Institutional Review Board Committee (IRB)
&
Protocol Review and Monitoring Committee (PRMC)

What's the Difference?

Melanie Locher, B.S., CIP

IRB Director

Research Protections Office

Christa Varnadoe-Rothman, DNP, MSN, AGNP-C, OCN, CCRP

Director, Cancer Clinical Trials , University of Vermont Cancer Center

Associate Professor, Larner College of Medicine

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Purpose and Authority of the Protocol Review and Monitoring Committee

- **Purpose:** Per NCI guidelines, cancer centers involved in clinical research must have a mechanism for assuring adequate internal oversight of the scientific aspects of all cancer-related protocols at the institution.

- **Authority:** The PRMC has the authority to approve protocols that meet the scientific merit and priorities of the UVM Cancer Center and to terminate protocols that do not demonstrate scientific progress.

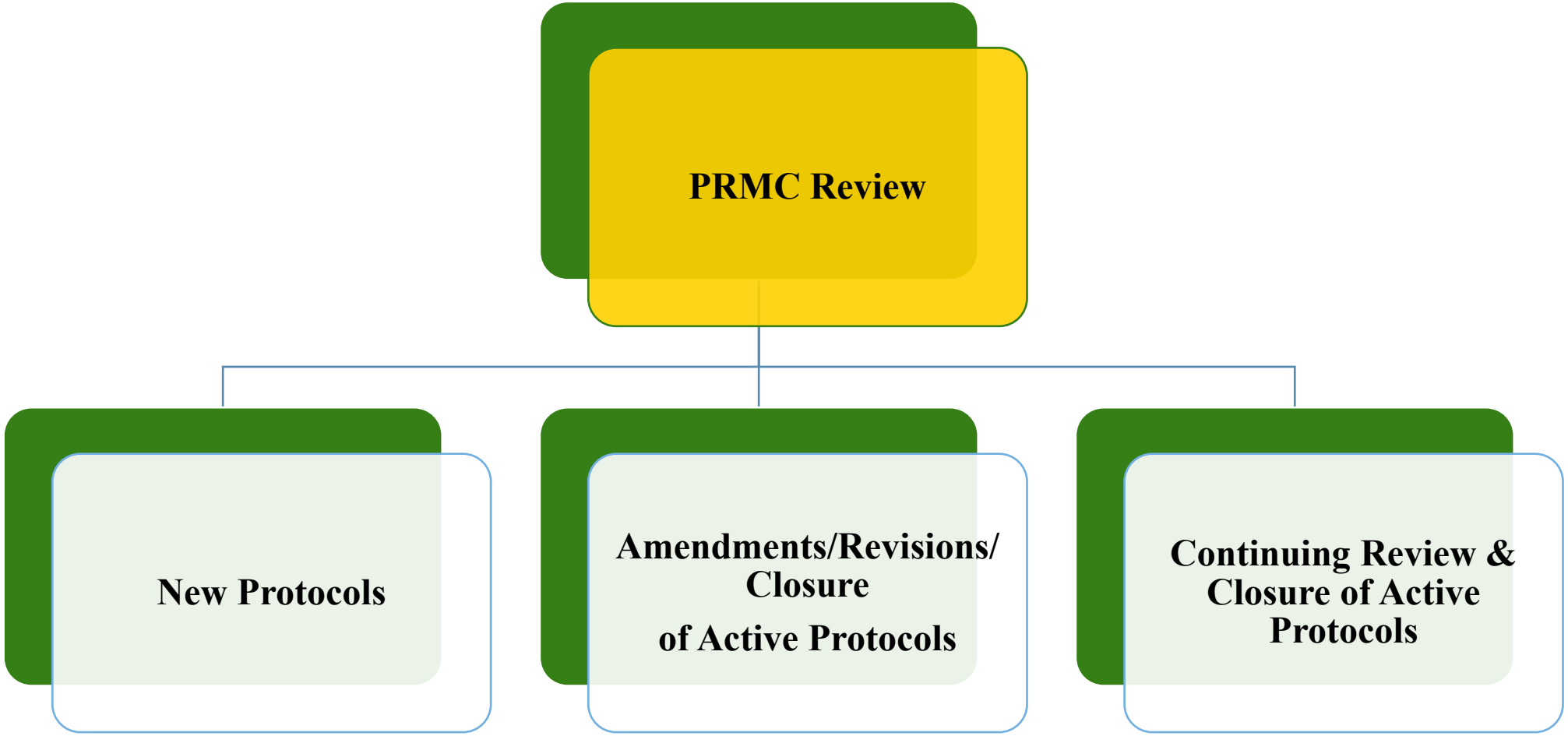
PRMC Responsibilities

- **The PRMC is responsible for:**

- Conduct a rigorous scientific review of all new protocols
- Ensure the clinical research portfolio is aligned with the research mission of the UVM Cancer Center
- Ensure thorough statistical review
- Oversee the appropriate prioritization of protocols within a given disease category with the input of the disease focus groups
- Ensure protocols have the potential to enroll underrepresented populations and other populations within UVM Cancer Center catchment area
- Monitor open protocols for ongoing scientific relevance, new safety information, and accrual
- Close protocols that do not meet accrual or scientific progress guidelines
- Evaluate the feasibility of the recruitment plan for study completion

THE University of Vermont CANCER CENTER

The PRMC ensures the scientific merit & ensures the continuing review of open protocols for cancer-related clinical research conducted at the University of Vermont Cancer Center



