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Demystifying Cancer Clinical Trials

Clinical Trials

December 16, 2016

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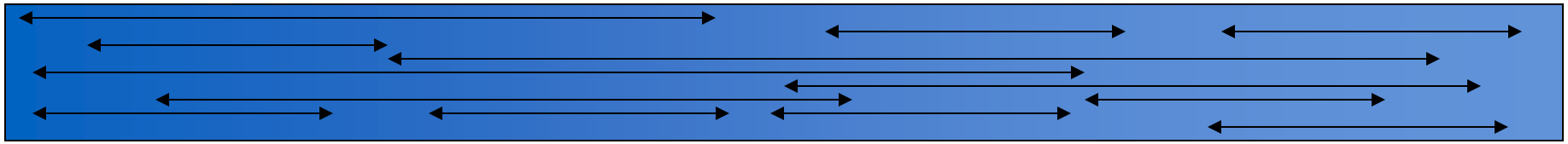
Clinical and Translational Science Awards (CTSA) Program

- National Institutes of Health (NIH) program
- Launched in 2006
- A national consortium of 64 institutions
- **Mission:** to develop innovative solutions that will improve the efficiency, quality and impact of the process for turning observation in the laboratory, clinic and community into interventions that improve the health of individuals and the public

Spectrum of Clinical and Translational Research



Bench to Bedside… ↔ **...to Widespread Clinical Practice…** ↔ **…to Public Health…** ↔ **…to Health Policy**

Translation (T1) *Translation (T2)* *Translation (T3)* *Translation (T4)*

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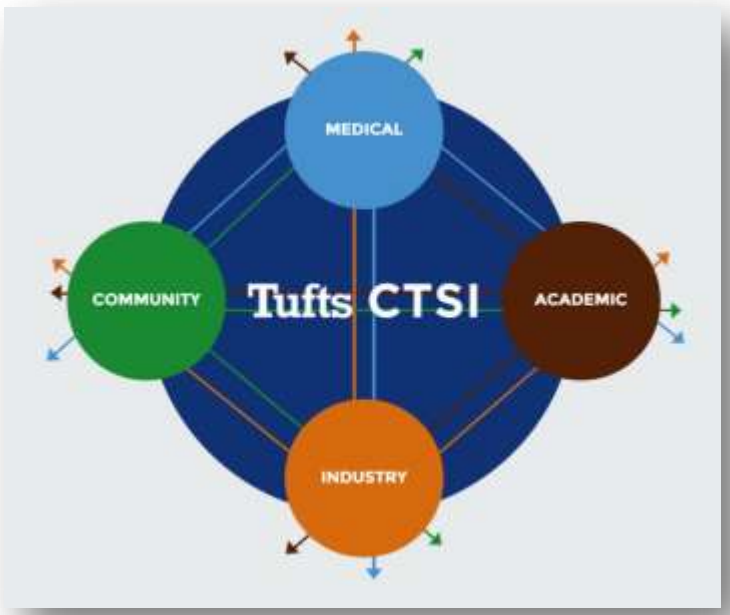
Tufts CTSI's Mission & Purpose

Established in 2008 to translate research into better health



- Stimulate and expedite innovative clinical and translational research, with the goal of improving the public's health
- *Entire spectrum* of clinical and translational research is critical to meeting the promise and the public's needs of biomedical science

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39 Tufts CTSI Partners

13 Tufts Schools & Centers

Cummings School of Veterinary Medicine
Fletcher School of Law & Diplomacy
Friedman School of Nutrition Science & Policy
Graduate School of Arts & Sciences
Institute for Clinical Research & Health Policy Studies at Tufts Medical Center
Jean Mayer USDA Human Nutrition Research Center on Aging
Sackler School of Graduate Biomedical Sciences
School of Dental Medicine
School of Engineering
School of Medicine
Tisch College of Citizenship & Public Service
Tufts Center for the Study of Drug Development
Tufts Innovation Institute

3 Academic Partners

Brandeis University
Northeastern University
RAND Corporation

7 Tufts-Affiliated Hospitals

Baystate Medical Center
Lahey Clinic
Maine Medical Center
New England Baptist Hospital
Newton-Wellesley Hospital
St. Elizabeth's Medical Center
Tufts Medical Center

6 Industry/Non-Profit Partners

Blue Cross Blue Shield of Massachusetts
Eli Lilly and Company
Institute for Systems Biology and P4 Medicine Institute
Minuteman Health Network
Pfizer, Inc.
Tufts Health Plan

10 Community-Based Partners

Action for Boston Community Development (ABCD)
Asian Community Development Corporation
Asian Task Force Against Domestic Violence
Asian Women for Health
Boston Chinatown Neighborhood Center
Center for Information and Study on Clinical Research Participation
Greater Boston Chinese Golden Age Center
Health Resources in Action
Museum of Science, Boston
New England Quality Care Alliance

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How Can CTSI Help?

- Connections with other researchers, industry, the community, and policy-makers across the Tufts CTSI network and national CTSA consortium via our **Navigators & Research Collaboration team**.
- Consultations on **comparative effectiveness**, **one health**, **research process improvement** and **stakeholder and community engagement** projects and grants, as well as **regulatory issues** and other areas of translation.
- Study design and data analysis (pre- and post-award) through the **Biostatistics, Epidemiology, and Research Design (BERD) Center**, including drop-in sessions.

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How Can CTSI Help?

- 24/7 clinical trial support through our **Clinical and Translational Research Center (CTRC)**.
- Informatics tools for electronic data capture (**REDCap**), resource sharing, and collaboration.
- Training & professional development including MS and PhD degrees, certificate programs, seminars & workshops, and **paid career development awards and fellowships**.
- Funding through one-year interdisciplinary **pilot studies grants** that support the initial stages of research.

