A B C OF CLINICAL TRIALS

ARE YOU CLINICAL TRIAL CURIOUS?

SRA INTERNATIONAL | SOCIETY OF RESEARCH ADMINISTRATORS INTERNATIONAL

"The cure for boredom is curiosity. There is no cure for curiosity."- Dorothy Parker

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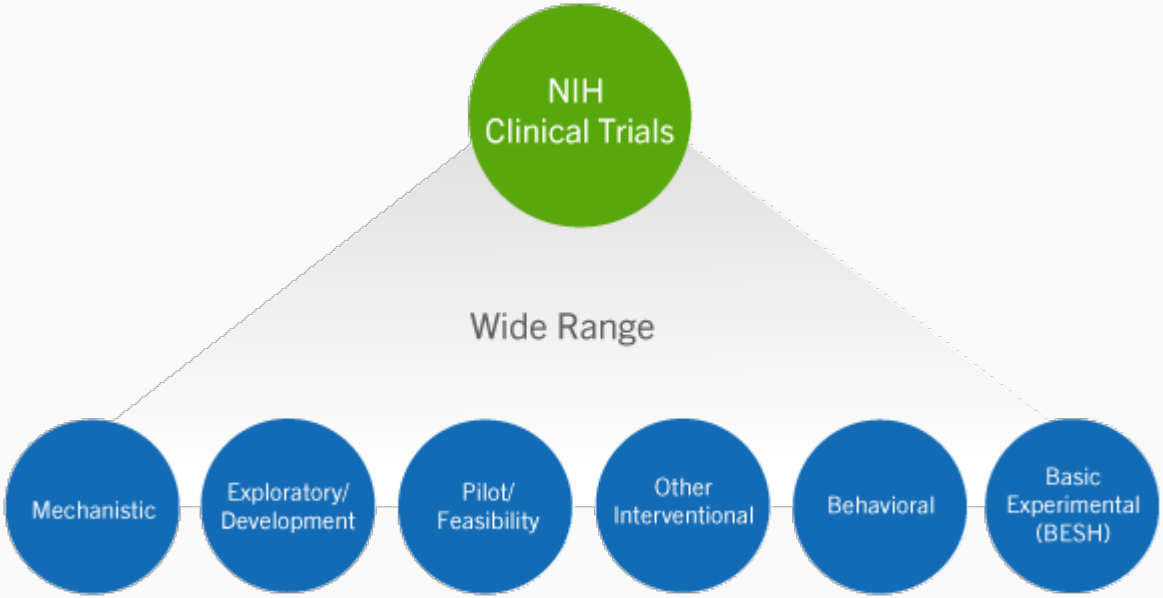
Research
Clinical Research
Clinical Trials

Clinical Trial Definition - NIH

NIH - Use the following four questions to determine the difference between a clinical study and a clinical trial: Tool Linked here

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?



Test Our Knowledge on NIH Definition

1. The study involves the recruitment of research participants who are randomized to receive one of two approved drugs. It is designed to compare the effects of the drugs on the blood level of a protein.

2. The study involves the analysis of de-identified, stored blood samples and de-identified medical records of patients with disease X who were treated with an approved drug. The study is designed to evaluate the level of a protein in the blood of patients that is associated with therapeutic effects of the drug.

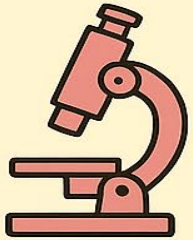
3. The study involves the recruitment of patients with disease X to be evaluated with a new visual acuity task. It is designed to evaluate the ability of the new task to measure visual acuity as compared with the gold standard Snellen Test

4. The study involves the recruitment of individuals to receive a new behavioral intervention for sedentary behavior. It is designed to measure the effect of the intervention on hypothesized differential mediators of behavior change.