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PRMC Review

- What is reviewed:
  - Protocol Submission Form, TDT form, Full protocol
  - Scientific Rigor, Eligibility Criteria, Statistical Plan, Feasibility.
- Possible outcomes of review:
  - Approved
  - Approved, pending clarifications (no protocol revisions required)
  - Approved, pending minor protocol revisions
  - Tabled until further clarifications/revisions are reviewed
  - Disapproved

Types of Review for New Trials

Full Review

- All IITs
- Foundation or industry sponsored studies

Basic Review

- Those already approved by an oncology peer-review process (eg NCTN studies)

Accelerated Review

- Emergent use
- Expanded access
- Eligible patient is waiting

Exempt from Review

- Retrospective studies
- Archived tissue
- Observational studies

Committee Determinations - Focus

- **Approved**
- **Approved pending clarifications, Approved pending minor protocol revisions**- When the resolution of minor issues, that are not fundamental to the scientific validity of the study, are pending.
- *The PI is responsible for providing responses/ revisions to the PRMC Administrator, who in turn corresponds with the original reviewers and the Chairs to determine whether the revisions adequately address the issues.*

- **Tabled until further clarifications/reviews are reviewed** - When significant issues concerning the science of the study remain. When revisions are received, Full board review is once again carried out at the next PRMC meeting.

- **Disapproved** - When there is insufficient scientific merit and priority to warrant opening the study at UVMCC.

PRMC Review for Amendments/Revisions

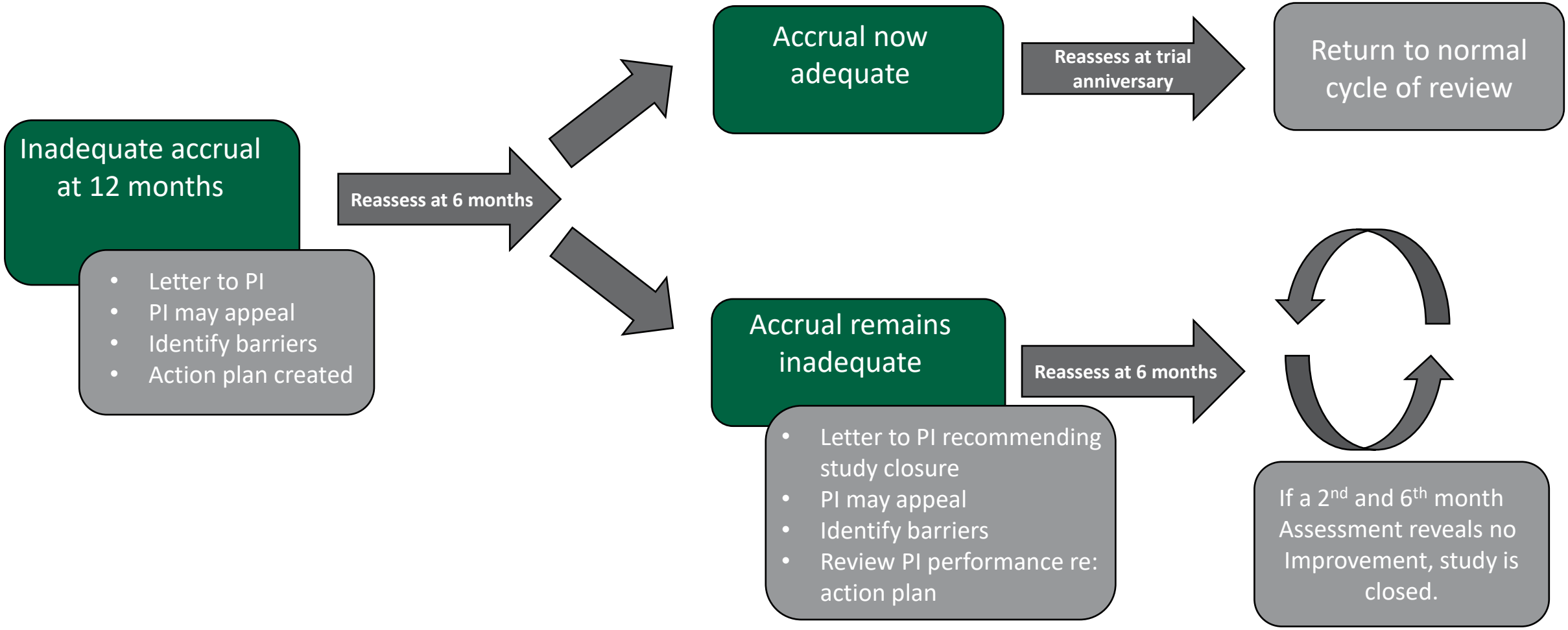
For institutional protocols, if the amendment meets any of the below conditions, the PRMC Administrator will forward the Amendment to the primary scientific reviewer who performed the Initial PRMC review:

- Change in scientific objectives
- Addition or deletion of a study arm
- Major change in eligibility criteria
- Addition or deletion of study agent
- Major change in treatment schedule
- Major change in accrual goals
- Change in analysis plan.