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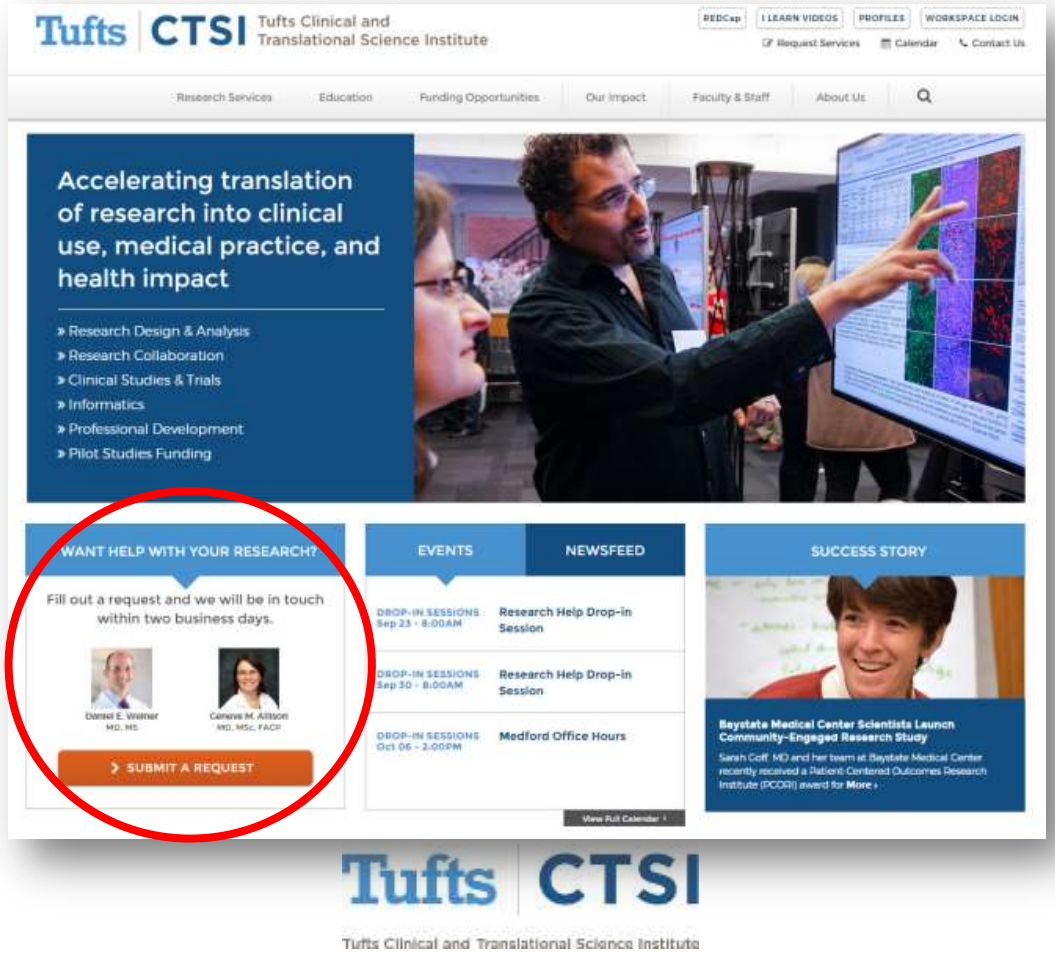
How to Request Tufts CTSI Services

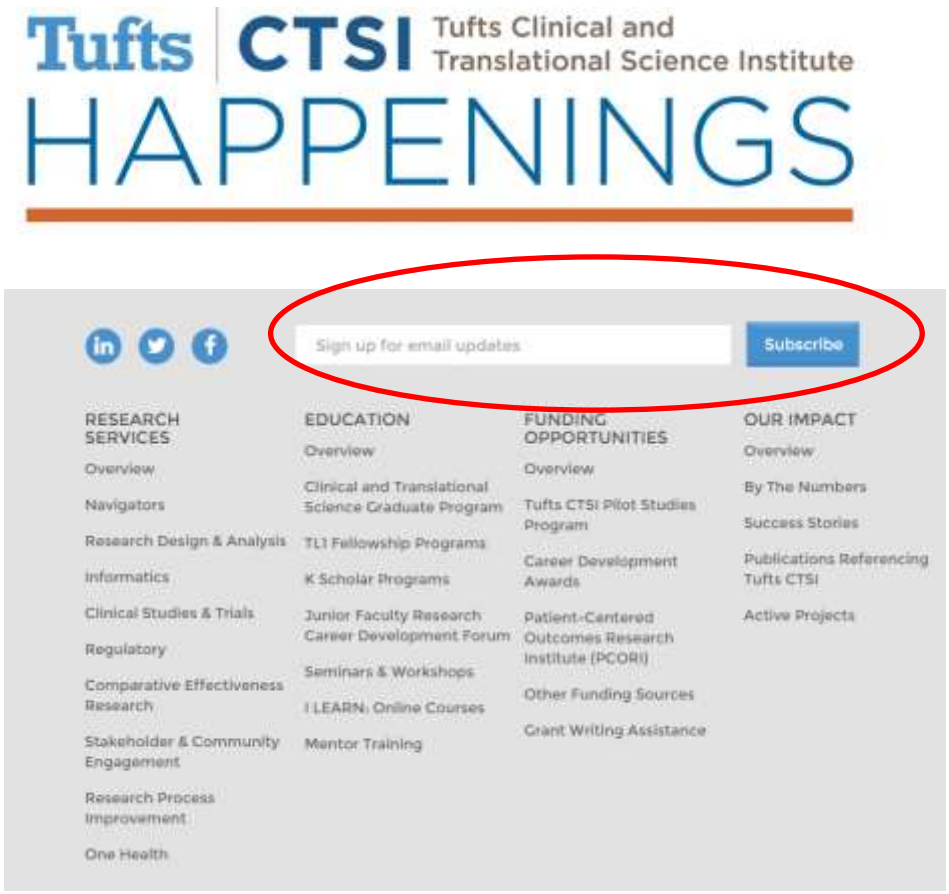
- Visit www.tuftsctsi.org and submit a request



http://ilearn.tuftsctsi.org/

Live seminars are recorded for our I LEARN site.
Seminar videos can be viewed at any time, and are free!

Get Connected: CTSI Happenings



- Weekly e-newsletter with news, professional development and funding opportunities, resources, and success stories.
- Issued every Monday at 8AM
- Sign up on our website or at *http://eepurl.com/C4d9X*