1. Clinical Trial? Yes or No
2. Clinical Trial? Yes or No
3. Clinical Trial? Yes or No
4. Clinical Trial? Yes or No

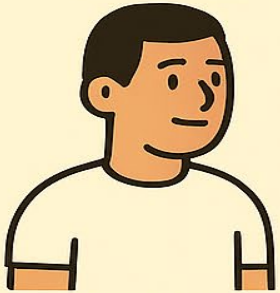
PHASES OF A CLINICAL TRIAL

0
PRE-CLINICAL



Lab-based research to tell if a treatment useful and safe

1
SAFETY



10–80 participants to assess effect of in humans

2
SAFETY & DOSING

100–300 participants to evaluate safety & effective dose of treatment

3
SAFETY & EFFICAY

300–3000 participants confirm benefit and safety of treatment

4
POST-APPROVAL

Post-approval surveillance to evaluate long term effects of treatment

Clinical Trial Parties and Their Roles

Commonly found ***within*** Institution

- **PI -** Physician who oversees the entire trial and responsible for participant safety and data integrity
- **Co-Is** - Support PI, may see patients or perform assessments outside of PI's specialty.
- Clinical Research Coordinator (CRC) -  Manages the day-to-day operations,, overseeing tasks like patient recruitment, data collection, and is the main point of contact for patients.
- **Regulatory Manager** - Prepares and maintains regulatory documents (IRB/EC submissions, FDA/EMA filings).
- **Research Nurse -** Provides hand-on nursing care such as administering treatments, monitoring side effects, and can advocate for patients.
- **Clinical Trial Project Manager** - Oversees the trial as a whole and coordinates teams

Clinical Trial Parties and Their Roles

Commonly found ***outside*** Institution

- **Sponsor –**
  - Funding Sponsor – Party that is suppling the financial support for the trial
  - Regulatory Sponsor – The party or individual responsible for the regulatory reporting and safety in the trial
    - You can have a funding sponsor that is a pharmaceutical company and the regulatory sponsor being the PI/Institution responsible for reporting to the FDA.
- Study Monitor -  Works for sponsor, visits sites to monitor compliance, review data, and ensure adherence to good clinical practice. Sometimes this is called a Clinical Research Associate (CRA).
- **Medical Monitor -** Physician reviewing safety data, advises on adverse events and serious adverse events 
- Contracted Research Organization (CRO) -  a specialized company that provides outsourced operational services for industry sponsors during. They can provide scientific, clinical and business continuity for sponsors.

Clinical Trial Protocol

CLINICAL TRIAL PROTOCOL SYNOPSIS

Protocol Title	Albumin in Acute Stroke Trial: A Phase III Randomized Multicenter Clinical Trial of High-Dose Human Albumin Therapy for Neuroprotection in Acute Ischemic Stroke
Acronym	ALIAS
Clinical Trial Phase	Phase III
Study Sites	• University of Miami (Study Chair Site and Fiscal Management Office) • DCU at MUSC (Data and Project Management and Statistics Center) • University of Calgary (Canadian Coordinating Center) • Approximately 60 clinical centers in US, Canada, and possibly other countries
Study Period	Planned enrollment period – 4 years Planned duration of the study – 5 years
Study Population	Acute ischemic stroke patients.
Primary Study Objective	To ascertain whether high-dose human albumin (ALB) therapy confers neuroprotection in acute ischemic stroke. (Specifically, to determine whether ALB therapy increases the proportion of acute ischemic stroke patients with favorable outcome compared to placebo therapy at 3 months from randomization.)
Secondary Study Objectives	To evaluate: • overall clinical outcome (as assessed by the global statistical test of NIHSS, mRS, and BI scores) at 3 months post-randomization. • neurological outcome as assessed by NIHSS score at 3 months post-randomization. • functional outcome as assessed by mRS and BI at 3 months post-randomization. • quality-of-life as assessed by EuroQol at 3 months and 1 year post-randomization, and by Stroke-Specific Quality of Life (SSQOL) instruments at 3 months post-randomization. • robustness of ALB therapy as measured by a favorable outcome of mRS of 0 or 1at 1 year post-randomization. • likelihood of recurrent ischemic stroke at 3 months and 1 year post-randomization, as assessed by Questionnaire to Validate Stroke-Free Status (QVSFS).

- **Definition**
  - It instructs the physician (primary investigator) and staff (study coordinators) how to execute the trial.
  - It describes how a trial is conducted, ensures the safety of study participants and ensures the integrity of the data collected throughout the trial.
  - It is also a communication tool with regulators and ethical review boards to share the intent and desired outcomes of a study.