Continuing Review of Open Protocols

- Assure continued scientific merit
- Monitor accruals
- Close studies with insufficient accrual

Process for Termination of Protocols



PRMC Structure

- PRMC Structure:
  - Leadership team: Chair, Vice Chair, Coordinator
  - Regular Members: Review protocols, vote on approvals
  - Non-voting Members: Liaisons to the CTO and IRB, trainees
  - Ad hoc Members: Invited as needed to provide specific expertise

Leadership

- **Jessica Heath, MD Chair**
- Leads monthly meetings
  - Approve minutes
- Reviews accrual
  - Ensure appropriate follow up for inadequate accrual
- Approve minor protocol amendments
- Coordinate efforts with CTO and IRB
- Ensure PRMC bylaws are up-to-date
- Management of membership
  - Appoint mentors for new members
  - Assure diversity among PRMC membership

- **Hibba Rehman, MD Vice Chair**
- Leads monthly meetings when Chair is unavailable
- Coordinates with Chair to revise and update bylaws
- Coordinates with Chair to manage PRMC membership & add new members

PRMC Membership

- Current Membership:
  - 13 voting members
  - Variety of specialties represented
  - Multiple members with basic/translational research experience
  - Actively Recruiting: Breast, Radiation Oncology

- Guidelines for Committee Membership:
  - Appointed by UVMCC Director, with recommendations provided by the PRMC Chair
  - Three-year renewable terms
  - Must attend 75% of meetings

Committee Member	Academic Rank	Role	Specialty
Heath, Jessica MD	Associate Professor	Chair; Primary Reviewer	Pediatric Hematology-Oncology
Rehman, Hibba tul MD	Assistant Professor	Vice Chair; Primary Reviewer	Medical Oncology (Lung, Sarcoma)
Adranzen-Herrera, Diego MD	Assistant Professor	Primary Reviewer	(Hematology)
Ahern, Thomas PhD, MPH	Associate Professor	Primary Reviewer	Epidemiology
Ahmed, Shahid MD	Assistant Professor	Primary Reviewer	Medical Oncology (GU, Cutaneous)
Cade, Robert PharmD	N/A	Ancillary Reviewer	Pharmacy
Callas, Peter PhD	Research Associate Professor	Ancillary Reviewer	Statistics
DeWitt John MD, PhD	Assistant Professor	Primary Reviewer	Anatomic Pathology (Neuropathology/Autopsy)
Garrison, Garth MD	Associate Professor	Primary Reviewer	Pulmonology
Hinton, Megan PharmD	N/A	Ancillary Reviewer	Pharmacy
Howe, Alan PhD	Associate Professor	Primary Reviewer	Pharmacology
Sajisevi, Mirabelle MD	Assistant Professor	Primary Reviewer	Otolaryngology
Stahl, Stephanie PA-C	Clinical Instructor	Nursing Reviewer	Hematology-Oncology
Thomas, Alissa MD	Associate Professor	Primary Reviewer	Neuro-Oncology
Locher, Melanie		IRB REP Non-Member	

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Slide Courtesy of Dr. Jessica Heath, MD

Pathways for UVM Cancer Center New Trial PRMC Review

First Stage Review – Cancer Center Transdisciplinary Teams

- Protocols reviewed for scientific integrity and institutional feasibility prior to PRMC submission
- TDTs aid with study prioritization
- TDT Leaders monitor their group's portfolio and can recommend closure of underperforming studies to the PRMC

Disease Specific Transdiscipinary Teams		
TDT	**Leader**	**Discipline**
Upper Gastrointestinal/Liver	Conor O'Neill, MD	Surgical Oncology
Lower Gastrointestinal	Jesse Moore, MD	Colon and Rectal Surgery
Genitourinary	Shahid Ahmed, MBBS	Medical Oncology
Lung	Farrah Khan, MD	Medical Oncology
Breast	Michelle Sowden, DO	Surgical Oncology
Hematology	Chris Holmes, MD, PhD	Hematology
Gynecology	Charles Ashley, MD	Gynecologic Oncology
Cutaneous	Christopher Anker, MD	Radiation Oncology
Head and Neck	Maura Barry, MD	Medical Oncology
Sarcoma	Alexandra Kalof, MD	Pathology
Neuro-Oncology	Alissa Thomas, MD	Neuro-Oncology
Endocrine	Mirabelle Sajisevi, MD	Otolaryngology
Non-disease Specific Transdisciplinary Teams		
Supportive Care/Survivorship	Kim Dittus, MD, PhD	Medical Oncology
Pediatrics	Heather Bradeen, MD	Pediatric Oncology

In Slide Show mode: Click on selection to see protocol flow pathway

No Cancer Center registration or review

- Archived tissue study
- Retrospective Chart Review or QA/QI study

Cancer Center registration required
Exempt from PRMC review
Requires CTO review if using CTO resources

- Investigator-Initiated Observational or Ancillary/Correlative Study NOT using CTO resources
- Investigator-Initiated Observational or Ancillary/Correlative Study **using CTO resources**

