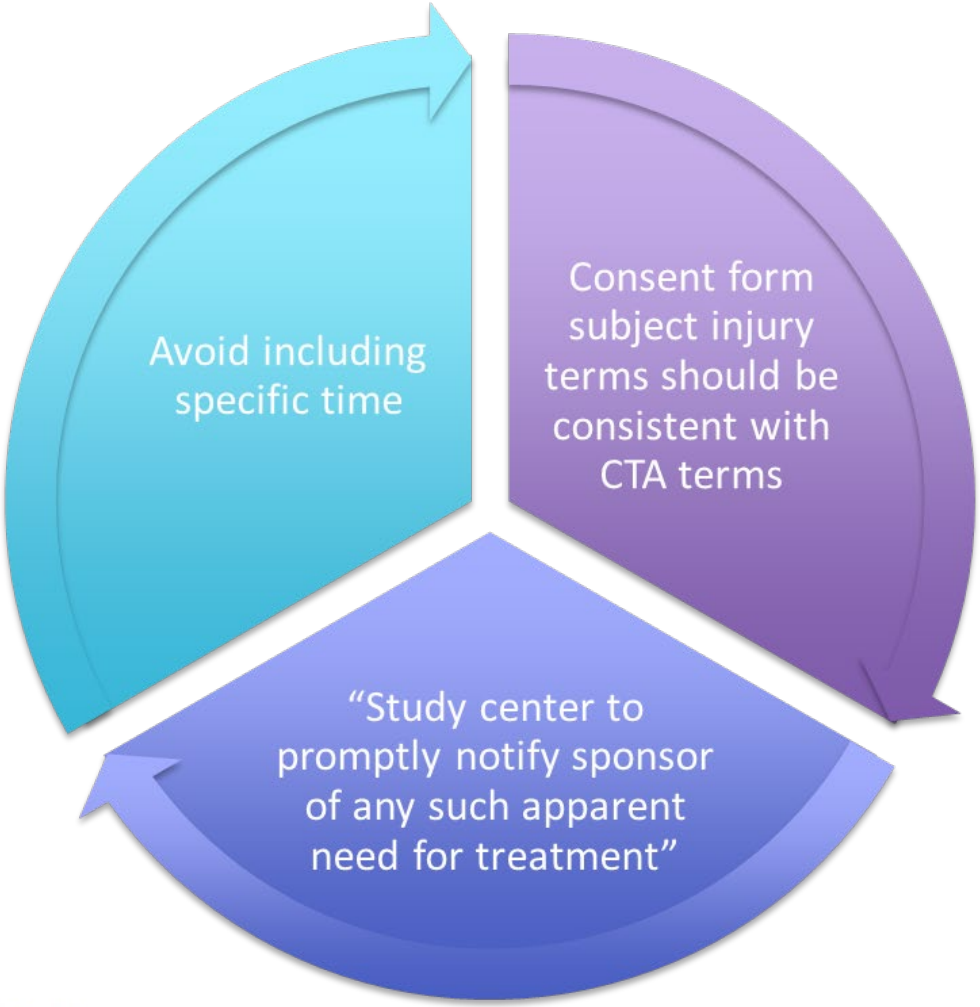
SUBJECT INJURY



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Equipment

- Sponsor may provide equipment for a study; or
- Site may have to rent or purchase
- Be mindful of:
  - Who is responsible for maintenance, replacement costs
  - Insurance coverage/ liability
    - NU: All indemnification sections where the sponsor is providing equipment must include indemnification language for the proper use of that equipment.
    - Lurie Children's – Ensure risk of loss is not with families for equipment used by patients (ipads, fitbits, etc)

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Equipment Continued

- Is there space for the equipment?
- Is additional committees need to review and approve (infection control, investigational equipment)?
- Extra time that may be required to complete a purchase or rental agreement (Lurie Children's: infusion pump example)
- Does the institution or investigator want to keep equipment at the end of the study?

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Enrollment

- Sponsor Request:

  "The Site understands and agrees that if Site has not enrolled at least one (1) Study Subject by the Key Enrollment Date, Sponsor may terminate this Agreement…"

  (Key Enrollment Date = 100 Calendar Days after Site Initiation Visit (being the date by which Site must enroll at least one (1) subject…)

  Should the site accept this language?

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Can the Site Accept Enrollment Deadline?

- Depends upon Site's policies on CTA signature, IRB approval, when SIVs can be scheduled, receipt of materials or equipment provided by sponsor or obtained commercially
- Depends upon when qualified subjects are at Site
- Patients may want to participate, but if not, Site cannot compel enrollment

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Can the Site Accept Enrollment Deadline?