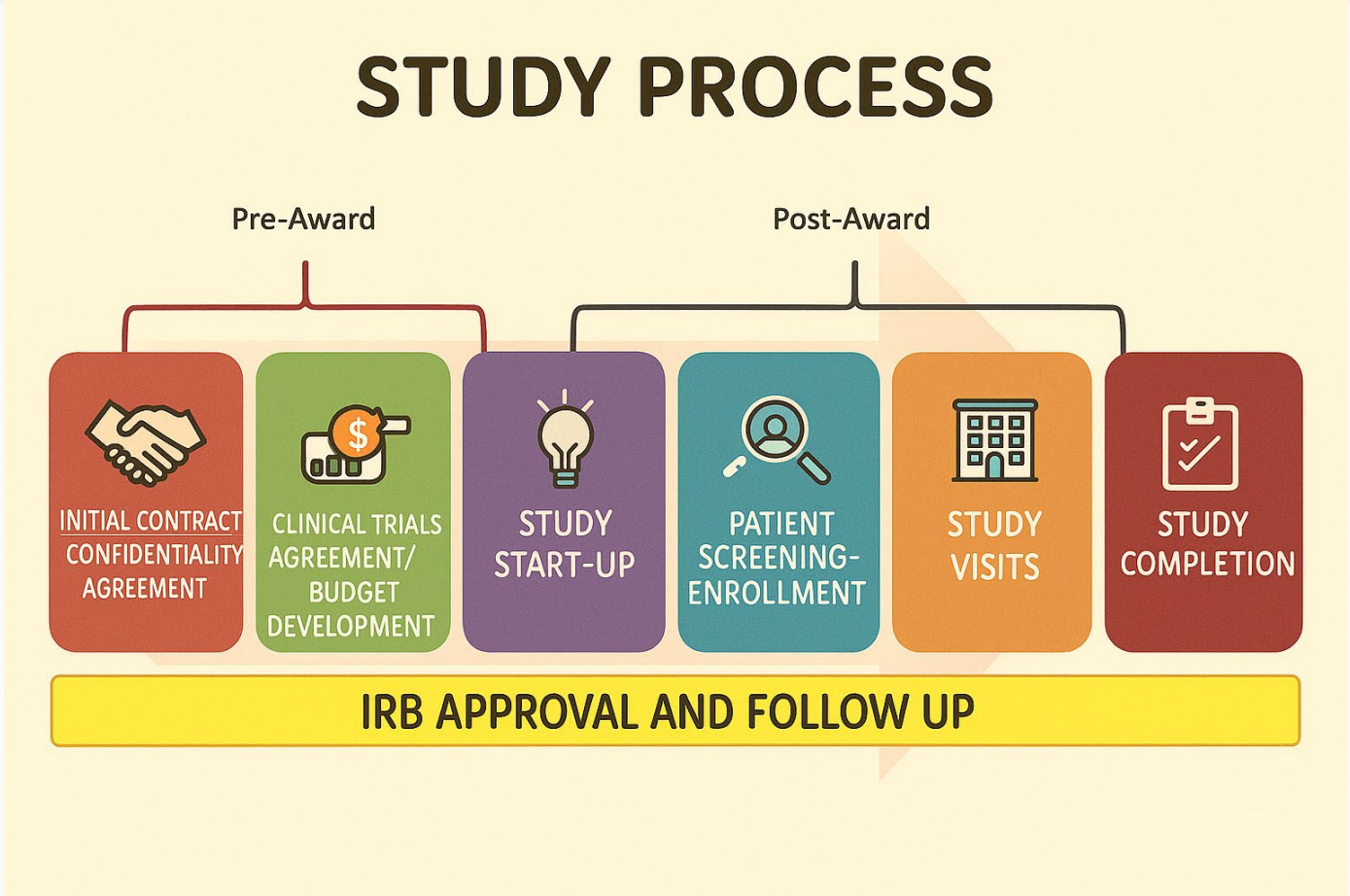
  - SOE: Table in a clinical trial protocol that provides a detailed timeline of all the study procedures, treatments, and assessments participants will undergo and when they will occur.
- Who drafts a protocol?
  - PI or Funder (ex: pharmaceutical company).
  - If PI drafts protocol, this is often called a Investigator Initiated Trial (IIT)