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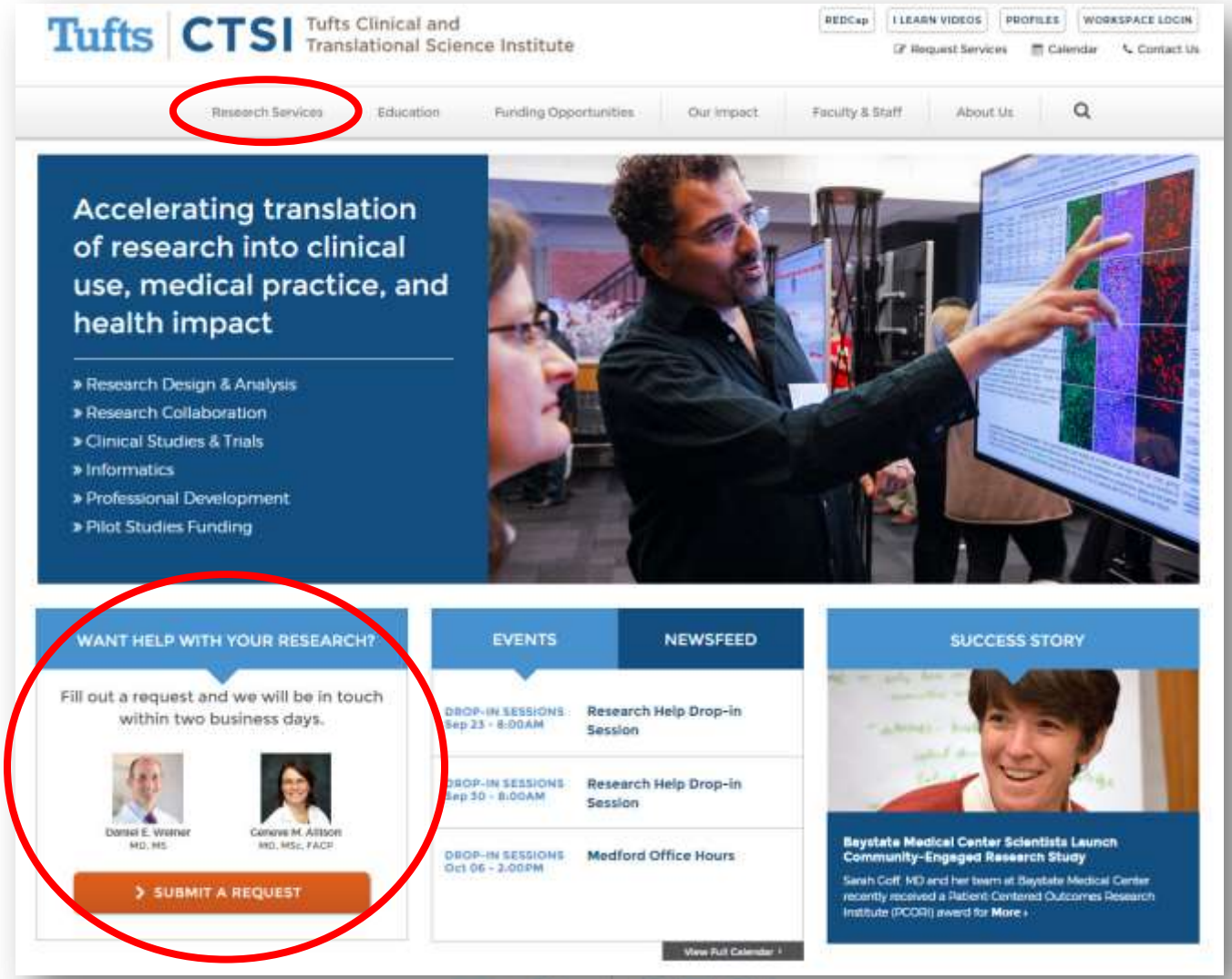
For more information: www.tuftsctsi.org



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Institutional Regulatory Review

John Erban, MD

Clinical Director
Tufts Cancer Center
Professor
Tufts University School of Medicine

Andreas Klein, MD

Director, Hematologic Malignancies Program
Assistant Director, Bone Marrow and Hematopoietic Cell Transplant Program
Chair, Tufts Health Sciences Campus Institutional Review Boards
Associate Professor, Tufts University School of Medicine

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PRMC and SRC Roles, Relationships and Functions

Jack Erban, MD

Clinical Director, Tufts Cancer Center
Medical Director, Neely Center for Clinical Care Research
December 16, 2016

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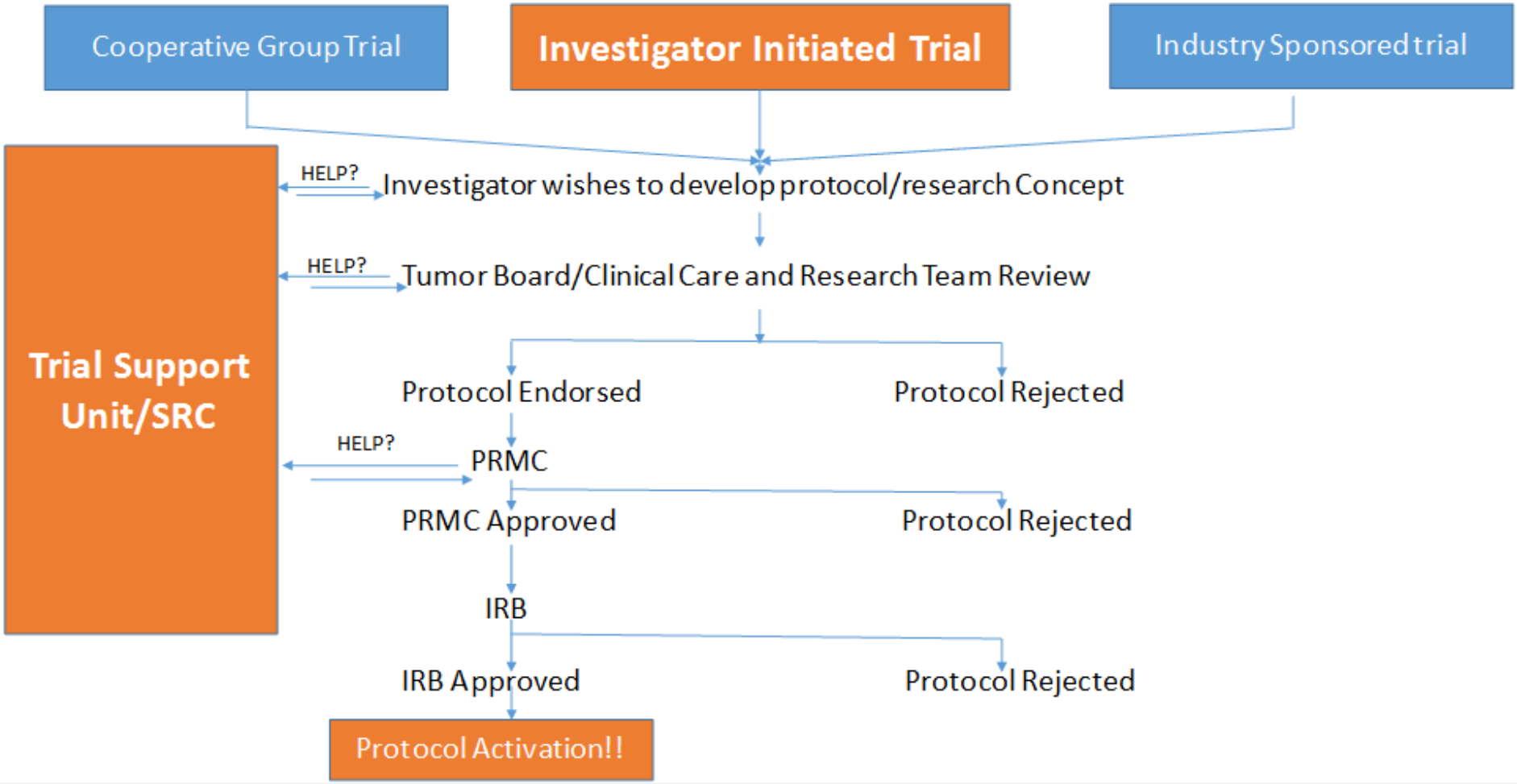
Clinical Research/Protocol Management Flow



Protocol Review and Monitoring Committee

The specific aims of a PRMC are:

- To review the scientific and operational progress of all new and active Cancer Center clinical research protocols.
- To prioritize competing studies and resources based on the Cancer Center's institutional prioritization plan.
- To assess the feasibility of all studies (institutional resources, focus and alignment with aims of the program, appropriate patient population).

