Navigating the Research Process at Carilion

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CARILION CLINIC

Objectives:

- Participants will have clear understanding of research process at Carilion Clinic
- Participants will be aware of the resources available to support their research endeavors
- Participants will be aware of the different entities at Carilion that are responsible for research oversight

Agenda:

- Navigating the approval process
  - R&D, IRB, COI
- Startup Process for Grants, Industry-funded trials, and non-funded studies
- Research oversight at Carilion
- SOPs governing clinical research

Introduction:

- Carilion Clinic is an Academic Medical Center with over 300 active research studies

- As we continue to grow, our goal is to educate our current and future researchers to ensure that their research endeavors are successful

Research Approval Process at Carilion:

- Research projects at Carilion require specific approvals before project initiation (R&D, COI, IRB)

- Additionally, research training is required by R&D and the IRB

Required Training

- Human subjects research requires CITI training (www.citiprogram.org)
  - Basic Biomedical and Good Clinical Practice module
  - GCP is required for FDA regulated research
- R&D Research Training
  - Research training is available by request from R&D representatives
- R&D Educational Modules are being updated and will be available for use in the spring

R&D Application

- When seeking approval for a new research project, the first step is to complete the Research and Development application. This is also known as the “Department Level Review” and requires a signature from the investigator’s department chair/leader.

- **This application is available electronically at:**
  - https://is.gd/RnD_eCRAF

- The R&D application provides department level approval for study personnel assignments and also serves as a trigger point for R&D to send the application to the Carilion Research Review Committee and/or to schedule a feasibility review meeting and begin contracting/budgeting, if needed.

R&D Approval

- CRRC reviews all non-funded studies
  - Data/Statistical Support
  - Privacy and Security
  - Human Resources/Feasibility
  - Contracts
- CRRC will provide feedback within 5 business days for studies that require revisions
- Industry funded studies are reviewed by Director of Clinical Trials
- Grant funded studies are reviewed by Grants Administrator
- Once study is deemed satisfactory by CRRC, Director of Clinical Trials, or Grants Administrator, R&D provides approval letter
- **The IRB will not approve a project without R&D letter of approval**

Conflict of Interest (COI)

- Funded studies also require COI disclosure
  - Contact Kristina Cooper to complete COI questionnaire (kecooper1@carilionclinic.org)
  - For investigators and study team members with a financial conflict, compliance will work with you to create a management plan. If a plan cannot be created, the study may not be able to be completed.
- Non-funded studies do not require COI disclosure
- This should be completed early in the process to avoid delays
- **The IRB will not approve a funded study without COI clearance**

IRB Approval

- Following R&D approval and COI clearance (funded studies only), the study team can submit to the IRB for the final step in the approval process.

- Carilion Clinic's IRB reviews all human subjects research and can provide QA/QI determinations for projects that do not meet criteria for HSR

- Industry-funded clinical trials are reviewed by Carilion Clinic IRB for personnel and local safety issues, but rely on Western IRB as the IRB of record.

IRB Approval, Continued

- The IRB has recently launched an electronic review system PRI3SM
  - https://carilionclinic.imedris.net
- The IRB will review your submission and provide feedback.
- The study may meet criteria for expedited review and can be reviewed without convening the IRB review committee
- If the study meets criteria for full board review, it will be brought before the IRB review committee for discussion with the investigator and study team.
  - Please visit the IRB's website for additional details regarding exempt, expedited, and full board criteria
  - https://www.carilionclinic.org/irb/policies
- Once the review is completed and the application is determined to be acceptable, approval will be granted.
- **Any changes to your study protocol, personnel, or study materials, such as the Informed Consent Form, require additional approval.**

What is the difference between IRB approval and R&D approval? Why are both necessary?

- The IRB is responsible for protecting the rights and welfare of human subjects research participants

- R&D is responsible for operational aspects of research such as billing compliance, contracting/budgeting, feasibility analysis, and personnel assignments.