Example of SOE

Time and Events Schedule (Schedule of Procedures) for a Single Ascending Dose, First-time-in-human (FTIH), IND-enabling Phase 1/Phase I Clinical Study Protocol (Clinical Pharmacology Study Protocol)

	Screen Day –28 to –1	CRU Admission (Baseline)	Day 1			Day X to X	Prior to Discharge (Day X)	Follow-up ≥3 days and ≤5 days after Discharge
			Pre-dose	Dosing	Post-dose	Post-dose		
Informed Consent Form Signed	X							
Eligibility Review and Confirmation	X	X	X					
Medical History	X							
Physical Examination	X	X					X	X
Height Assessment	X							
Weight Assessment	X	X	X				X	
Urine Drug Test	X	X						
HIV & Viral Hepatitis Screen	X							
Vital Signs	X	X	X		X	X	X	X
12-lead ECG	X	X	X		X	X	X	
Clinical Laboratory (Blood) and Urinalysis	X	X	X		X	X	X	
Prior Medication Assessment	X	X	X					
Serum Pregnancy Test	X							X
Urine Pregnancy Test		X						
CRU Admission		X						
Randomization			X					
Administer Study Drug				X				
Pharmacokinetic Sampling (Blood)			X		X	X	X	
Pharmacokinetic Sampling (Urine)			X		X	X	X	
Treatment-Emergent Adverse Events				X	X	X	X	X
Concomitant Medication Assessment				X	X	X	X	X
CRU Discharge							X	X

Timeline for an Individual Clinical Trial Protocol



Clinical Trials - Pre-award (Study Startup)

Initial Contact / Request Confidential Disclosure Agreement (CDA/NDA)

Pre-study visit and site selection

Initiate Clinical Trial Agreement (CTA) and budget negotiations

Prep Regulatory Documents for Institutional Review Board (IRB) approval

IRB Approval, CTA agreed upon, budget agreed upon = Execute CTA

Site Initiation Visit (SIV)

*Startup events can happen in varying orders from above or several events in parallel

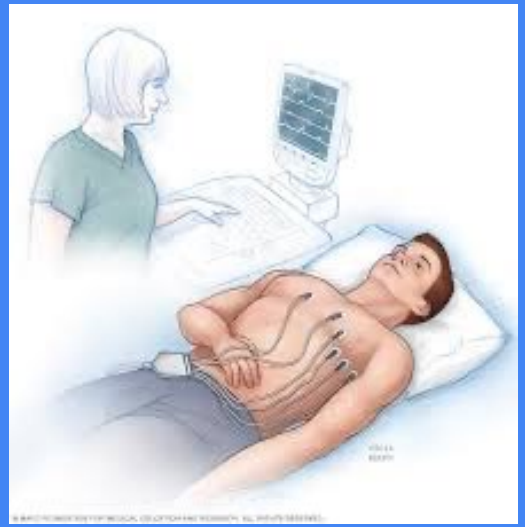
Clinical Trial Study Startup: Common Research Administrator Involvement

- Development and negotiation of CDA and (CTA)
  - Research Related Injury
  - Intellectual Property
  - Publication and Data rights
- Enforcing institutional specific policies
- Ensuring budget, contract align, and informed consent form (ICF) align
- Help study team think through feasibility / logistics
- Depending on institution and individual positions may be involved in other tasks related to regulatory, feasibility, or conducting the trial

Clinical Trial Study Startup: Common Research Administrator Involvement

- Development and negotiation of budget
  - Fixed Price Contract vs. Cost-Reimbursable
  - FTE vs. Per Patient Budget
  - Ensure effort is captured for study team
  - Coverage analysis
  - Payment Terms
  - Hospital Costs - CPT Codes (uniform language for coding procedures/services)
  - Invoiceables – fees directly related to the work on the clinical trial but happen at varying frequencies.