The specific qualities sought by PRMC:

- High scientific merit– strong rationale, tight study design, appropriate bio-statistical input.
- Clinical feasibility-great question, but is it feasible?
- Accrual : Capable of completion within a practical time frame?
- Suitable/matched to the populations we serve?
- Adequacy of funding.
- Monitoring of Progress
  - Accrual
  - Quality/Compliance Issues
  - Change of Personnel

Some factors considered by PRMC

i. Scientific rationale– does it make sense scientifically

ii. Study design– does it support the rationale

a. Primary/secondary end points– clear , concise, important?

b. Inclusion/exclusion criteria

c. Adequacy of biostatistical input

d. Inclusion of translational research

iii. Feasibility for completion within a reasonable time period/Feasibility of Accrual

iv. Scientific impact/relative value to the cancer center/resource allocation

viii. Competing trials

v. Provision of novel options for patients/subjects

vi. Alignment with goals of the cancer programs and scientific mission of the cancer center

vii. Review relationships with Sponsors/External collaborators

Scientific Review Committee

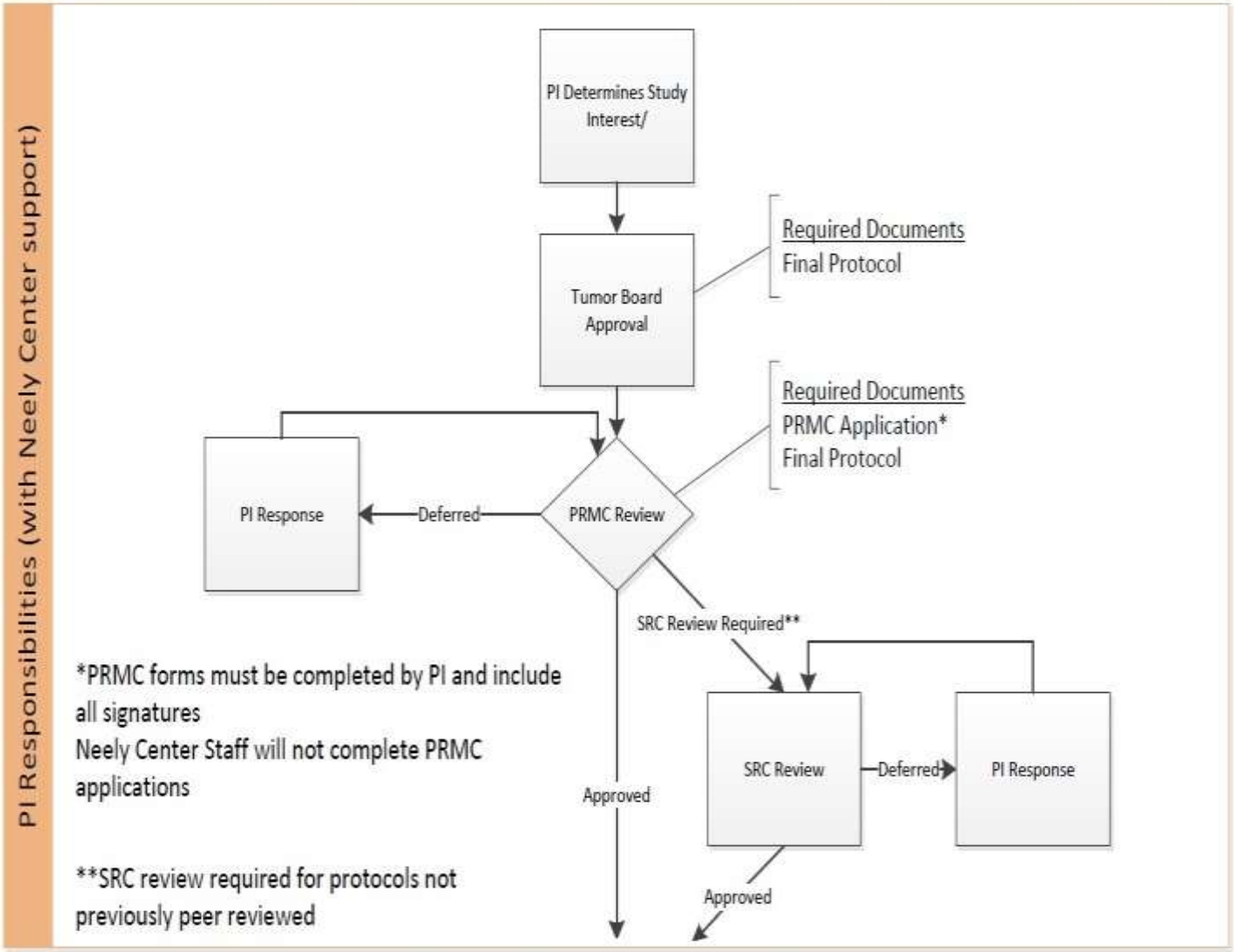
The specific aims of the SRC include:

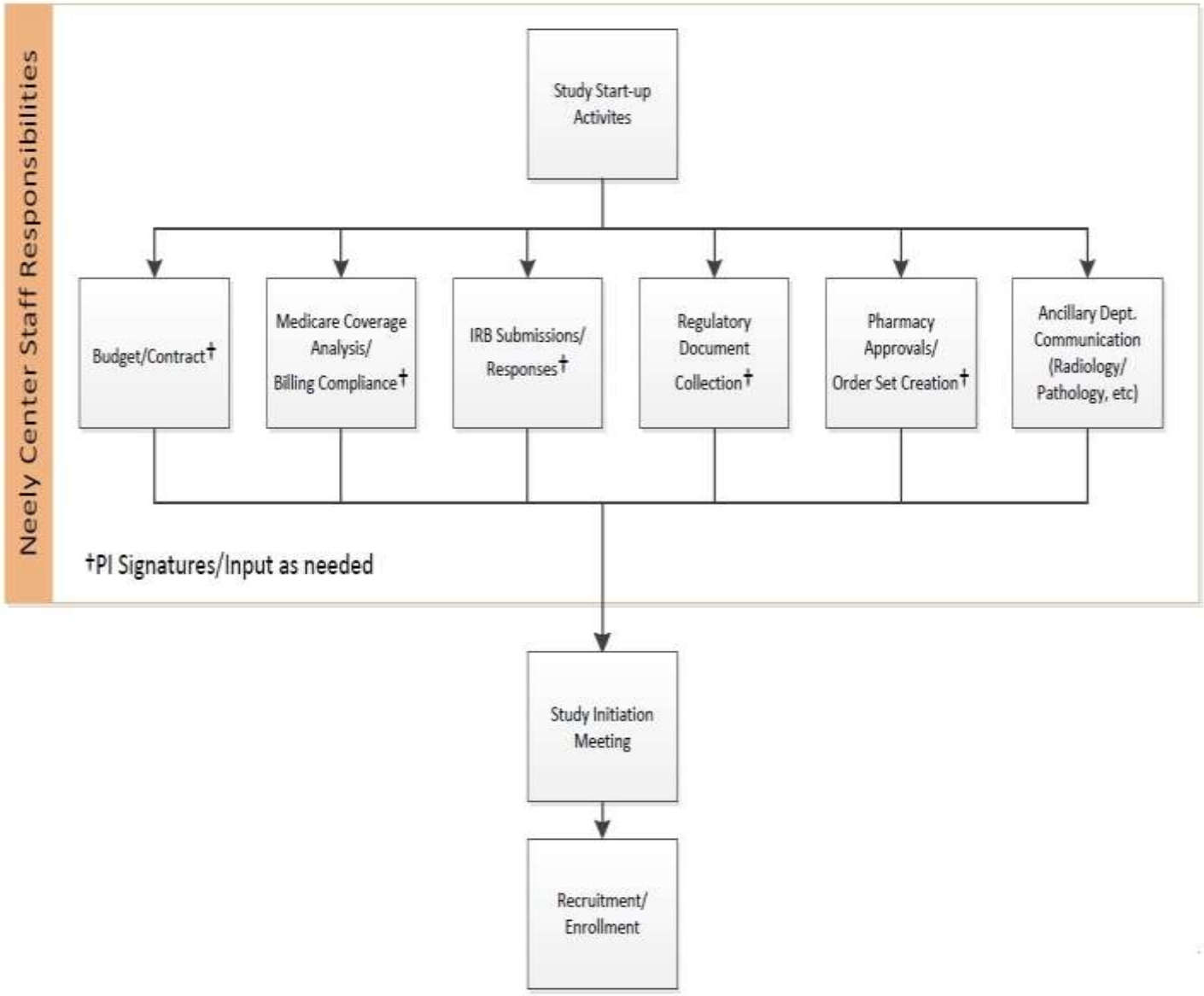
1. To establish and maintain a review committee of sufficient size, expertise and research accomplishment to be able to conduct a thorough, unbiased and scientific review of institutional cancer-related research involving human subjects
2. To conduct a thorough scientific review of all non-peer-reviewed, cancer-related clinical protocols based on specific, pre-determined review criteria

