University of CINCINNATI

Investigator Initiated Trials: Best Practices and Lessons Learned

Thursday, September 21st, 2023

Friday, October 6th, 2023

Electronic Pathways: HIPAA, Texting, Emails

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This First Friday Session will be offered IN PERSON, MSB Rm E684, along with a virtual option to join as well

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Compliance Corner

Clinical Research Device Study Procedures for UC Health Evaluation and Approval

There is a new process required for Evaluation of Clinical Research Devices within the UC Health System. If the clinical research device involves a cost to UC Health, requires any type of management of the equipment by UC Health, involves the UC Health Supply Chain, or requires sterile processing, the study team will need to submit for a value analysis (VA) here. If the device does not fall into these categories, there is no need to submit for VA. See details here.

For any questions or further information, please contact Nate Harris at harrisnl@ucmail.uc.edu or anyone from the Office of Clinical Research

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Today's Presentation:

Investigator Initiated Trials: Best Practices and Lessons Learned

Join the UC Cancer Center Clinical Trials Office staff for an informative presentation on Investigator Initiated Trials (IITs). You will learn how to identify the resources needed to conduct an IIT, how to write an effective research protocol, as well as tips for navigating the study start-up process. UCCC CTO staff will share their lessons learned and best practices for effectively opening and running IITs.

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Casey Allen
Allie Forsythe
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University of Cincinnati Cancer Center

Investigator Initiated Trials (IITs) Best Practices & Lessons Learned

Presented on September 21, 2023

Allie Forsythe, UCCC CTO Project Manager/IIT Monitor
Amy Hoffman, UCCC CTO Project Manager/IIT Monitor
Casey Allen, UCCC CTO IIT Data Manager
Michelle Marcum, UCCC CTO Director
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University of CINCINNATI CANCER CENTER

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Agenda

1. **What is an IIT & how complex can it be? (Michelle)**
    i. Definitions and average time to complete
2. **Resources & Feasibility: (Michelle)**
    i. Budget, contracts, staffing, sample collection & storage at a single or multiple sites, Drug/device procurement, subject availability
3. **Writing an IIT protocol (Nicky)**
    i. Feedback on design, Templates to use, QC for real world usage, developing other documents (SOPs, MOPs, DSMP) and EDC
4. **Navigating the start-up process (Nicky)**
    i. Internal reviews, UC committees & IRB, FDA & ct.gov
5. **Best practices & lessons learned (Casey/Allie/ Amy)**
    i. Internal QC (audits, HRPP, DSMB), database reviews, regular documented meetings with teams, protocol amendments

Definition & Types of IITs

- An IIT is a clinical trial or study that is primarily initiated and sponsored by an individual ("PI" or "Principal Investigator") rather than by an organization (NIH, NCI) or company (Pharmaceutical or device makers).
- An IIT can involve the support of an organization (e.g., funding, staff, facilities) or the support of a company (e.g., funding, or drug/device provided) but will be primarily written & conducted by the PI.
- An IIT can be any phase of research (Pilot or Phase I-IV).

Types of IITs Cont.

- Very simple IITs: chart reviews or only sample collection, single center & minimal risk
- Moderately complex IITs: single center, SOC procedures, no contracting, working with non-vulnerable adult populations
- Complex IITs: single center with industry or grant support but no FDA IND/IDE, working with vulnerable populations
- Very complex IITs: multi-center with PI-held IND/IDE and industry support, or single center with PI-held IND/IDE and industry support
- Always expect delays- and budget for at least 1 year longer

IIT Resources & Feasibility

- Budget to support design – how to build a budget and find fiscal support
- Contracting
- Staffing & facilities & training
- Test article (drug/devices) from company
- Sample collection & shipping & storage
- Availability of participants
- Time-frame – months/year to open

Budget Guidance

- **Direct Costs**: Direct costs are costs that can be identified specifically with a particular sponsored project that can be directly assigned to such activities relatively easily with a high degree of accuracy.
  - Personnel-salary/benefits and estimate of time required
  - Lab Supplies-sample collection materials, reagents, gloves, shipping supplies, storage costs
  - Participant support-travel allowances, remuneration, stipends
- **Indirect Costs**: Overhead, Facilities & Administrative costs; "Cost of doing business" (ex. Building maintenance, SRS, custodial, standard computers and office phones.)

