Responsibilities of the Principal Investigator Part 1: What you need to know & do before your protocol starts

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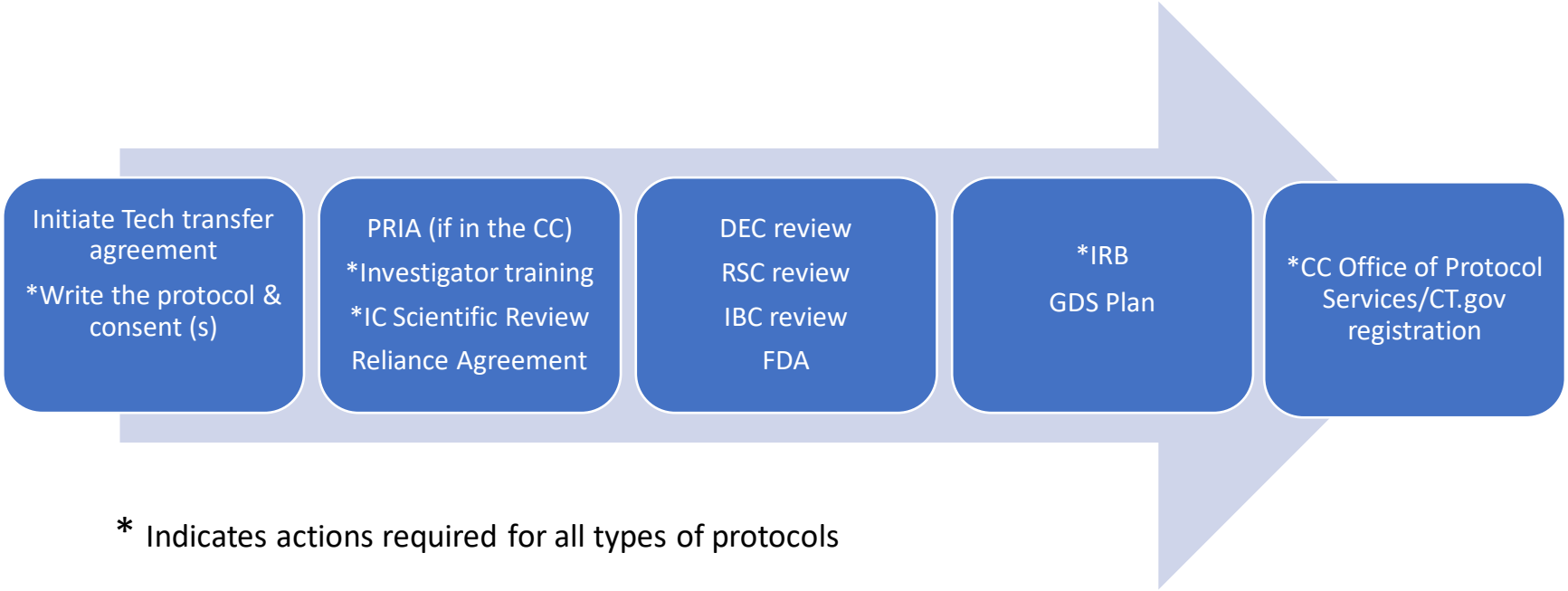
Protocol Development Workflow



* Indicates actions required for all types of protocols

Protocol and consent development

- Who will be responsible for writing the protocol & consent?
- Which of the protocol and consent templates is the right one to use?
  - Templates are posted on the IRBO website
- Do you have a reference library (recommend EndNote)?

If a study using a drug/device:

- Will the drug/device manufacturer need to review the protocol & consent prior to IRB submission?
  - If so, identify one person who will be the POC with the company to ensure version control
- Do you have the current Investigator Brochure (IB?). The current IB needs to be used to write the protocol.

Identify the associate investigators & their affiliations

- All people who are “engaged” in Human Subjects Research (HSR) for your protocol need to be listed as an investigator on the study (Policy 300).
- An investigator is “engaged” in HSR when they:
  - Obtain information or biospecimens through intervention or interaction with subjects; or
  - Obtain consent from subjects; or
  - Obtain, use, study, analyze, or generate identifiable private information or identifiable biospecimens; or
  - Analyze coded data/samples yet can reidentify subjects based on their access to the code key or prior involvement in the protocol
- The roles of each investigator must be clearly identified on the Study Personnel Page
- If any of the people who are engaged in HSR work for a different institution, a Reliance Agreement between NIH and that institution may need to be established

- All investigators must complete their required CITI training as per Policy 103

Are other sites involved who are engaged in HSR?