The specific functions of an SRC are to:

- Review the scientific merit of cancer-related research involving human subjects
- Facilitate development of innovative, collaborative, and scientifically-sound studies that focus on the prevention, detection, diagnosis, and treatment of cancer as well as long-term follow-up and care
- Review the merits of research procedures proposed relative to the primary and secondary aims of the protocol
- Assist investigators in the development of scientifically- and clinically-sound research through well-written and well constructed proposals
- Provide standards for protocols submitted for review of scientific feasibility and merit

Cancer Center Clinical Research Study Start-up Flow




Neely Center Staff Responsibilities
Study Start-up Activites
Budget/Contract†
Medicare Coverage Analysis/ Billing Compliance†
IRB Submissions/ Responses†
Regulatory Document Collection†
Pharmacy Approvals/ Order Set Creation†
Ancillary Dept. Communication (Radiology/ Pathology, etc)
†PI Signatures/Input as needed
Study Initiation Meeting
Recruitment/ Enrollment

Thank You

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Institutional Regulatory Review: The IRB

Andreas Klein, MD

Chair, Tufts Health Sciences Campus IRB

Background

- State of HSR prior WWII
- Essential documents
  - Nuremberg Code
  - Beecher NEJM article
  - Declaration of Helsinki
  - Belmont Report
- National Research Act of 1974

National Research Act 1974

- Established IRB system
- HHS promulgated rules in Title 45 CFR Part 46
- “Common Rule”
  - Adopted by 17 federal agencies
- FDA
  - Maintain own set of rules in 21 CFR 50
  - Specific regulations re drugs and devices

Institutional Review Board

- Institutional
  - Local context
- Review
  - Federal Wide Assurance (FWA)
- Board
  - Membership
    - *Scientific & non-scientific*
    - *Community representation*

Limitation to IRB Authority

- IRB does not oversee clinical care
- Regulations never intended to harm or limit care to patients
- Always do what is right for your patients, when health/safety at risk, you are obligated to act accordingly

Initial Review of Human Subjects Research

- Is it research?
- Triaged on arrival
  - NHSR
  - Exempt
  - Expedited
  - Full

Testing whether or not animals "kiss"

Annual Renewal

- Interval determined by IRB
  - Minimum one year
- Expedited & Full studies
- Full studies may be expedited
  - No enrollment locally, and
  - No problems at any site

Amendments

- Adherence to protocol
- Deviations must be approved
- Exception to address immediate apparent hazard
  - Report within 5 days

Elements of IRB review

In order to approve human subjects research the IRB must determine that seven essential requirements are met:

1. Risk are minimized
   - Procedures c/w sound research design
   - Procedures already done for clinical care
2. Risks are reasonable
   - Expected benefits and
   - Knowledge expected to result

Elements of IRB review

3. Selection of subjects is equitable
   - Take into account purpose and setting
   - Vulnerable subjects
4. Informed consent will be sought for each subject
   - LAR may substitute
5. Informed consent is properly documented
   - May require signed ICF
   - Exceptions
     - No procedure usually requires signed consent
     - Signed ICF only link to study

Elements of IRB review

6. Adequate plan for monitoring data
   - Ensure subject safety
7. Adequate plan for protecting Privacy
   - Protect privacy and maintain confidentiality

Oversight

- Ongoing review of protocols
- Assure adherence to protocol
  - IRB may audit study records, observe procedures
- Prompt reporting of problems
- Prompt reporting of suspensions, etc

Devices and Drugs

- Studies regulated by FDA cannot be expedited
  - Investigational New Drug application
  - Investigational Device Exemption
- IRB can determine IND/IDE requirements do not apply
  - IND waivers in cancer are common
  - May require input of FDA
- IRB can grant IDE for non-significant risk devices

Emergency Use*

- Applies to devices
- Unapproved can be used to save life or treat life threatening condition
- Requires notification of IRB within 5 days

* Consult your IRB for guidance

Compassionate Use*

- Treatment only protocol
- Provides access to promising drug ahead of approval
- Requires approval of manufacturer and FDA
- IRB approval required if sufficient time to review

* Consult your IRB for guidance

Humanitarian Use Device

- Intended to benefit patients by treating disease or condition affecting fewer than 4,000 pts / yr
- Demonstrates safety only, not efficacy
- Use is clinical, but subject to IRB oversight
- Use in research requires IDE

Multi-site Research

- Individuals / Institutions bound by FWA
  - Review required by assigned IRB
  - IRB may cede responsibility to another IRB
  - IRB may accept responsibility from another institution

- Individuals / Institutions not bound by FWA
  - Individual signs agreement to be bound to IRB
  - Institution may be required to obtain FWA

Multi-site Research

- Challenges
  - Who is responsible for research oversight?
  - Who is responsible for disciplinary action?
- Potential solutions / new models
  - IRB RELY / IRB SHARE
  - SMART IRB

Review Metrics

2016 Metrics					
		20.00	45.00	71.00	Approved studies (40)
	16.50	20.00	47.00	73.00	All studies (45)
SRC Assessment	SRC	IRB	PI	Total	
		Median	Median	Median	

Barriers to approval

- Protocol must be designed (and documented) to meet each of the 7 requirements for approval (45 CFR 46.111)
- All procedures described in the protocol must be included in the informed consent form
- Fill out required forms fully – information is being captured for a reason

Your IRB: Cute and Fuzzy!