- Enrollment timeframe may be too short
- NU will not agree to a "best efforts" standard in terms of enrollment goals. *"Reasonable* (best) efforts" is preferred.
- Lurie Children's: Also does not accept "best efforts" standard and prefers "reasonable" or "Site shall endeavor to enroll qualified subjects…"

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Can the Site Accept Open-Ended Enrollment?

On the other hand, should the site accept open-ended enrollment timeframe?

Example:

> "Institution has agreed to enroll qualified Study participants during the CRO-specified enrollment period, unless CRO modifies the enrollment period by written notice. …"

Can the Site Accept Enrollment Deadline?

Open-ended enrollment may pose an operational hurdle when:

1) Enrollment will be difficult

- Pool of eligible subjects is small

- Study is not appealing to potential subjects;

And/or

2) PI wants to open a study that would compete

Can the Site Accept Enrollment Deadline?

Lurie Case Study: We had a study in which the PI wanted to participate, but the same PI was also planning to open another study in the future that would compete for subjects.

- Competing studies would pose operational and ethical conflict which we needed to avoid
- Attempts to negotiate the termination section were not successful

Can the Site Accept Enrollment Deadline?

Lurie Case Study: How did we handle?

- Attempts to negotiate the termination section were not successful
- Negotiated enrollment section instead:
  - "Subject Enrollment. Institution has agreed to enroll qualified Study participants until March 31, 2014 unless this timeline is extended by written agreement of the parties."

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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.**
- **Also important to consider when all data will be available for entry (ie lab results), not just availability of personnel**

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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.

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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

- **Northwestern 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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RECORD RETENTION

Contract Negotiation Preferences

- Lurie prefers to be able to destroy once legal or policy requirements are met
  - Contract states Lurie will retain for as long as required by law or institutional policy, then Lurie may destroy
  - Lurie will provide sponsor an opportunity to take custody of records before destruction
  - Sponsor make take custody of records at its expense
- This approach helps Lurie raise this issue with sponsor, as opposed to waiting for notification from sponsor

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RECORD RETENTION

- ICH 5.5.12 - Sponsor is responsible to notify site when records may be destroyed
  - The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.
- BUT, Sponsors and CROs are not consistent in providing notification

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Publication

- **Thirty (30) days prior** to submission for Publication, Institution shall submit to Sponsor for review and comment any proposed oral or written Publication ("Review Period"). Institution will consider any such comments in good faith but is under no obligation to incorporate Sponsor's suggestions. If during the Review Period, Sponsor notifies Institution in writing that: (i) it desires patent applications to be filed on any inventions disclosed or contained in the disclosures, Institution will defer Publication for a period **not to exceed sixty (60) days,** to permit Sponsor to file any desired patent applications; and (ii) if the Publication contains Sponsor's Confidential Information and Sponsor requests Institution in writing to delete such Sponsor's Confidential Information, the Institution agrees to delete such Sponsor's Confidential Information only to the extent such deletion does not preclude the complete and accurate presentation and interpretation of the Study results.
- Multi-Center studies: if no multi-center publication is submitted within **eighteen (18) months** after conclusion, abandonment, or termination of the Study at all sites…Institution may submit publication

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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
  - In the event of early termination, make sure time frames do not interfere with efforts to safely withdraw patients from the study

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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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Final Report

- No later than **ninety (90) days** after the completion or early termination of this Study, Institution will furnish an acceptable final report to Sponsor.

CONSIDERATIONS:

- Does this timeline align with the PI's expectations?
- What is an 'acceptable' report to the Sponsor? Try to strike vague requirements
- Is submission of the final report a condition to receipt of final payment? If so, ensure the timeline of the submission of the final report aligns with any payment terms

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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."*
- **NU 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."*
- **NU OSR prefers invoices to be paid within thirty (30) days.**

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PAYMENT TERMS

FINAL PAYMENT RECONCILIATION

- *"Site will have forty-five (45) days from the receipt of final payment to dispute any payment discrepancies during the course of the Study."*
- Lurie aims for **60 or 90 days** to complete final reconciliation
  - Accounts for delays between receipt of payment and posting it to research account for study team to view
  - Allows time for all study-related expenses to post to research account
  - Allows study team time to review records and complete accurate reconciliation