- Are these sites domestic or foreign?
  - Identify the FWA of each participating site
- Does the sIRB policy or Cooperative Research Provision apply?
  - The NIH does not have any reliance agreements with foreign sites (they have local IRB review only)
- Is there a reliance agreement already in place or will a new agreement need to be executed?
- Can the SMART IRB reliance platform be used?

Identify personnel/facility resources required

- Do you have the support staff needed to operationalize this protocol?
  - Research nurse/study coordinator
  - Genetics counselor
  - Data management
  - Lab availability to perform tests (do staff work at the time that specimens need to be processed, e.g. weekends and nights?)
- If your protocol will be conducted in the Clinical Center, you must complete the PRIA form
  - Consider requirements of CC departments when writing your protocol
    - DTM: has specific requirements for a person to be able to have an apheresis procedure performed
    - Pediatrics: there is no NICU or PICU at the CC
    - CLIA lab availability: Note that any result returned to the patient/available in the medical record must be performed in a CLIA certified lab

Determine if the protocol requires DEC review

- Is this a “covered” protocol per Policy 102?
- A covered research protocol is defined as: *(1) studies of investigational drugs and devices, (2) studies with a research question about a commercially available drug or device, and (3) studies involving collaborations with a substantially affected organization (SAO) or other for-profit entities when the entity is receiving data or specimens from the NIH for the purpose of developing a product.*
- Do you or any of your AIs have a patent/licensing of a product related to the protocol? If so, this must be disclosed.
- The Conflict of Interest guide must be sent to all AIs (Policy 102)
- Identify who is not a NIH employee (contractor, fellow, volunteer)
  - Non-NIH employees need to sign and return a COI form that you submit to the DEC office
  - If the study will be under an IND/IDE, all investigators may need to sign a financial disclosure form from the IND/IDE Sponsor
- Who will be the statistician? This person also requires DEC review even if not engaged in HSR.

Who will enroll in your study?

- What are the requirements to enroll in this study?
- Are you excluding any populations? If so, you must provide either a safety or scientific rationale for their exclusion.
- Are you including any federally defined “vulnerable” populations? If so, you must provide the rationale for their inclusion and describe how you are minimizing risks to this population

- How will you recruit subjects to your protocol?
- Will you be able to reach your recruitment goal in a reasonable amount of time?

- Clinical Center Office of Patient Recruitment is a good resource to help you with recruitment.

What data will you collect?

- What database will you be using (should be 21 CFR Part 11 compliant)
- Will the protocol require Third Party data transmission (and can your data base/support staff do this?)
- What data do you want to collect (think of the end result: what do you need for your publication?)
- What data do you NOT need to capture?
- Need to specify your data sharing plan

What specimens will you collect?

- What scientific methods are you using? Do these relate to your stated objectives?
- What labs are specimens being processed in? Are there special requirements? These should be specified in a Manual of Procedures (MOP).
  - If you are collecting multiple samples, it is helpful to create a table that specifies each sample, the timepoint it is collected, how it is processed, how and where it is delivered, etc.
- How long do you plan to store samples? Will you keep them for future research?
- How will samples be tracked? Will they be coded or have identifiers?

Does your protocol involve genomic sequencing?

- If you are planning to do any genomic sequencing, or may do this in the future, this needs to be described in both the protocol and consent. Your consent must contain required information about the data sharing in it (see the NIH consent template for language)
- Determine if the Genomic Data Sharing Policy applies to your protocol.
  - If yes, you must develop and submit your data sharing plan

- Will you return primary findings? You can only do this if the test is performed in a CLIA lab.
- Will you return incidental or secondary findings?
  - Good resource: NHGRI's Secondary Genomics Findings Service

- Who will provide genetic counseling if needed?

What is your data safety and monitoring plan?

- Consider the risk level of the protocol
- Monitoring can range from:
  - PI monitors their own data
  - Safety Monitoring Committee
  - Safety Assessment Committee
  - Independent Safety Monitor
  - Data Safety Monitoring Board
- Will you have external/independent monitoring performed? If so, who will do this and who will pay for it?

- Your plan for this needs to be described in the protocol

Will you be paying subjects to participate?