Happy Holidays from the TMC/TUHS IRB!

PI Responsibilities

Susan Parsons, MD, MRP

Founding Director, Reid R. Sacco Adolescent and Young Adult Program for Cancer and Hereditary Blood Diseases

Director, The Center for Health Solutions at the Institute for Clinical Research and Health Policy Studies

Professor, Tufts University School of Medicine

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PI Responsibilities

To

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PI responsibilities change over the project lifespan

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Planning and Design

- Scientific integrity of the study
- Hiring and training of study staff
- Adherence to regulatory requirements
- Creation of regulatory binder (or eBinder)
  - Protocol documents
  - Correspondence with IRB
  - Conflict of Interest forms
  - CITI training for all staff
- Creation of study processes to ensure standardization, data management, confidentiality

After Activation

- Understand reporting requirements of sponsor
- Oversee the conduct of the research by study staff—

  Train, observe, retrain….
- Conduct regular project meetings
  - Monitor accrual
  - Monitor adverse events
  - Be available to answer questions
  - Monitor for study deviations and exceptions. Know the IRB process at your site(s) to report them.
  - Determine if/when clarifications/modifications are needed, ***but always get an amendment before making changes***

After you've met accrual

- Notify IRB that you have completed accrual
- Transition to "data analysis" phase
- Review your analysis plan
- Be sure to partner with a superb statistician
- Maintain study records securely

When in doubt, *don't* throw it out!!

Summary

- You are responsible for all study related events, data, activities, and products.
- Create a great team.
- Maintain secure records.
- Establish rapport with IRB and follow the rules.
- Spend wisely and publish often.

Publication Planning

- Form a publication committee for the study
- Discuss authors and expectations for authorship before you start your first paper
- Think about your audience for each paper
- Create a timeline for papers and planned presentations

Remember: No papers, no grants!!

Know Your Budget

- Review the grant award carefully
- Understand your annual spending levels
- Understand rules, if any, for reporting variance
- Work closely with your administrator
  - Set the budget
  - Review monthly spending
  - Anticipate problems (e.g., slow accrual, personnel changes)

After you've completed your papers

- Congratulations!!
- Notify the IRB that you are done
- Continue to maintain study records securely
  - Duration may vary by sponsor
- Debrief with collaborators
- Think about next project

Thank You

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Biospecimens and Clinical Trials

Sandra M. Gaston PhD

Scientific Director, TMC Biorepository
Director, Molecular Biomarkers Research Laboratory
Department of Pathology and Laboratory Medicine
Tufts Medical Center
December 16, 2016

Tufts Medical Center Biorepository

- Accredited by the College of American Pathology (CAP)
- Service of the Department of Pathology and Laboratory Medicine
- Supports Research Requiring Annotated Human Tissues and Body Fluids

College of American Pathology (CAP) Biorepository Accreditation

cap.org

Biospecimens and Clinical Trials

- Requests for biospecimens for clinical trials may include body fluids or tissues
- Biospecimens are often requested during study enrollment to confirm eligibility
- On-study biospecimens may be requested to monitor response
- Biospecimens may be requested for unspecified future studies (“banking”)

Study Enrollment Specimens

Tissue from the diagnostic FFPE block is often requested at the time of study enrollment. It's important that those diagnostic specimens not be depleted in such a way as to compromise future clinical care

Laws and Regulations

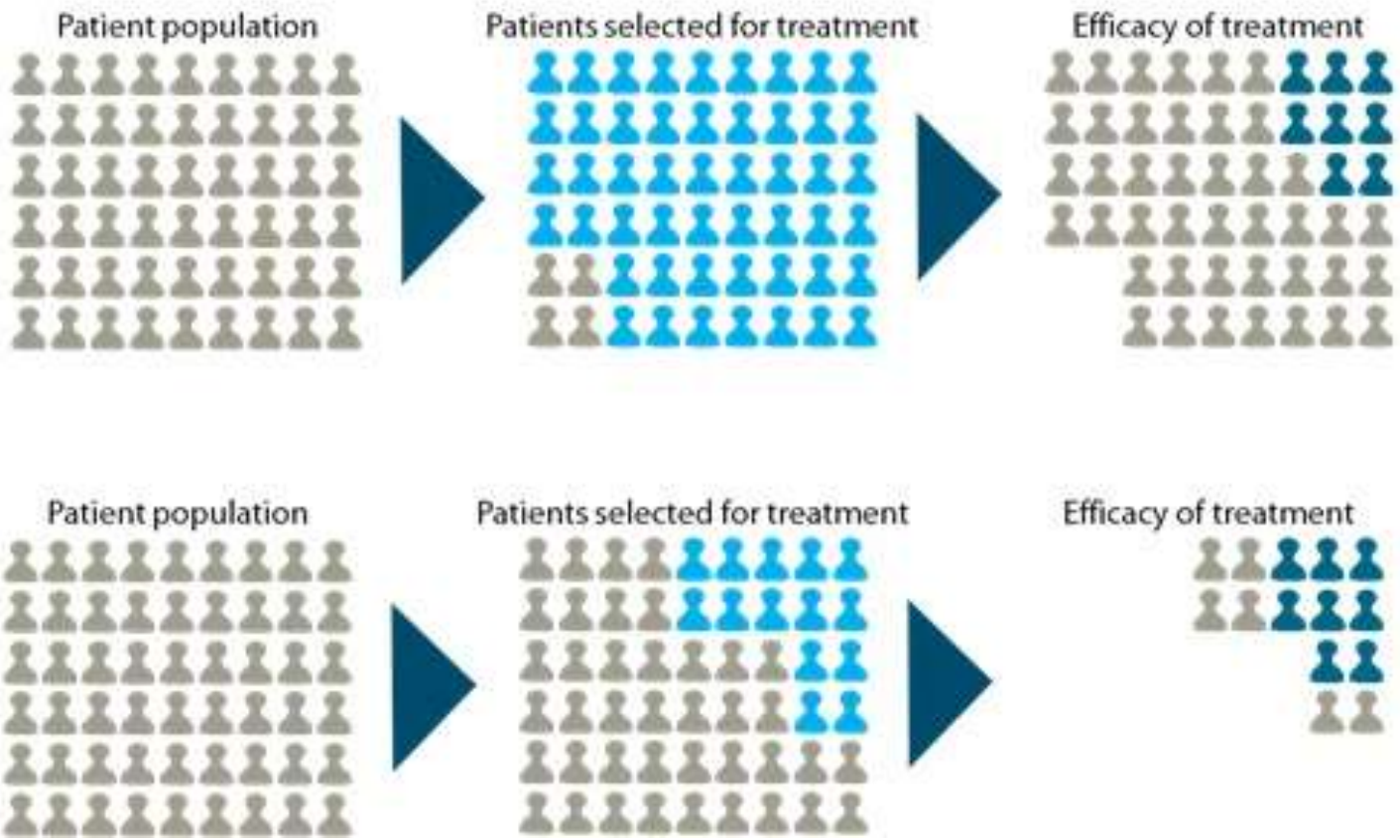
Retention of diagnostic slides

CLIA/CMS	10 years
State of Massachusetts	7 years
CAP	10 years
Tufts Med Center	10 years (15 for tumor slides)