In a Nutshell

- IRB approves studies if they are safe and ethical

- R&D approves studies if they are feasible for the organization and have reasonable contract terms

Which studies require a feasibility meeting?

- Any study that prospectively enrolls patients and involves an intervention.
  - I.e., a drug, device, or research procedure is being studied

- Survey studies, observational studies, and retrospective studies **do not** require feasibility meetings.

What is discussed at a feasibility meeting and why is that important?

- Approval from ancillary departments
- Coverage analysis
- Budget development and review
- Contract review
- Logistical flow of study schedule of events
- Appropriate patient population – TriNetX
- Any glaring issues that would keep us from being successful?

Industry Funded Clinical Trial Startup Process

- Non-Disclosure Agreement/Confidentiality Agreement (NDA or CDA) – negotiated and executed by R&D and sponsor R&D application is submitted

- Site/Institution assesses feasibility of protocol

Contract and Budget Negotiation

- Once feasibility has been confirmed, Carilion (Institution/Site) begins budget and contract negotiations
- Institution/Site must ensure that the contract protects us and our patients' best interests, while also working quickly with the sponsor to execute the agreement
- The calculated internal costs to complete the study are compared to the sponsor's proposed budget (external budget).
- If the budget is comprehensive enough to cover our internal costs, it is accepted (this is rare).
- If the budget does not cover internal costs, negotiations begin. Carilion applies a 30% overhead fee to all costs associated with industry-sponsored clinical trials.

IRB Submission

- Upon contract execution, clinical trials are submitted to the Institutional Review Board.
- Some institutions may not require contract execution prior to IRB submission but Carilion Clinic requires this for financial risk management.
- Carilion has an agreement with Western IRB for review of all industry-funded trials. WIRB is a central IRB, meaning that a protocol for a multi-site trial can be reviewed once and approved for many sites, rather than each individual site's IRB granting approval.

Site Initiation Visit (SIV)

- Following IRB approval, the study sponsor holds a site initiation visit. This is a comprehensive training visit for all study staff

- Once the SIV has been completed, the site may begin enrolling patients to the trial.

Sample Schedule of Events

APPENDIX I

STUDY FLOW CHART

Procedure/Test	Visit #1 (Baseline)	Visit #2 (Study Days 5-7)	Visit #3 (Study Days 2-4 after therapy)	Visit #4 (Study Days 21-28 after therapy)	Early Withdrawal
Medical History	X				
Physical Exam	X	X	X	X	X
Chest X-ray	X		X	X*	X*
Culture & Gram stain	X		X	X*	X*
Blood Samples	X		X		X
Pregnancy Test	X				
Pharmacokinetics	X	X			
Urinalysis	X		X		X
Signs and Symptoms	X	X	X	X	X
Adverse Events		X	X	X	X
Clinical Response			X	X	X

* Repeat only if positive at Visit #3 (Study Days 2-4 After Completion of Therapy)

Sample Budget

Carilion Medical Center

Investigator:	**Smith**
Protocol #:	**NDP-1003**
Sponsor:	**CCRP Pharma**
Project Period:	
Minimum # of Pts:	20
Manimum Expected Payment:	$ 80,964.00