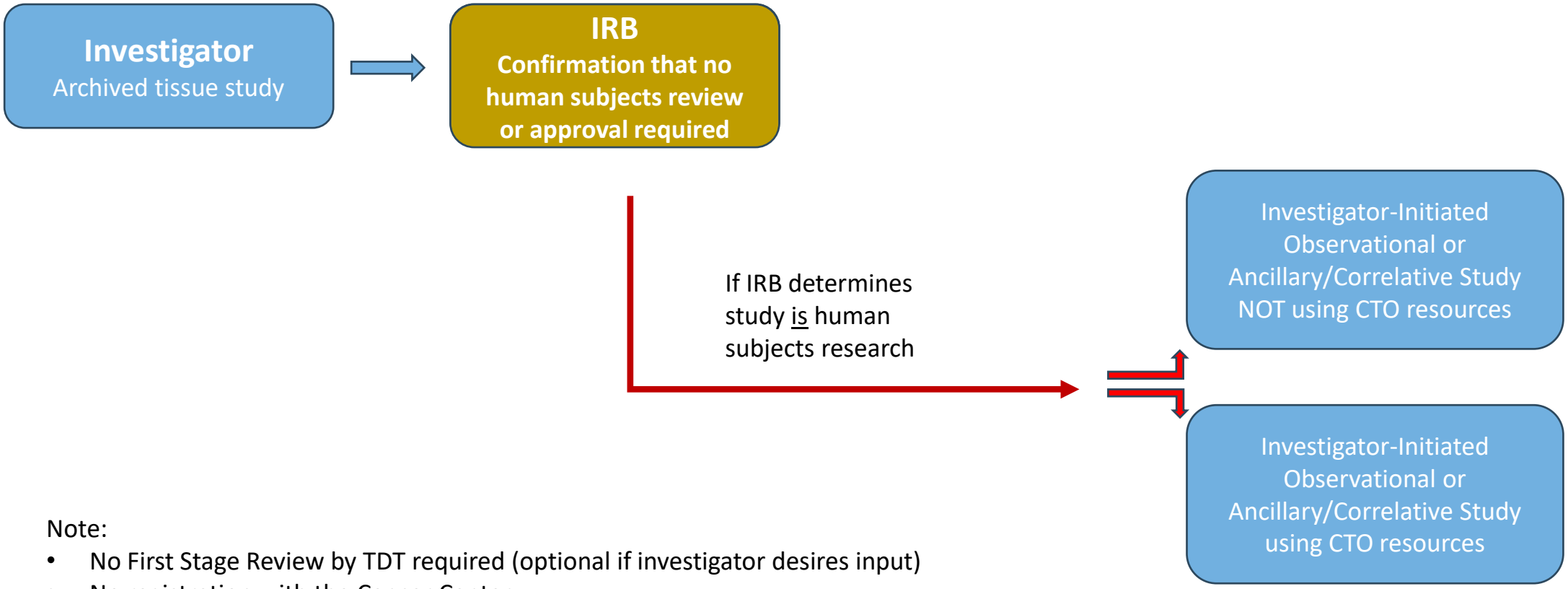
PRMC review required

- NCTN trial
- Industry Trial
- Investigator-Initiated Interventional Trial NOT using CTO resources
- Investigator-Initiated Interventional Trial **using CTO resources**

List of CTO resources

Entry Points for Investigators

Archived Tissue Study



Note:

- No First Stage Review by TDT required (optional if investigator desires input)
- No registration with the Cancer Center
- No PRMC review required

Back to top

Retrospective Chart Review and QA/QI Studies

Investigator
Retrospective Chart

→

IRB
Confirmation that no human subjects review or approval required

- No First Stage Review by TDT required (optional if investigator desires input)
- No Cancer Center registration
- No PRMC review required

Investigator
QA/QI study

→

IRB
Confirmation that no human subjects review or approval required

If IRB determines study is “research”

→

Appropriate study category pathway

Back to top

IIT-Observational/Correlative-No CTO Resources

TDT input is recommended but optional

Investigator
Investigator-Initiated Observational or Ancillary/Correlative Study NOT using CTO resources

TDT
Protocol review to assess science, protocol design, feasibility, overlap with other trials, available study population

New Study Intake & PRMC Coordinator

1

OnCore Coordinator
Registration, Accrual Tracking

Iterative protocol optimization process

2

3 business days

PRMC review exemption letter signed by PRMC Chair or Vice-Chair to investigator

IRB

- First stage review by TDT optional
- Cancer Center registration required
- Exempt from PRMC review

Back to top

IIT-Observational/Correlative-CTO Resources

Protocol Writer
Protocol & budget development

TDT input is recommended but optional

Investigator
Investigator-Initiated Observational or Ancillary/Correlative Study **using CTO resources**

TDT
Protocol review to assess science, protocol design, feasibility, overlap with other trials, available patient population

New Study Intake & PRMC Coordinator

1

Activation Specialist
RAE

2

CTO Medical Director
CTO Admin. Director
Approval of CTO resource utilization

3
yes

4

OnCore Coordinator
Registration, Accrual Tracking

5

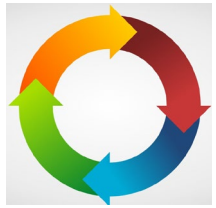
PRMC review exemption letter signed by PRMC Chair or Vice-Chair to investigator

IRB

no

CTO resource use NOT approved

Investigator-Initiated Observational or Ancillary/Correlative Study NOT using CTO resources pathway