Retention of tissue blocks

CMS	2 years
State of Massachusetts	7 years
CAP	10 years
Tufts Med Center	> 15 years

Biospecimens Support the Development and Use of Molecular Biomarkers in Clinical Trials




Formalin Fixed
Paraffin Embedded
(FFPE) Tissues

Department Response When Receiving a Request to Send Tissue to a Clinical Trial

	No. (%)
Usually comply by submitting a paraffin block	107 (17.9)
Usually comply by submitting unstained sections	83 (13.9)
Usually comply by having the pathologist determine whether a block or unstained sections is more appropriate depending on how much tumor is present	337 (56.4)
Decline all such requests	5 (0.8)
Other	65 (10.9)
Total	**597** (100)

Table 2

Fitzgibbons Arch Pathol Lab Med. 2011

Department Response When Entire Lesion (Tumor) Is Confined to a Single Block

	No. (%)
Send the block	88 (14.8)
Send unstained recuts, but not the block	419 (70.3)
Submit a core or a portion of the block, but not the cassette	11 (1.8)
Send nothing	19 (3.2)
Other	59 (9.9)
Total	**596** (100)

Table 6

Fitzgibbons Arch Pathol Lab Med. 2011

Recent Neely Center Request to the Biorepository

Enrollment. At the time of registration the clinical trial sponsor requires either the diagnostic tissue blocks OR cores and slides from those blocks be submitted for central pathology review and for gene expression profiling. **No gene expression results will be returned to the patient/subject**.

Specified cores and slides from the diagnostic FFPE block:

- One (1) H&E slide and twenty (20) 4 µm unstained air-dried charged slides
- One (1) or more core punches (minimum of 4mm diameter)

FOUNDATIONONE® Heme

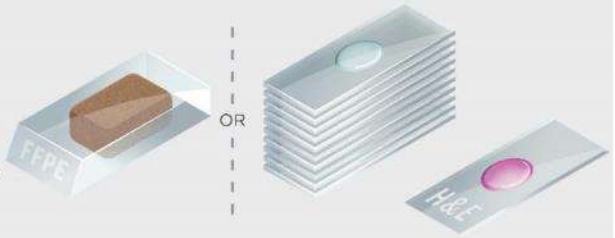
FFPE SPECIMEN (SLIDES OR BLOCK SUBMISSION) PREPARATION INSTRUCTIONS

1 SAMPLE TYPE

FFPE BLOCK OR 16 UNSTAINED SLIDES (+ 1 H&E SLIDE)

Tissue should be formalin-fixed and embedded into a paraffin block. If sending slides, send 16 unstained slides (charged and unbaked, with tissue cut at a 5 micron thickness) plus 1 H&E slide, ensuring that primary specimen containers are labeled with two patient-specific identifiers.

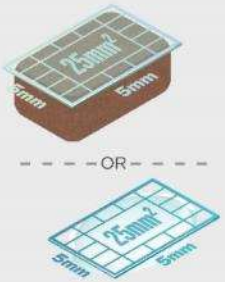
Specimens of suboptimal size, cellularity, or tumor content may require additional unstained slides or an alternate tissue block.



2 SURFACE AREA

OPTIMUM: 5 X 5 mm²

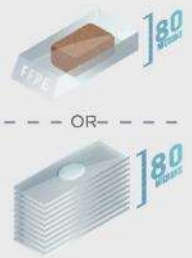
Tissue should have a surface area of at least 25 mm² (5 x 5 mm², 2.5 x 10 mm²)



3 SURFACE VOLUME

OPTIMUM: 2 mm³

Optimal sample volume can be achieved by sending optimal tissue surface area (25 mm²) at a depth of ≥80 microns. For suboptimal tissue surface area, additional depth is required.



4 NUCLEATED CELLULARITY

Nucleated cellular elements dictate DNA yield as DNA is extracted from nucleated cells. Samples with low nucleated cellularity (eg. those with abundant mature erythrocytes, lesional cells that contain excessive cytoplasm, or tissue with extensive associated fibrosis) may require greater tissue volume to yield sufficient DNA at extraction.