Example Grid #1

Procedure	Fee	Screening	Biopsy	Chemotherapy	Surgery	Recurrence	SFU1	SFU2	SFU3	SFU4	SFU5
Biopsy	SOC		SOC		SOC	SOC					
Tissue Requests- Pathology	300		300		300	300					
Tissue Shipping and Handling Effort	50		50		50	50					
Blood collection	SOC		SOC		SOC	SOC					
Blood Processing	75		75		75	75					
Blood Sample Shipping and Handling	50		50		50	50					
Chemotherapy	SOC			SOC							
Surgery	SOC				SOC						
Informed consent	200	200									
Inclusion/exclusion	50	50									
Data	75	150	150	150	150	150	75	75	75	75	75
Subtotal (direct costs)		$ 400.00	$ 625.00	$ 150.00	$ 625.00	$ 625.00	$ 75.00	$ 75.00	$ 75.00	$ 75.00	$ 75.00
Direct cost per patient	**$ 2,800.00**										

Budget Guidance

- Excel grids are a helpful starting point:
  - Clinical Care costs
  - Pharmacy fees
  - Supplies
  - Database development, analysis and stats support costs
  - IRB fees, other committee fees
  - CRC costs, monitoring costs
  - PI effort (required if funded)
- OH rate-dependent on funding source
- Hospital approval/Medicare coverage analysis – confirm if the standard practice of the PI is actually allowed to be charged to insurance

Example Grid #2

Procedures									
	Unit Cost	Frequency	Screening	Pre-treatment	C1D1	C2D1	C3D1	C4D1	C5D1
TESTS & OBSERVATIONS									
LP-108 dispensing	$50.00	13					1	1	1
LP-108 compliance	$50.00	13						1	1
Prevnar 20 product	$400.00	1							
Prevnar 20 administration, 90471	$100.00	1							
CT CAP (if applicable)	$4,500.00	0		INV					
BM- biopsy	$3,200.00	SOC		SOC					
Disease assessment	$300.00	2					1		
QOL	$50.00	3		1					
Correlative Labs/Biopsy (CRP)	$50.00	11		1			1		
PERSONNEL									
Treating Investigator	$150.00	24.25	1	1	1	1	1	1	1
Clinical Research Coordinator	$75.00	52.5	4	3	2	2	2	2	2
Data Entry	$50.00	50	2.5	2	2	2	2	2	2
Monitor	$100.00	24.25	1	1	1	1	1	1	1
Sub-total			**$675.00**	**$675.00**	**$500.00**	**$500.00**	**$600.00**	**$600.00**	**$600.00**
PI effort	**10% direct budget**		**$67.50**	**$67.50**	**$50.00**	**$50.00**	**$60.00**	**$60.00**	**$60.00**
Overhead Rate	**35%**		**$259.88**	**$259.88**	**$192.50**	**$192.50**	**$231.00**	**$231.00**	**$231.00**
Total			**$1,002.38**	**$1,002.38**	**$742.50**	**$742.50**	**$891.00**	**$891.00**	**$891.00**

Example Grid #2-correlative budget

Sample Collection	
Proteomic Stabilizer PROT1	$2,500.00
Storage, shipping and handling	$2,500.00
consumables (tubes, tips, etc)	$2,000.00
Flow cytometry	
Antibodies and buffers	$45,000.00
Consumables (plasticware, tips, etc)	$5,000.00
Flow cytometer maintinence	$5,000.00
Travel	$5,000.00
Vaccine response assessment	
Mayo Clinical Laboratories	$20,000.00
Publications	$4,000.00
Salary	
Senior technician (salary + inflation 3% + fringe)	$51,680.00
DirectTotal	$ 142,680.00
PI oversight fee, per policy	$ 14,268.00
Indirects (35% industry contract rate)	$ 54,931.80
grant total	$ 211,879.80

Contracting Guidance

- UC Office of Sponsored Research Services
  - https://research.uc.edu/support/offices/srs

If your IIT has an industry partner or is working with another site you will need a contract – if not these won't apply