- How will you be paying subjects (gift/debit card, through the Clinical Research Volunteer Program (CRVP), etc.)
- How much will you be paying for each procedure?
  - Ensure that subjects undergoing the same procedure for research purposes are paid equally (e.g. affected and non-affected subjects)
- Consider the timing of payment to ensure it would not be considered undue influence or coercion

- Note that payment via the CRVP requires the subject to provide their social security number
  - If the subject receives over $600 total/year, they will receive a 1099-M
  - Some or all of that payment may be garnished if the subject has outstanding debts to the federal government.

Establishing a Technology Transfer Agreement

The NIH Technology Transfer offices serve as the focal point for implementing the Federal Technology Transfer Act to utilize patents as incentive for commercial development of technologies and to establish research collaborations and licensing among academia, federal laboratories, non-profit organizations, and industry. Because the NIH is a Federal government entity, it cannot commercialize or manufacture its discoveries. However, TTC proactively facilitates partnerships with outside organizations so that these discoveries can reach the public.

- NIH Tech Transfer office
- NCI Tech transfer office which serves NCI and 9 other ICs and Centers
  - CRADA
  - CTA
  - MTA
  - Licensing/patents

Bottom line: establish your TT agreement early as this may be the part that takes the longest

Does your protocol require review by the Radiation Safety Committee (RSC)?

- Uses a radioactive research drug(s) regulated under the FDA requirements for review by the Radioactive Drug Research Committee (RDRC)
- Involves the use of any radiation in pediatric participants (<18 years old) with an annual effective dose ≥0.5 rem or healthy pediatric volunteers (any dose level)
- Uses any radiation in healthy adult volunteers, excluding DEXA and chest X-Ray
- Uses therapeutic administration of radioactive materials
- Involves novel uses of radiation, including any radioactive Investigational New Drugs (IND) and radiation-producing investigational devices
- The radiation itself is the research agent being studied in the protocol

Your protocol requires review by the RSC

- Calculate the total dosimetry based on your protocol
- Determine who will serve as the Clinically Authorized User (if required) on your application
- Complete the “NIH Radiation Safety Form” in iRIS to submit to the RSC
- The RSC meets once/month. Look up their submission deadlines and meeting dates.

Does this protocol require an IND/IDE?

- Is the product you will be using commercially available?
- Are you using the product as per the package insert?
- Who is providing the product/how will you pay for it?
- If an IND/IDE is required: Who will be the Sponsor?
- Who will draft the IND (preclinical and CMC sections)?
- Who will obtain the letter of cross reference (if obtaining a product manufactured by a company who holds an existing IND/IDE)
- Does any CC Department need to be involved in the manufacturing/packaging/processing of the product? If yes, contact the appropriate department during your concept development stage to ensure they can do what you need!
  - Investigational Drug Management and Research Section
  - Positron Emission Tomography Department (Radiopharmaceuticals)
  - Center for Cellular Engineering

Does your study need to be reviewed by the Institutional Biosafety Committee (IBC)?

- The introduction of recombinant or synthetic nucleic acid molecules (as plasmids, as gene transfer vectors, as viral vectors, etc.) into human subjects, and/or
- The introduction of human, animal or plant cells including autologous or allogeneic blood or tissue cells or established cell lines that have been treated, transfected or transduced with recombinant or synthetic nucleic acid molecules or gene transfer vectors, or whose genome has been modified by gene editing methods into human subjects, and/or
- The introduction of genetically engineered micro-organisms into human subjects (including live vaccines if they are experimental in nature and/or not FDA approved for use in the specific human study population), and/or
- The introduction of biohazardous organisms or materials handled at Biosafety Level 2 or higher into human subjects (if they are experimental in nature and/or not FDA approved for use in the specific human study population)

Your protocol requires review by the IBC

- For detailed instructions on this process, refer to this website
- Set up the PI in the Dashboard (the electronic submission system) and assign proxies
- The NIH IBC meets once per month. Look up their submission deadlines and meeting dates.

Identify if this will be an applicable clinical trial (ACT)

- Is the study an applicable clinical trial?
- NIH definition of a CT: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
  - Under the FDAAA 801 all phase 2 and 3 clinical trials must be registered and report results
  - Under NIH policy, requirements include phase 1 clinical trials and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions
- Identify who will be the responsible party for study registration
  - OPS will register NIH investigator-initiated studies on behalf of the PI
  - Must be registered no later than 21 days after enrollment of the first participant.
- Identify the responsible party for results reporting into clinicaltrials.gov within 12 months of the primary completion date
- What are the specific outcome measures that are being used to evaluate each one of your study objectives?