Example of CPT Codes and Budgets: ECG Tech Fee

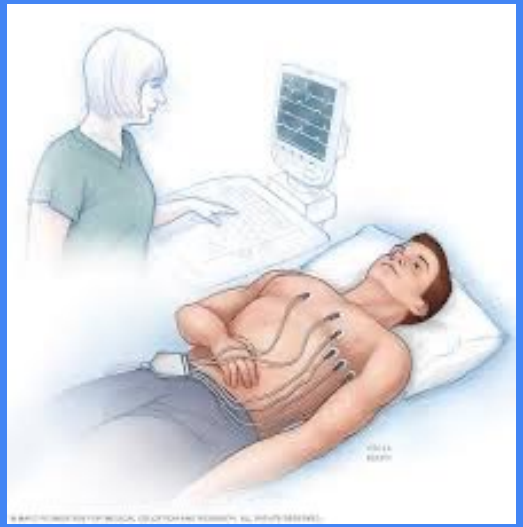


Tech Fee: These are charges related to the use of technology or equipment during a medical procedure or service. For example, if a patient undergoes imaging studies (like X-rays, MRIs, or CT scans), the tech fee would cover the costs associated with the use of the imaging equipment, maintenance, and the technical staff who operate the machines.

	Procedure Name	CPT	Price
Tech Fee	HC ECG HOSP	93005	$ 1,692*

*Every institution uses their own fees for CPT codes and apply research discounts in based on their own practices

Example of CPT Codes and Budgets: ECG Pro Fee

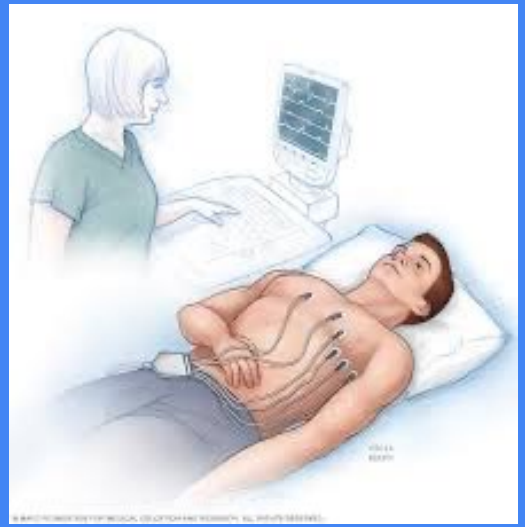


Pro Fee: These fees are associated with the professional services provided by healthcare providers, such as physicians, surgeons, or specialists. Professional fees compensate the healthcare provider for their expertise, time, and the clinical services rendered to the patient. This could include consultations, examinations, procedures, and follow-up care.

	Procedure Name	CPT	Price
Pro Fee	ECG ROUTINE ECG W/LEAST 12 LDS W/I&R	93000	$ 124*

*Every institution uses their own fees for CPT codes and apply research discounts in based on their own practices

Example of CPT Codes and Budgets: Pro + Tech Fee



	Procedure Name	CPT	Price
Tech Fee	HC ECG HOSP	93005	$ 1,692*
Pro Fee	ECG ROUTINE ECG W/LEAST 12 LDS W/I&R	93000	$ 124*
TOTAL Fee	ECG Fee Total	NA	$1,816

- For the budget: multiple the total fee by the # of occurrences for the procedures in the SOE.
- Some initiations add in inflation and contingency if hospital costs change yearly

*Every institution uses their own fees for CPT codes and apply research discounts in based on their own practices

Coverage Analysis

- What - Coverage Analysis is a systematic review that determines how each protocol-required item/service should be billed: to the study participant (insurance) or to the research account (sponsor). Started in 2000 when medicare implemented its first Clinical Trial Policy (NCD 310.1), which established rules for Medicare to cover "routine costs" in qualifying trials. The practice expanded with other regulations, such as the 2007 revision to the Medicare policy and the 2014 Affordable Care Act
- It requires a three-part process according to NCD 310.1 to determine:
  - Whether a study meets Medicare's definition of a Qualifying Clinical Trial that may support billing to a payor
  - Which items/services meet Medicare's definition of a Routine Cost
  - Whether other Medicare rules allow or limit coverage for the items/services (e.g., NCDs/LCDs)

*The document resulting from the review is referred to as the coverage analysis (CA).