- CDA – confidentiality agreement, allows for sharing of the protocol, investigator's brochure and other proprietary materials
- CTA – clinical trials agreement – defines who is providing what, paying for what, and when certain activities must occur
- MTA – Materials Transfer Agreement – use if you are only sending or receiving research samples (no money or test article involved)
- DUA – Data Use Agreement – use if you are only sending or receiving a limited data set (PHI) (no money or test article involved)

Staffing & Facilities Guidance

- The PI and any delegated staff must have adequate training and experience to carry out the trial/perform their roles
  - A Delegation of Authority Log – best practice to have, and helps meet FDA requirements (if applicable)
- Students (undergrads, med students, residents)
  - Need mentorship and have turnover issues
- PI Oversight: takes time and training to do well
  - Build in time for regular meetings with research team
  - Ensure staff are really trained in research best practices and protocol
- Facilities: space for sample storage, space for private consent conversations and procedures to occur, adequate lab equipment

Research Sample Guidance

- Samples at standard of care timepoints – save time and money
  - Would labs be collected even if patient never was on study? Yes = SOC
- Confirm enough extra tissue or blood etc.. will be available if you intend to collect from a SOC procedure
- Know what experiments will be run – impacts viability (fresh/frozen)
- Who will collect? Are they trained/qualified to do so?
- If participants will self-collect (stool, saliva, urine) procedures in place to de-identify sample or make it easy for the participants to do?
- Shipping and storage locations, duration and costs
- UC Biorepository https://med.uc.edu/research/core/Index/195/Facility/
- UC Histopathology https://researchdirectory.uc.edu/facilities/194

Availability of Subjects

- Work with a statistician to determine how many participants you really need to meet your proposed endpoints
  - Stats consults (non biomedical) https://www.artsci.uc.edu/departments/math/division-of-statistics-and-data-science/statistics-consulting-center.html
  - Biostatistical consults https://med.uc.edu/depart/eh/divisions/bio
- Determine if enough participants exist locally
  - Consider barriers to participation and how they can be removed (fewer visits, use SOC timepoints)
  - Consider recruitment strategies (flyers, websites, community groups, provider referrals, EMR review) and plan for IRB approval.
- Multi-center studies – can help enroll hard to find populations
- The longer it takes to meet enrollment goals, the more money you will need.

Writing an IIT Protocol

- The first step to writing a protocol is to NOT write a protocol
  - Get as much feedback on your design as possible – meet with a statistician for your endpoints and colleagues/CRCs for feasibility
  - Ensure your design meets the budget (# participants, time to complete)
  - Do a lit review – has your study already been done?
- Use the right template: UC IRB, NCI, NIH, or industry (ICH-GCP defines the core components of a protocol)
  - Do NOT borrow an existing protocol & modify it – risk of leaving in unintended/unapplicable content
- Use version dates and a shared editing platform (OneNote)

Writing an IIT Protocol Cont.

- Be clear about what is being done ONLY for research vs standard of care in the protocol (spell it out expressly)
  - Helps IRB correctly evaluate risk level
  - Helps ensure budget correctly reflects what study must pay for (protocol updates when writing, re-check your budget)
- Write *precisely* to increase reproducibility of results and limit protocol deviations:
  - Don't abbreviate without definitions, be consistent in your terminology and use tools like schema and study calendar
  - Avoid compound sentences with eligibility criteria: For example: 1. Males who are bald vs 1. Male 2. Bald. Or X procedure must be done before Y.
- If multi-center specify what activities can follow each site's own practices vs the protocol's requirements

Writing an IIT Protocol Cont.