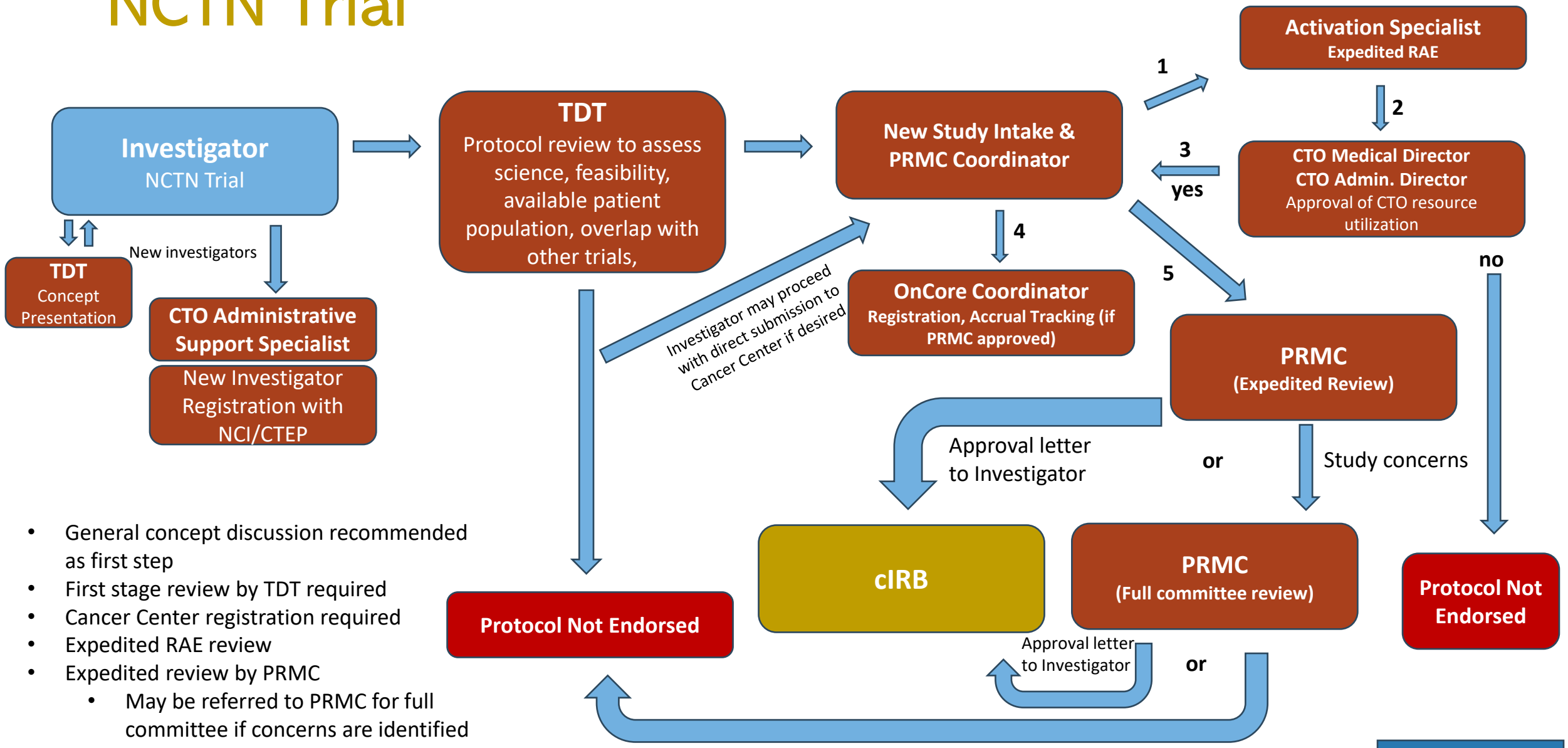


Iterative protocol optimization process

- First stage review by TDT optional
  - May be requested by CTO Medical Director prior to CTO resource utilization approval
- Cancer Center registration required
- Resource Allocation Evaluation (RAE) review by CTO required
- Exempt from PRMC review