Visit Number or Title	CPT Code	Unit Cost	Baseline Visit 1	Day 5-7 Visit 2	D 2-4 after tx Visit 3	D 21-28 after tx Visit 4	Early W/D Visit	Total
Coordinator Time: $/hour		**$ 60.00**	**$ 480.00**	**$ 105.00**	**$ 105.00**	**$ 105.00**	**$ 105.00**	**$ 900.00**
Informed Consent	-		1.00					
Medical History	-		1.00					
Con Meds	-		1.00	0.25	0.25	0.25	0.25	
Vital Signs	-		0.25	0.25	0.25	0.25	0.25	
Follow-up Form	-		0.50					
Subj # Assignment	-		0.25					
Adverse Event Assessment	-			0.25	0.25	0.25	0.25	
Data Entry	-		2.00	1.00	1.00	1.00	1.00	
Prescreening	-		2.00					
Physician Time: $/hour		**$ 200.00**	**$ 100.00**	**$ 50.00**	**$ 50.00**	**$ 50.00**	**$ 50.00**	**$ 300.00**
Eligibility Review	-		0.25					
Signs & Symptom Assessment	-			0.00	0.00	0.00	0.00	
Clinical Progress/Response	-				0.00	0.00	0.00	
Physical Exam	-		0.00	0.00	0.00	0.00	0.00	
PI Oversight			0.25	0.25	0.25	0.25	0.25	
Office Visits:			**$ 200.00**	**$ 162.00**	**$ 162.00**	**$ 162.00**	**$ 162.00**	**$ 848.00**
Screening	**90801**	$200.00	1					
Follow-up 1	**99213**	$162.00		1	1	1	1	1
Laboratory			$ 176.00	$ 14.00	$ 113.00	$ -	$ 113.00	**$ 416.00**
Respiratory Culture	**92312**	$45.00	1		1	0	1	
Gram Stain	**92465**	$22.00	1		1	0	1	
Susceptabilities	**93308**	$20.00	1					
Pathogen identification	**94242**	$23.00	1					
Phlebotomy	**36628**	$4.00	1		1		1	
Hematology	**59874**	$15.00	1		1		1	
Chemistry	**56492**	$15.00	1		1		1	
PK Shipping & Handling	**22485**	$14.00	1	1				
Urinalysis	**61324**	$12.00	1		1		1	
Urine Pregnancy Test	**31656**	$6.00	1					
Pharmacy			$ 50.00	$ 25.00	$ -	$ -	$ -	**$ 75.00**
Randomization		$10.00	1					
Drug Dispense		$15.00	1					
Drug Accountability		$25.00	1	1				
Radiology			$ 150.00	$ -	$ 150.00	$ -	$ 150.00	**$ 450.00**
2 view X-ray (PA & Lat) - HB	**71020**	$100.00	1		1	0	1	
2 view X-ray (PA & Lat) - PB	**71020**	$50.00	1		1	0	1	
Subject Stipend			$ 25.00	$ 25.00	$ 25.00	$ 25.00	$ 25.00	**$ 125.00**
Stipend		$25.00	1	1	1	1	1	
Subtotal Per Patient/Per Visit			**$ 1,181.00**	**$ 381.00**	**$ 605.00**	**$ 342.00**	**$ 605.00**	**$ 3,114.00**
Indirect Cost Rate		***30%***	***$ 354.30***	***$ 114.30***	***$ 181.50***	***$ 102.60***	***$ 181.50***	***$ 934.20***
TOTAL PER PATIENT PER VISIT			**$ 1,535.30**	**$ 495.30**	**$ 786.50**	**$ 444.60**	**$ 786.50**	**$ 4,048.20**

Initiation and Maintenance Fees (FIXED budget)

			FEE	OVERHEAD	TOTAL
Start-up Total:					**$ 9,282.00**
Startup Up		**to be invoiced**	$ 3,240.00	$ 972.00	$ 4,212.00
Contract & Budget Negotiations		**to be invoiced**	$ 3,900.00	$ 1,170.00	$ 5,070.00
Close out Fee/Document Storage		**to be invoiced**	$ 500.00	$ 150.00	$ 650.00
Pharmacy Start-up		**to be invoiced**	$ 1,000.00	$ 300.00	$ 1,300.00
Pharmacy Annual Maintenance Fee		**to be invoiced**	$ 1,000.00	$ 300.00	$ 1,300.00
Chest x-ray (as needed at V4 & EW)	**71020**	**to be invoiced**	$ 150.00	$ 45.00	$ 195.00
Respiratory Culture (as needed at V4)	**92312**	**to be invoiced**	$ 150.00	$ 45.00	$ 195.00
Gram Stain (as needed at V4)	**92465**	**to be invoiced**	$ 150.00	$ 45.00	$ 195.00
Follow-up (as needed), up to amount		**to be invoiced**	$ 285.00	$ 85.50	$ 370.50
Screen Failures, up to amount		**to be invoiced**	$ 861.00	$ 258.30	$ 1,119.30
IRB Resubmissions/continuing reviews		**to be invoiced**	$ 80.00	$ 24.00	$ 104.00
Contract Amendments		**to be invoiced**	$ 174.28	$ 52.28	$ 226.56
Protocol Amendments		**to be invoiced**	$ 80.00	$ 24.00	$ 104.00
SAE Reporting		**to be invoiced**	$ 80.00	$ 24.00	$ 104.00
Monitoring Visits - daily fee		**to be invoiced**	$ 160.00	$ 48.00	$ 208.00
Advertising		**to be invoiced**	$ 5,000.00	$ 1,500.00	$ 6,500.00