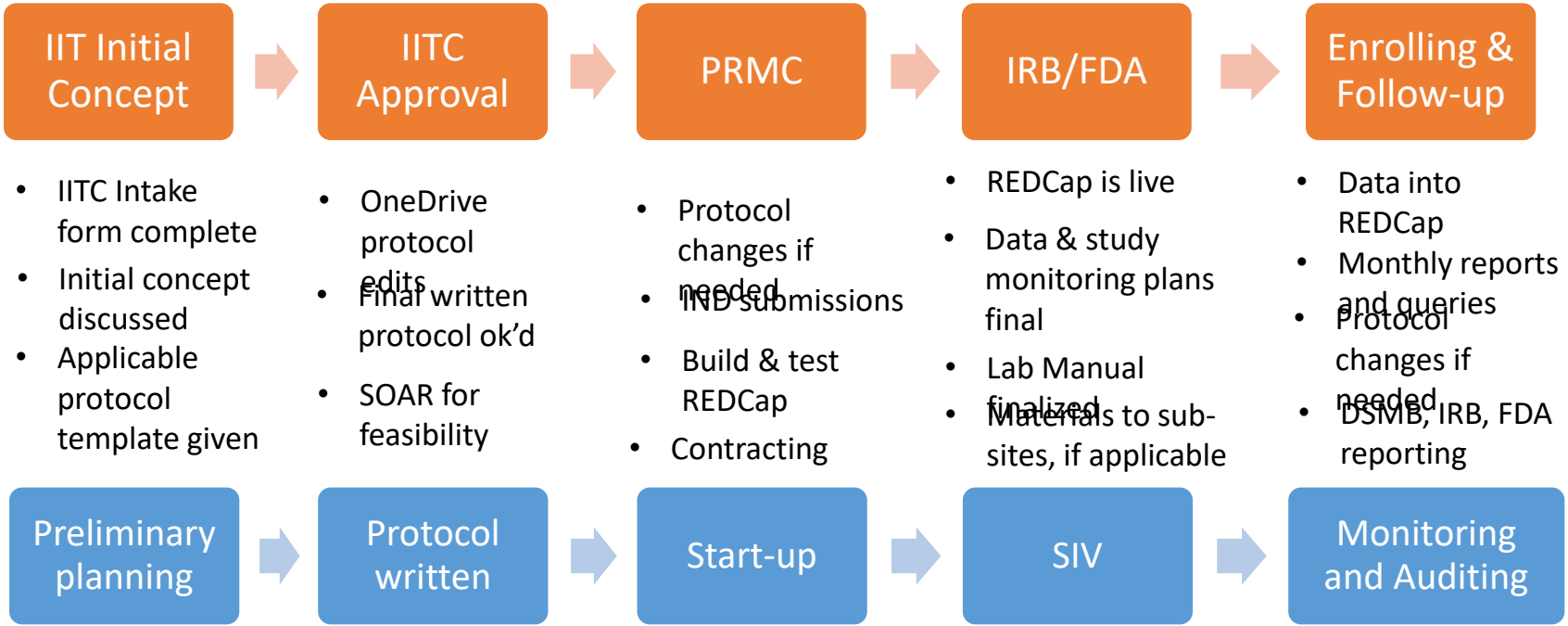
- A protocol can be a few pages to hundreds of pages long
- Use tools like a study schema (visual representation of the study) and a schedule of assessments/study calendar for complex trials
- Do not repeat similar information throughout the protocol – use internal references (e.g., See section 1 for information on timing of AE collection).
- **QC the final version** by having someone unfamiliar with the study **pretend to enroll a participant**.
- **Have the protocol be assessed against reality** - if you intend to recruit in a clinic setting or perform procedures in certain locations/timepoints is it possible to do in practice?
  - Be sure to meet with the staff/persons who oversee the locations you intend to work in
  - Think about how long the patient will actually be on site – would the average person actually agree to the activities and length of participation?

Other IIT Documentation

Most will require IRB approval before use

- Consent form & HIPAA Authorization (paper or electronic)
- Recruitment materials
- QOL forms & standard assessments or surveys, pill diaries
- Standard operating procedures (SOPs) or a Manual of Procedures (MOP) to outline how to perform certain study procedures
- Monitoring Plan, Pharmacy Manual, Data Guides
- Case Report Forms (CRFs) and/or study database (excel, REDCap) - ensure these comply with Good Clinical Practice data practices if FDA regulated in particular ALCOAC
  - (Attributable, Legible, Contemporaneous, Original, Accurate, Complete)
- Laboratory Manuals for sample collection & processing

Overview of IIT Start-up Process at UCCC



Start-up Process for IITs

- Pre-award: grants/contracts execution
- Budget/feasibility – departmental level (UCCC SOAR)
- Scientific review – departmental level (UCCC PRMC)
- Radiation Safety/Biosafety committees at UC
- Conflict of Interest – mitigation plans
- FDA submissions – IND/IDEs & monitoring plans
- IRB submissions – local IRB
- Clinicaltrials.gov registration
- Hospital approval/Medicare coverage analysis
- Site Initiation Visit – training your team and getting essential documents if FDA regulated
  - 1572, DOA logs, IB receipt, IP accountability etc..