Back to top

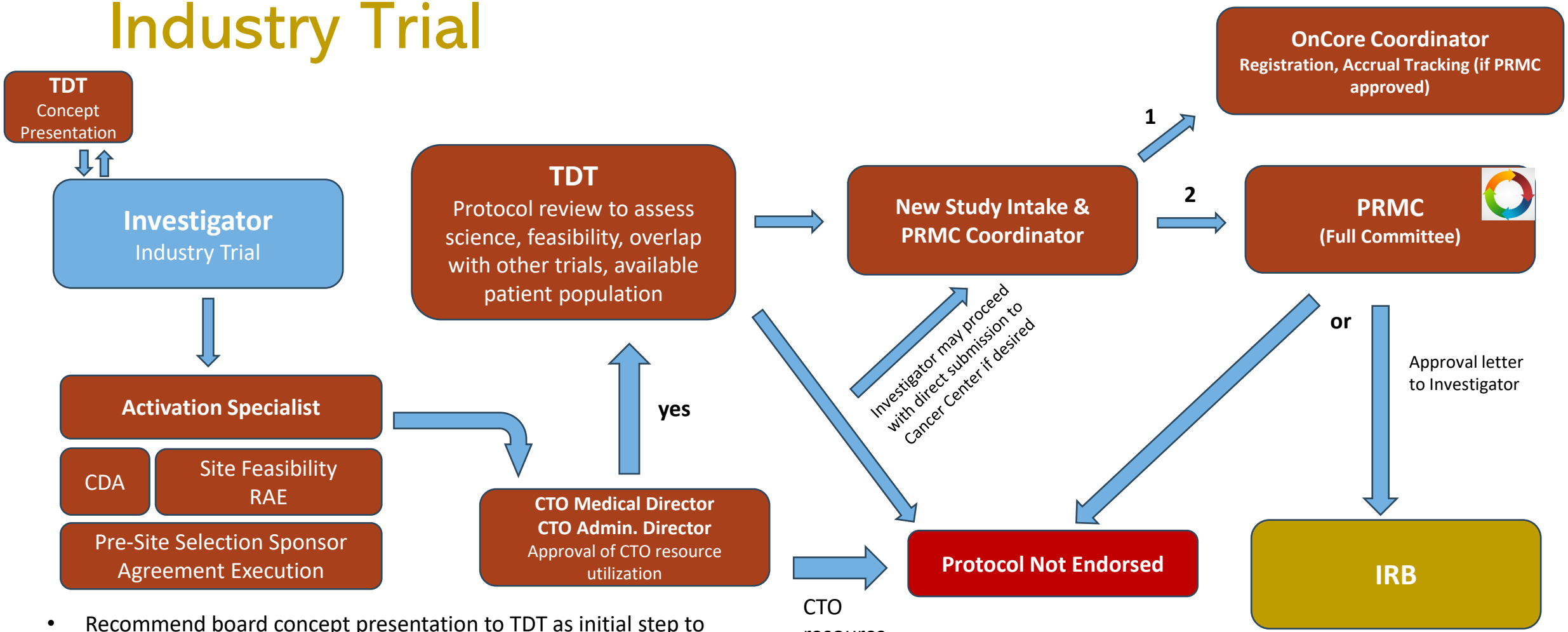
NCTN Trial



- General concept discussion recommended as first step
- First stage review by TDT required
- Cancer Center registration required
- Expedited RAE review
- Expedited review by PRMC
  - May be referred to PRMC for full committee if concerns are identified
- Accelerated review available if required (primarily utilized for COG or patient ID to enroll)

Back to top

Industry Trial



- Recommend board concept presentation to TDT as initial step to ensure general support
- Execution of CDA required as next step to obtain full protocol
- Site feasibility approval required
  - Includes resource allocation evaluation (RAE)
  - Pre-Site Selection Sponsor Agreement must be executed
- First stage review by TDT required
  - Concept approval by TDT prior to site feasibility recommended
- Cancer Center registration and full PRMC committee review required

Back to top

Interventional IIT-CTO Resources

Protocol Writer
Protocol & budget development

Budget concerns identified

Activation Specialist
RAE

1

2

Investigator
Investigator-Initiated Interventional Trial **using CTO resources**

TDT
Protocol review to assess science, protocol design, feasibility, overlap with other trials, available patient population

New Study Intake & PRMC Coordinator

3
yes

CTO Medical Director
CTO Admin. Director
Approval of CTO resource utilization

TDT
Concept Presentation

Iterative protocol optimization process

4

OnCore Coordinator
Registration, Accrual Tracking (if PRMC approved)

5

no

CTO resource use NOT approved

Protocol Not Endorsed

Investigator may appeal TDT decision to AD-CTR for submission to New Study Intake Coordinator for PRMC review

PRMC
(Full Committee review)

or

Approval letter to Investigator

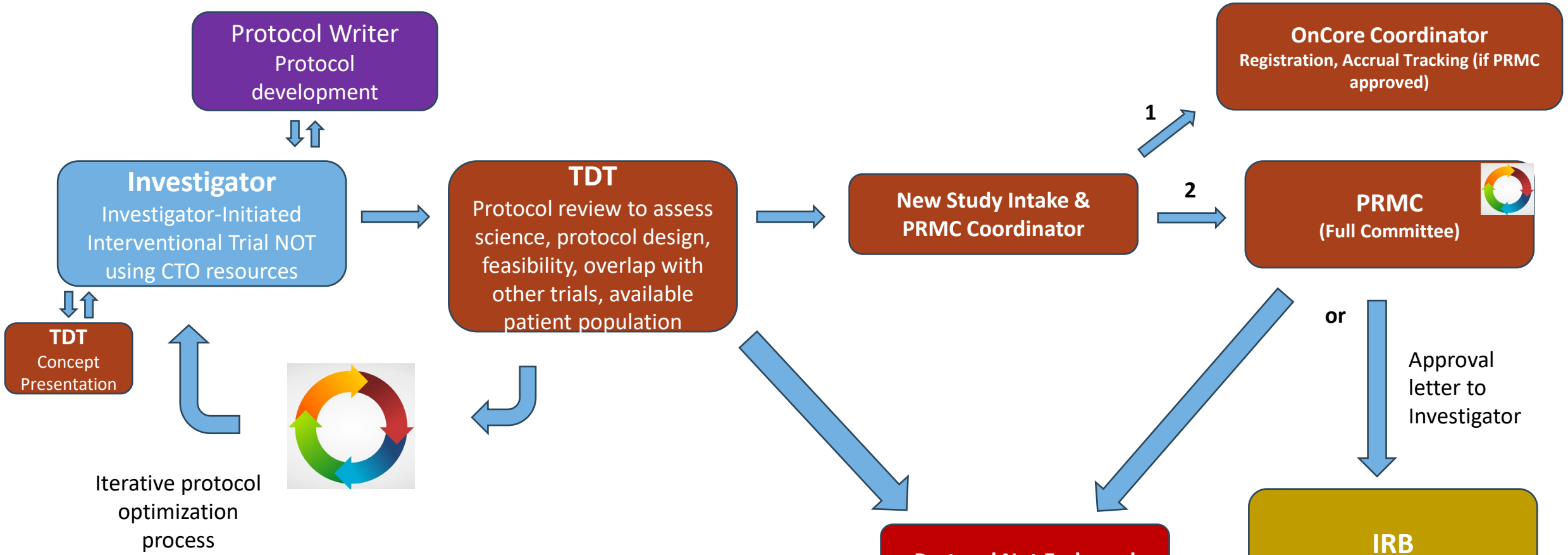
IRB

Investigator-Initiated Interventional Trial NOT using CTO resources

- First stage review by TDT required
- Protocol required prior to TDT approval
  - Concept presentation to TDT prior to formal protocol development recommended
- Completed budget development required prior to RAE review
- Cancer Center registration required
- PRMC full committee review required