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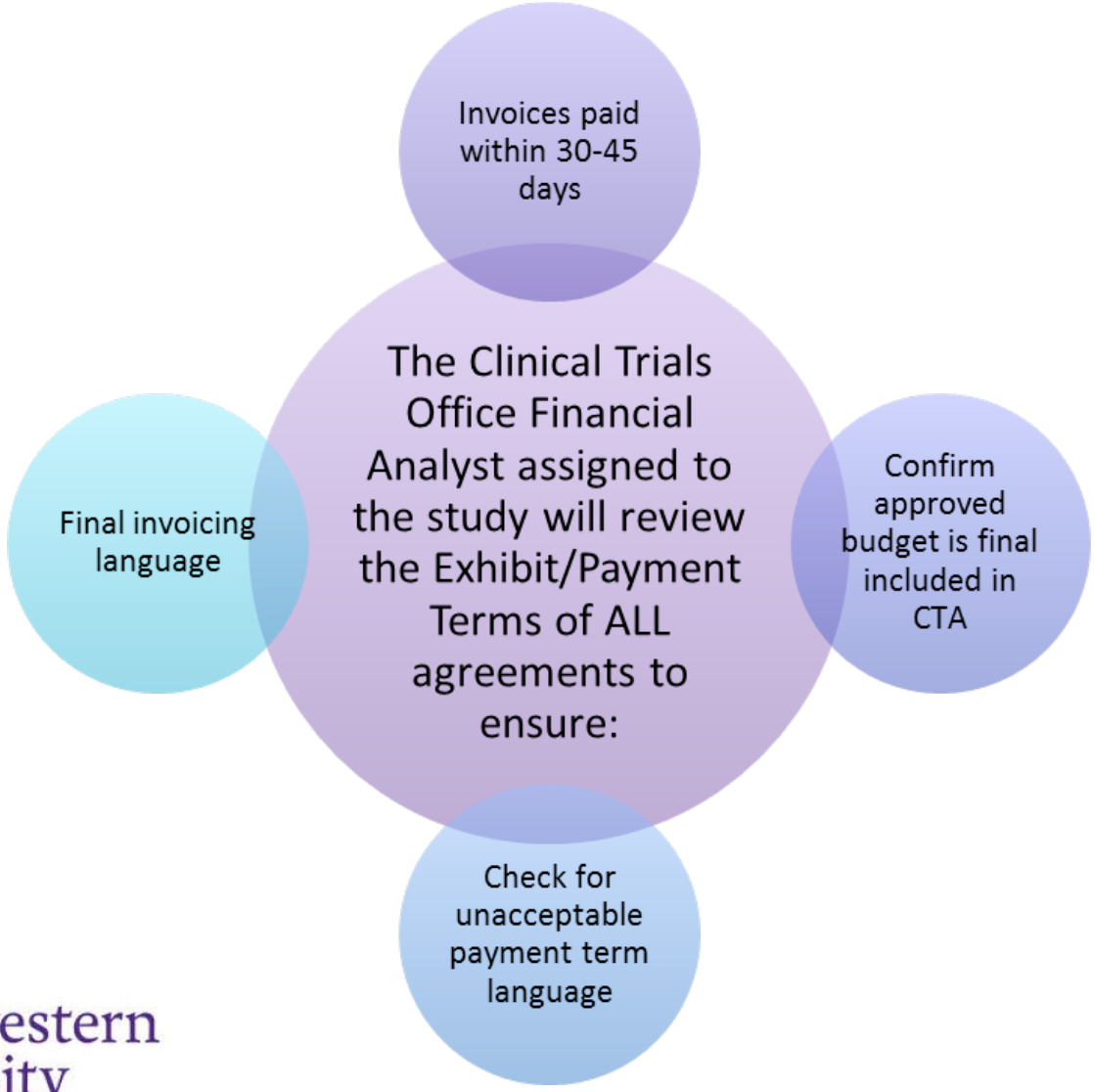
PAYMENT TERMS



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Investigator-Initiated Studies

- PI = sponsor, which changes some of the timing and obligations
- PI may be holding IND
- Site research program is probably more geared toward operating as a Site and not a sponsor

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Subcontractors/ Vendors

- Often requires sponsor written approval
- Make sure the CTA permits it or secure permission from sponsor in advance (usually easier to do during initial negotiation)
- Build additional time into the CTA to receive data or notices from the subcontractor or vendor
- Flow down terms from prime agreement as appropriate

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Insurance

- CTA language on insurance usually states:
  - "Site represents it maintains coverage sufficient to cover its obligations under this agreement…" or
  - Sponsor requires specific types of insurance and amounts

- Risk Management should be able to inform as to the typical policy coverage that Site can represent
  - Do not agree to variations from those
  - Site is not likely to modify coverage for any one particular study

Insurance

- Avoid granting sponsors right of subrogation
- Avoid naming sponsor as Additional Insured
- Avoid requests for site insurance to be "primary"

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How to Learn about Site Operations

- Ask questions!
  - Schedule phone call or meeting with PI or coordinator
    - "Tell me about your study"
    - Review protocol, budget and/or informed consent
  - Intake Form
  - Ask colleagues about contract provisions
  - Read site policies that may impact research

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Thank You

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