Ways to Improve Your Data

PROMOTE A DATA-DRIVEN CULTURE

FOCUS ON TRAINING AND REMINDING

COMMUNICATION

ENSURE DATA IS TIMELY AND UP TO DATE

CONDUCT REGULAR AUDITS OF THE DATA

Basic Practices

- Written procedures
  - Follow the workflows and instructions
- Proper training
  - Receive training from team
- Appropriate access
  - IRB Approved*
  - GCP training
  - Delegated by the PI
  - Signed and dated CV (within 2 years)
- Verify EDC in development
  - Provide feedback before study goes live

Basics Practices

- Data Monitoring
  - Double data entry (third-person adjudication)
    - 2 people enter data, a 3rd verifies

    → Gold Standard
  - Single data entry with a review
    - 1 person enters data, 1 person verifies

    → Study Monitoring

Ways to Reduce Data Entry Errors

- Have appropriate resources (staffing, time, tools, etc.)
- Hard code data validations in the EDC
- Design EDC to look as close to the CRF as possible
- Standardize data entry
- Identify sources of inaccuracies
- Reduce data redundancy or useless data
- Enable automation

EDCs

- Electronic Data Capture

- https://www.cctst.org/
  - Click on Research Resources

Best Practices: Open & Active IITs

- At SIV, if a protocol amendment is upcoming mention it.
- Submit protocol amendments to the IRB before implementing changes – amendments happen!
- Work in an "audit ready" state – have all research notes and source documentation completed in as close to real time as possible.
  - **If it is NOT documented, it did NOT happen**
- Maintain communication amongst start-up teams, project managers, and study teams to minimize delays in opening.
- Routinely meet with the study team to ensure they have a chance to ask questions and receive ongoing training on study procedures and amendments.
- QC study data – have a neutral party audit or have team members cross check each other's work to avoid transcription errors/missing source/protocol deviations.

Best Practices: Open & Active IITs

- Routine monitoring visits- Verification that source, data, procedures, and documentation are being collected in accordance with ICH-GCP guidelines.
  - The earlier in the study timeline, the better!
- When updates are made regarding procedures or order of operations, ensure updates are being made to SOPs and workflows to ensure consistency amongst staff.
- Routinely review data collected to confirm it is what is needed for publication and to check on safety.
- Check in with the lab to ensure all samples are being collected and stored properly.
- Ensure continuing review is completed within the IRB specified time-frame.

IITs: UCCC Lessons Learned

- IITs often under-estimate cost and time to completion, as well as the number of participants who can be recruited.
  - Impact of sub-sites
- Almost all IITs will have protocol amendments - red flag if they don't.
  - Incorporate revisions in order to minimize number of amendments
  - Ensure ICF and Lab Manual are updated as applicable
- Research sample analysis is often an afterthought.
  - If samples are not processed/stored appropriately downstream experiments will fail/can't occur.
  - If sub-site is performing analysis, ensure MTA is in place (if CTA is not in place) to allow for samples shipped to correct lab

IITs: UCCC Lessons Learned Cont.

- Eligibility criteria are usually too broad or too strict initially.
  - When lab values are used for eligibility, institutional ranges need to be considered.
- Following procedure and visit windows is key to avoiding protocol deviations.
  - If a research visit involves another physician/team for surgery or a procedure, CRCs may need to coordinate with other team to collect necessary samples, questionnaires, AEs.
  - Review window for procedures and visits to make sure it is feasible clinically.
  - Deviations collected in as close to real time as possible
- Training on protocol amendments.
  - Discuss changes with team
    - Samples appropriately collected, stored, and shipped
    - Reconsent procedures if applicable
    - Imaging requirements
    - Inclusion/exclusion criteria

Thanks for Listening!

Questions?

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