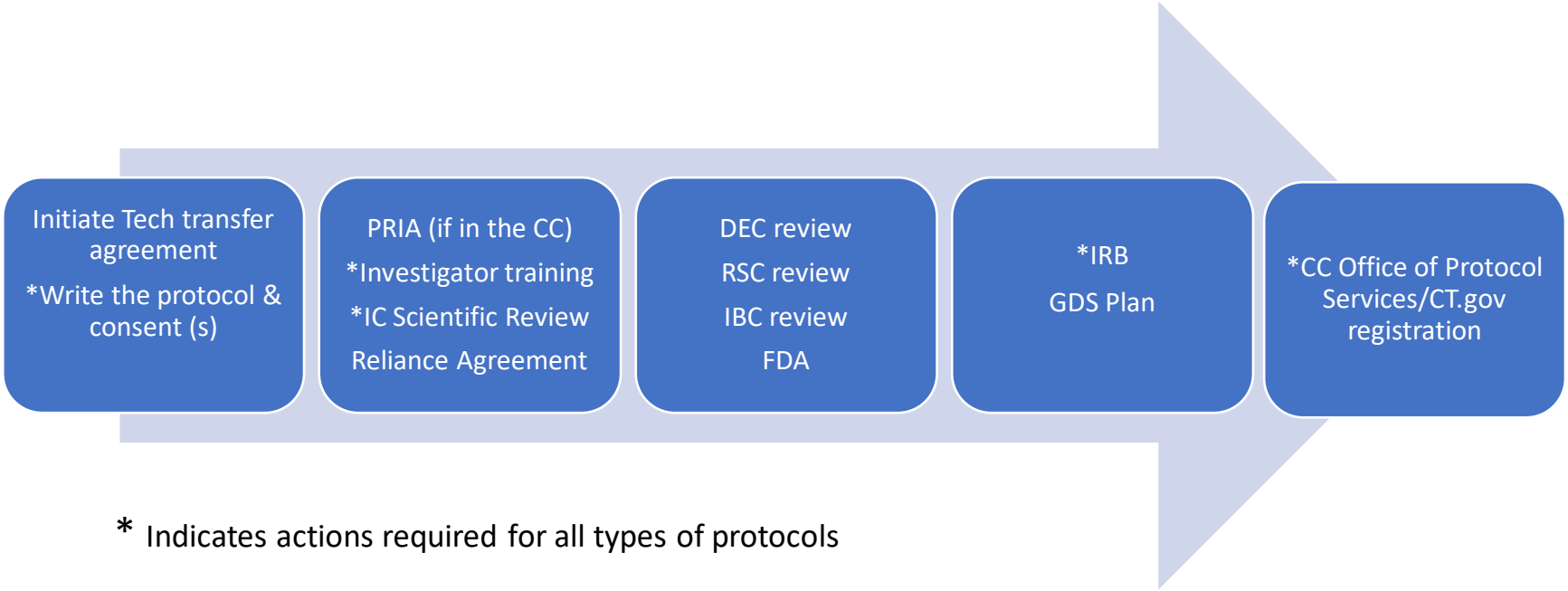
What else?

- All studies must undergo Scientific Review
- If the study is being conducted in the Clinical Center or will otherwise use CC resources, you must complete and submit the Protocol Resource Impact Assessment (PRIA) via iRIS
  - This form should be submitted at the same time you are submitting to Scientific Review
- If the study is being conducted in the Clinical Center, you must complete the Reimbursement for Travel and Subsistence form (otherwise known as the “DRTS”) via iRIS
- Identify the Z number that the protocol will be reported under for your annual report to the IC
  - A Z number is a unique number assigned to each project for easy tracking. You may be asked to provide your Z#s when you submit a manuscript to a journal, submit an EIR to tech transfer or submit a protocol in iRIS.

Submitting to the IRB: What do you need?

- Complete Study Application in iRIS
- Clean protocol
- Clean consent/assent
- Recruitment materials
- Approvals of ancillary committees/reviews
  - Scientific review
  - DEC
  - PRIA
  - RSC
  - IBC
  - FDA/Sponsor

Protocol Development Workflow



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QUESTIONS?
COMMENTS?
CONCERNS?