Back to top

Interventional IIT-No CTO Resources



- First stage review by TDT required
- Protocol required prior to TDT approval
  - Concept presentation to TDT prior to formal protocol development recommended
- Cancer Center registration required
- PRMC full committee review required

Investigator may appeal TDT decision to AD-CTR for submission to New Study Intake Coordinator for PRMC review

Back to top

UVMCC CTO Resources

Pre Study

budget development

- CDA coordination for industry studies or multi-site IITs
- Site feasibility questionnaire and site visit for industry studies or multi-site IITs
- Regulatory activities and preparation of documents for IRB submission
- FDA submission for IITs if required
- Assistance with Data Safety and Monitoring Plan creation
- Pre-Award Industry Clinical Trial Agreement, and Budget/Contract Negotiation Oversight
- Completion of Sponsor Questionnaires & Conduct of Pre-Site Visits for Industry Sponsors
- Investigational Pharmacy Support including Beacon Builds
- Data Usage & Material Transfer Agreements
- Database Development
- Coordination of EPIC and Oncore Study Builds
- Study Initiation Visit (SIV) coordination

Review

- Resource Allocation Evaluation by CTO and UVMMC
- Coordination of Ancillary reviews including Radiology, IBC etc
- Quality Assurance oversight and implementation of the Data Safety and Monitoring Plan
- TDT (disease team) review and input
- PRMC review and accrual monitoring
- Assistance with Clinicaltrials.gov registration
- Accelerated/Emergency PRMC review for special circumstances

Cancer Center Data & Safety Monitoring Committee is available for investigator-initiated trials

On Study

Screening, enrollment and patient follow-up

- Source Documentation Development of case report forms
- Data Management Services including coordination in Oncore and through industry platforms
- RECIST read Coordination through Yunu Platform
- Ongoing regulatory activities for modifications, amendments, continuing reviews, and Reportable New Events with IRBs of Record
- Quality Assurance support with monitoring, auditing, Adverse Events/Serious Adverse Events, & Data Safety and Monitor Plan implementation
- Industry Budget Development and Negotiation Amendment Oversight
- Industry Clinical Trial Agreement Negotiation and Execution Amendment Oversight

Back to top

New Study Intake & PRMC Coordinator

Ben Briggs
Benjamin.briggs@med.uvm.edu

PRMC Leaders

Activation Specialist

Emma Armstrong
Emma.Armstrong@uvmhealth.org

CTO Administrative Support Specialist

Wren Zegans
Daniel.Zegans@med.uvm.edu

Protocol Writer
Protocol & budget development

Tracy Smith

Thanks to Dr. Randall Holcombe and Dr. Jessica Heath for the use and/or reproduction of your slides in this presentation. Thanks Liz Abrecht, MS for your expertise.

Back to top

What is the Institutional Review Board?

The IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated.

The IRB has the authority to approve, exempt, disapprove, monitor, and require modifications in all research activities that fall within its jurisdiction as specified by both the federal regulations and institutional policy.

What is the Purpose of the IRB Review?

The UVM IRB Committees have been established to review all research protocols and activities involving human subjects to:

- ✓ ensure the rights and welfare of those involved,
- ✓ are adequately protected and treated ethically,
- ✓ the methods used to obtain informed consent are adequate and appropriate,
- ✓ any risks to research participants are out-weighed by the potential benefit to them or by the general importance of the knowledge to be gained.

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FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Enhancing the health and well-being of all Americans

To approve research, IRB members must determine that all of the following criteria are satisfied (45 CFR 46.111 and 21 CFR 56.111)

Risks to subjects are minimized	Risks to subjects are reasonable in relation to anticipated benefits	Selection of subjects is equitable	Informed consent will be sought from each prospective subject or the subject's legally authorized representative
Informed consent will be appropriately documented	When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects	When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Additional safeguards have been included in the study to protect the rights and welfare of vulnerable subjects.

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Risks to Participants are Minimized

by using procedures which are consistent with sound research design, and which do not unnecessarily expose participants to risk.

by using procedures already being performed on the participants for diagnostic or treatment purposes.

Risks to participants are ***reasonable in relation to anticipated benefits***, if any, to participants, and the importance of the knowledge that may reasonably be expected to result

Risks to subjects are reasonable in relation to anticipated benefits

Is the protocol using procedures which are consistent with sound research design, and which does not unnecessarily expose subjects to risk?

Sound research design definition –

(1) well-defined goals and objectives which have scientific and social value,	(2) scientific validity consistent with the stated objectives,	(3) is feasible,	(4) the researcher is capable of successfully conducting the proposed research and	(5) the plan provides sufficient evidence to ensure the likelihood of fruitful results.

and whenever appropriate, is the protocol using procedures already being performed on the subjects for diagnostic or treatment purposes

Selection of Participants is Equitable

Selection of participants is equitable considering the purposes of the research, the setting in which the research will be conducted, the special problems of research involving vulnerable populations, the selection criteria, and the recruitment procedures.