Coverage Analysis

- When - The initial review and draft is completed in pre-award before patient enrollment. Then the CA is followed in post-award to help direct the flow of hospital charges in the compliant direction (insurance vs. sponsor).
  - This helps inform the budget on if we need to include clinical costs for sponsor to pay or if the procedure is standard of care(SOC) this is left out of the budget.
    - A patient's SOC refers to an item or service done as part of their routine care
- Why - Helps ensure clinical research billing compliance is followed to protect both the participant and the institution.
- Who - Depends on the institution (dedicated institutional official, third party vendor, or PI) - It is best an individual who has the knowledge of medicare billing compliance.

Example of Coverage Analysis - Billing Grid

Example of a coverage analysis grid

RBC-Patient Insurance Paid													
S-Sponsor Paid		Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	End of Study	Follow-Up				
Required Studies	**CPT/HCPCS**		Day 1	Day 1	Day 1	Day1	Day 1						
Physical											**NCD/LCD**	**Coverage Analysis Notes**	**Protocol Notes**
Physical Exam, History, Vital Signs	99211, 99212, 99213, 99214, 92201, 99202, 99203, 99204, 99205, G0463	S	RBC	RBC	RBC	RBC	RBC	S	RBC		No NCD/LCD	No NCD/LCD for this service. NCD 310.1 allows for coverage of routine cost of conventional care of items or services that are typically provided absent a clinical trial	
Laboratory													
CBC w Differential	85025	S	RBC	RBC	RBC	RBC	RBC	S	RBC		NCD 190.15	NCD 190.15 Blood counts are used to evaluate and diagnose diseases relating to abnormalities of the blood or bone marrow. Many treatments and therapies affect the blood or bone marrow, and blood counts may be used to monitor treatment effects	
Specimen Submission													
Research Blood for Banking	N/A	S					S	S	S			Research Lab	Protocol Notes: Collect specimen for research purpose
Research Tissue for Banking	N/A	S					S	S	S			Research Lab	Protocol Notes: Collect specimen for research purpose
Scans													
CT Chest w Contrast	71260, Q9967	S	RBC				RBC		RBC		LCD:L33459	LCD:L33459 The following clinical indications apply to the computerized axial tomography (CT or CAT) of the thorax. Diagnosis and/or staging of neoplastic and hematologic processes arising in the thorax or with potential involvement of the thorax	Protocol Notes: Disease assesements and CT/MRI mut be performed every 8 weeks)+/- 1 week)
Drug Administration													
Infusion 1st hr of Administration	96413		R	R	R	R	R				No NCD/LCD	No NCD/LCD for this service. NCD 310.1 allows for coverage of routine cost of conventional care for items or sevices that are required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent)	

Clinical Trials - Post-award

Recruitment / Screening - finding patients who are eligible in the trial

Enrollment - Patient approached with Informed Consent Form (ICF) and agrees to be in trial

Conduct Study visits outlined in protocol, monitor study, and collect data

Invoicing sponsor and financial reconciliation

Managing protocol and study amendments

Study closeout / Sponsor reviews data for next phase

Clinical Trial Post-Award - Common Research Administrator Involvement

- Monitoring the budget
  - Especially with a fixed price trial - costs can fluctuate but the payment remains the same.
- Invoicing
  - Sending sponsor invoices for milestones met in contract (could be visits completed and data entered into EDC💡)
  - Working with CRC and PI to
- Financial reconciliation
  - Review hospital charges and they were charged based on CA.
  - Track payments received by sponsor
- Amendments to budget and contract
  - Can be driven by protocol amendment
  - Not all protocol amendments needs budget and contract amendments
- Ensuring compliance with award terms
  - Ex: Sabbaticals or disengaging in clinical trial
- Final Closeout - Final invoicing

How can RA’s help clinical trials?

- Act as central point of contact and liaison with stakeholders (study team, IRB, sponsor, CRO, institutional officials, etc.)
- Helping navigate institutional and federal compliance and processes
- Provide support with budget development and management
- Support contract drafting, execution, and management of amendments
- Help streamline complex processes and lessen administrative burdens


Questions?