Grant Startup Process

- Please notify R&D as soon as you plan on submitting an extramural application
- Grant Administrator works with study team to prepare budget, gather documentation (such as biosketches, institutional forms, etc), and determine requirements for submission
- If external collaborators (sub-investigators) are involved, letter of commitment must be received to confirm participation
- eCRAF (R&D Application) must be completed and approved by Dept Chair prior to submitting application package

Grant Startup Process, Cont.

- Grants that involve prospective patient enrollment with research intervention will require feasibility meetings prior to submission.
- Depending on grant type, IRB approval also may be required for interventional studies prior to submission/award.
- If grant is awarded, the agreement/contract will be negotiated and study will be submitted to IRB, if not already done in pre-award.

Grant Submission Deadlines

- The PI/PD must submit the budget and budget justification for review and approval no later than **10 business days** prior to the sponsor submission deadline.
- All collaborative/subaward materials (letters of commitment, budget and budget justification, biosketches, statement of work, etc.) must be received at least **5 business days** prior to the sponsor submission deadline.
- With at least **3 business days** lead time prior to the sponsor submission deadline, R&D will perform a complete final proposal review
- R&D will submit with no less than **1 business day** prior to the application deadline.

Non-Funded Study Startup Process

- R&D eCRAF is submitted (electronic application)
- R&D reviews application and provides feedback, if necessary
- Sponsored project administrator begins contracting process if external collaborators are involved.

Non-Funded Study Startup Process, Cont.

- Depending on external collaborator's institution, IRB approval may be required prior to contract negotiation.
- Proceed directly to IRB submission following R&D approval (*if a contract is required, negotiations will begin in the background)
- CRRC review for privacy & security, data and analytics, and human resource allocation takes place during the IRB application review process

Contracts

- Carilion Clinic does not permit investigators to sign contracts on behalf of the organization.

- All contracts must be reviewed centrally by R&D and signed by our institutional signatories (Dr. Harrington and Dr. Whatley).

Resources for Research

- Central Clinical Research Coordinator support
- Central budgeting for grants and clinical trials
- Central regulatory management for industry-funded clinical trials
- Central post-award financial management for grants and industry-funded clinical trials
- Central contracting – CDAs, CTAs, Grant Agreements, Non-funded agreements (DUAs, MTAs, RCAs, etc)
- Assistance with project development and protocol development
- Feasbility review

Research Oversight at Carilion

- R&D
- Compliance
- IRB

- R&D, Compliance, and the IRB are all responsible for research oversight at Carilion.
  - Each of these departments can conduct quality reviews and/or study audits to ensure that researchers are following organizational policies/SOPs and federal regulations.
  - Additional education will be provided as needed to study teams.
  - When in doubt, reach out to these departments for guidance. It is better to ask questions than to make assumptions that can lead to mistakes.

Clinical Research SOPs

- Standard Operating Procedures provide specific guidance to our investigators for conducting clinical research at Carilion Clinic
- Standardized procedures increase compliance, reduce errors, and allow new investigators to learn the proper way to conduct clinical research
- Our SOPs are based on federal regulations, FDA guidance, and local best practices
- https://www.insidecarilion.org/system/files/2018-11/Clinical%20Trial%20SOPs_2018.pdf

- Questions?