IRB Members Review and Considerations

The purpose of the research and the setting in which the research will be conducted

Ensure no one is being excluded or included without appropriate rationale

- Children are excluded, why?
- Pregnant women are excluded, should they be?

Consider whether any additional safeguards are required to protect the rights and welfare of vulnerable populations, if included (e.g., fetuses, prisoners, children, persons with diminished capacity to consent, , economically or educationally disadvantaged persons, homeless, etc.)

Consent will be sought and documented

Consent will be sought from each prospective participant or the participant's legally authorized representative.

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IRB Members Review and Considerations on Obtaining Consent

I. Does the proposed consent process respect subject's timing/location?

II. Are there any additional consents to the main study that also require IRB review (pregnancy or repository or PK studies)?

III. Is the consent process documentation clearly outlined?

IV. Does the consent form adequately convey in layman’s terms what their participation requires?

Safety Monitoring

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants and protecting the validity and integrity of study data in clinical trials.

Researchers should develop a risk-based monitoring plan.

Minimal Risk: Requires ongoing monitoring by PI and IRB

Greater than Minimal Risk: Requires ongoing monitoring by the PI and IRB and may also require monitoring by an Independent Safety Monitor or an Independent Data and Safety Monitoring Board

IRB Members Review and Considerations

Are the provisions for data monitoring adequate for the protocol?

Data Safety Monitoring Boards (DSMB's) Independent committee set up to specifically to monitor data throughout the duration of the study to determine if continuation is appropriate both scientifically and ethically.

- Large multi-center trials; study population may have an elevated risk of death or other serious outcomes, used with fragile populations (elderly, children, terminally ill); study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion; possible serious toxicity

Data Safety Monitoring Plans (DSMPs) Purpose of DSMP is to ensure the safety of participants, validity of data and integrity of study, and appropriate termination of study. The DSMP is commensurate with risk. The DSMP may include a DSMB. DSMP may include independent or internal individuals.

Clinical Trial Steering Committees – May include investigators, other experts not otherwise involved in the trial, and usually representatives of the sponsor to oversee daily data collection.

Site/Clinical Monitoring - They perform "on site" monitoring of individual case histories, assess adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and in general assess adherence to good clinical practices.

Are there adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data?

IRB Members will Review and Consider:

- *Data Security and Management Plan*
- *Access to data*
- *Location of data*
- *Security of data*
- *Exchange of data*
- *Disposition of data once study complete*

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Vulnerable populations

When some or all the participants are likely to be vulnerable to coercion or undue influence, additional safeguards are included in the study to protect the rights and welfare of these participants.

Children,

Prisoners,

Persons with diminished capacity to consent,

Economically or educationally disadvantaged persons

Subpart C of the DHHS regulations, for prisoners;

Subpart D of the DHHS and FDA regulations, for children.

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IRB Members Review and Considerations

For Children

- The level of risk to children is based upon risks in relation to potential for direct benefits. IRB is required to document this determination (risk level 1, 2, 3 or 4).
- For protocols in which there is a potential for benefit - one parent may sign consent
- For protocols in which there is no direct benefit - both parents **must** sign the consent document
- Is the child able to assent? If so, should the assent be separate or part of the parental consent?
- Can other tools or media be used for explaining the research to the child?

For Cognitively Impaired Adults

- Is the request for use of a Legally Authorized Representative appropriate given the protocol?
- Has an assessment of capacity to consent been outlined in the protocol? Periodic re-assessment? Are these appropriate?

Required Elements of Consent

1. A statement that the study involves research.

2. An explanation of the purposes of the research.

3. The expected duration of the participant's participation.

4. A description of the procedures to be followed.

5. Identification of any procedures which are experimental.

6. A description of any reasonably foreseeable risks or discomforts to the participant.

7. A description of any benefits to the participant or to others which may reasonably be expected from the research.

8. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.

9. A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained.

10. An explanation of whom to contact for answers to pertinent questions about the research.

11. An explanation of whom to contact for answers to pertinent questions about the research participant's rights.

12. An explanation of whom to contact in the event of a research-related injury to the participant.

13. Contact information for the research team for questions, concerns, or complaints.

14. Contact information for someone independent of the research team for problems, concerns, questions, information, or input.

15. A statement that participation is voluntary.

16. A statement that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled.

17. A statement that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

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Information that must be provided as part of the interaction with the participant and in the documentation of the consent process, unless waived or altered

Additional required information, to be provided to each participant, when appropriate

For FDA-regulated research:

1. A statement that notes the possibility that the FDA may inspect the records.

For research involving **more than minimal risk**:

1. An explanation as to whether any compensation is available if injury occurs.
2. If compensation is available, what it consists of, or where further information may be obtained.
3. An explanation as to whether any medical treatments are available if injury occurs.
4. If medical treatments are available if injury occurs, what it consists of, or where further information may be obtained.

Additional consent information, to be provided to each participant, when appropriate

1. A statement that the particular treatment or procedure may involve risks to the participant which are currently unforeseeable.
2. A statement that if the participant is or may become pregnant the particular treatment or procedure may involve risks to the embryo or fetus that are currently unforeseeable.
3. Anticipated circumstances under which the participant's participation may be terminated by the Researcher without regard to the participant's consent.
4. Any additional costs to the participant that may result from participation in the research.
5. The consequences of a participant's decision to withdraw from the research.
6. Procedures for orderly termination of participation by the participant.
7. A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant.
8. The approximate number of participants involved in the study.
9. The amount and schedule of all payments to the participant.