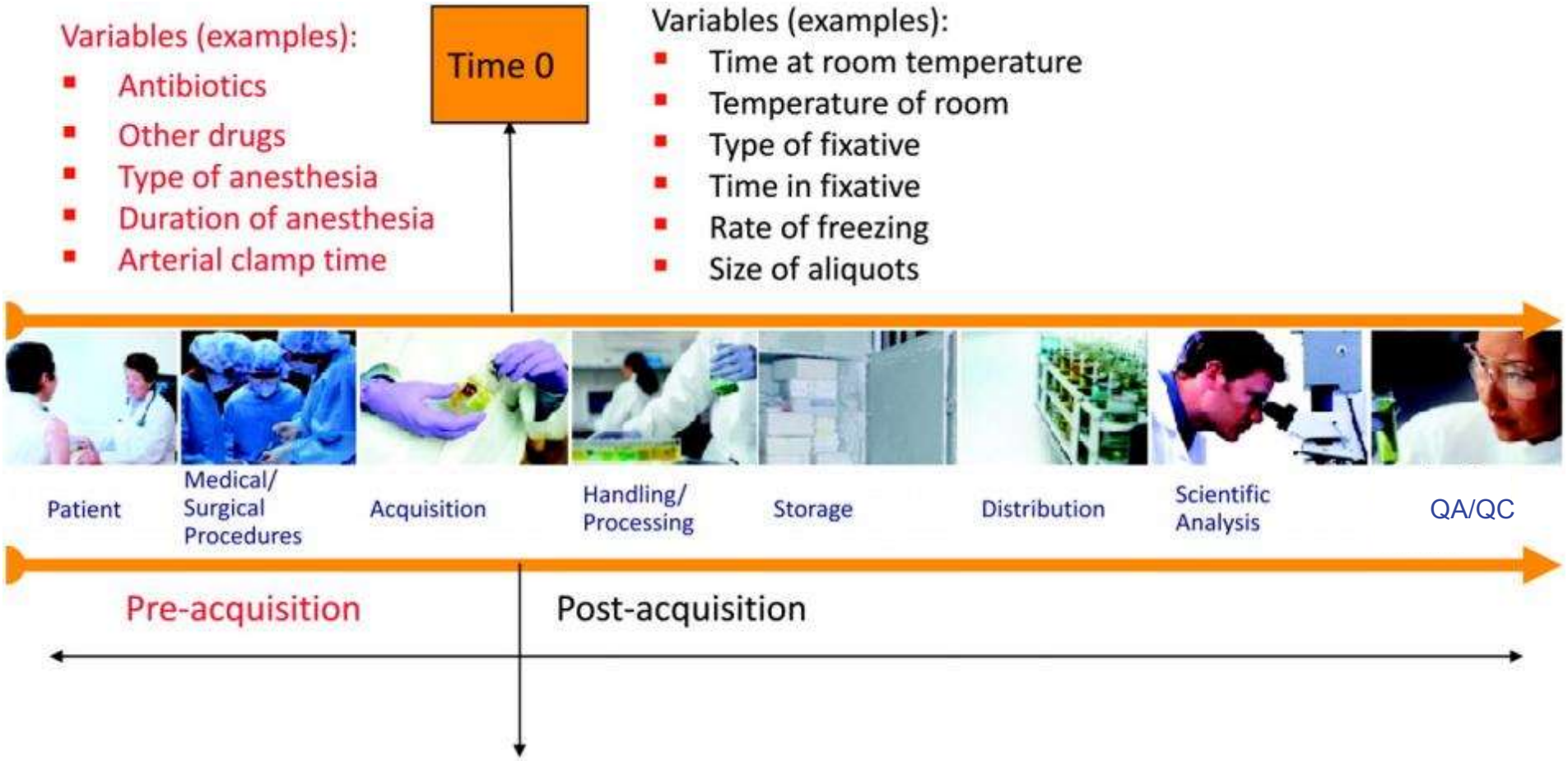
5 TUMOR CONTENT

MINIMUM: ≥20%

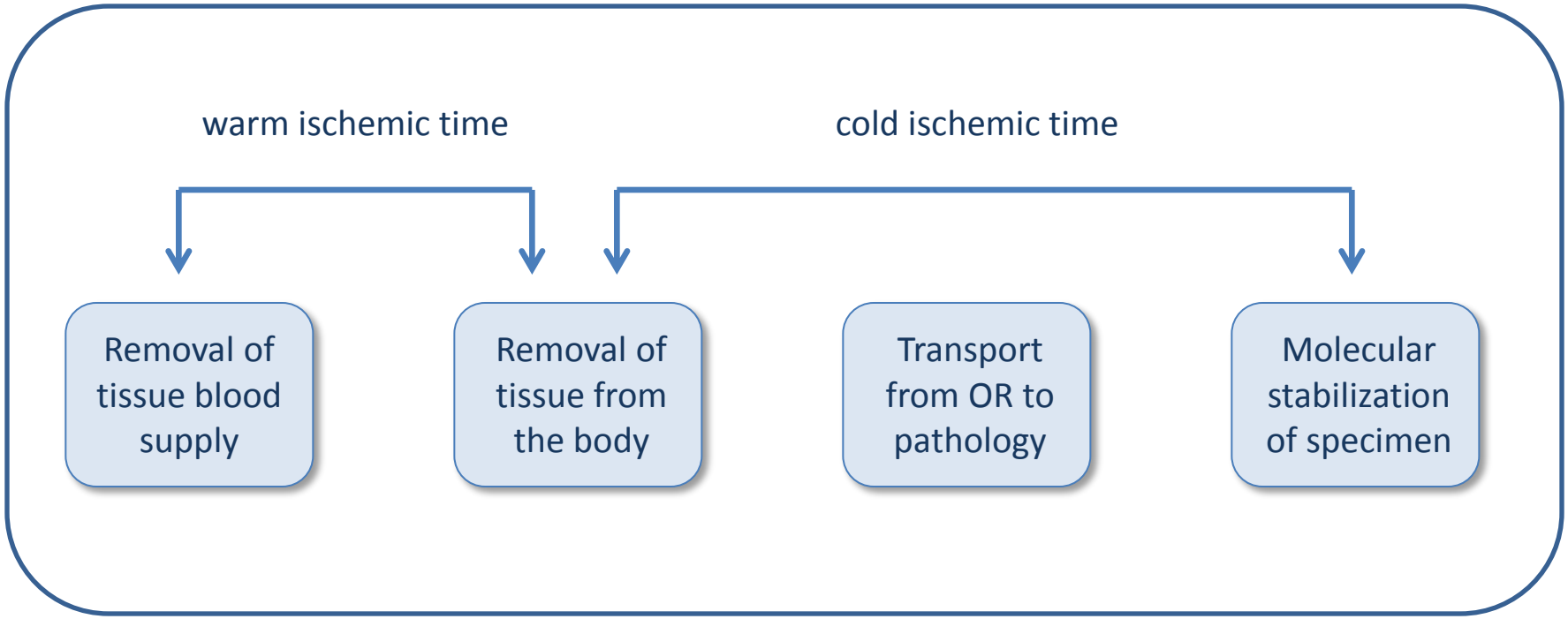
If the ratio of nucleated malignant to nucleated non-malignant cells is too low, sensitivity of detection of certain classes of alterations is reduced and may result in a qualified report or may require an alternate specimen for analysis. High tumor content is preferable.

Note for liver specimens: Minimum tumor content is ≥40%

Pre- and post-analytical variables affect the molecular integrity of the sample



Modified from Vaught J et al. *J Natl Cancer Inst Monogr.* 2011; 2011:1-7.


warm ischemic time
cold ischemic time
Removal of tissue blood supply
Removal of tissue from the body
Transport from OR to pathology
Molecular stabilization of specimen

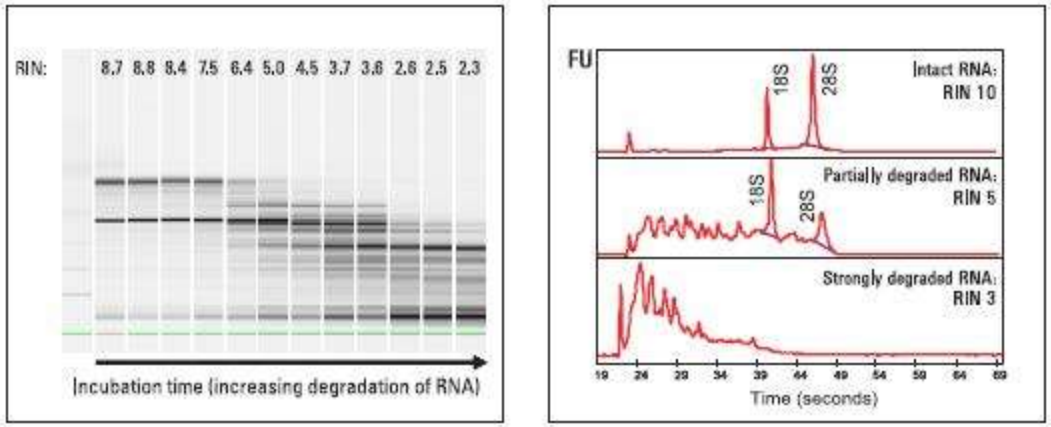
FFPE Tissues and Molecular Biomarkers

Issues of concern:

- Original state of the tissue
- Degradation during warm and cold ischemic intervals
- Fixation related issues (both under-fixation and over-fixation can cause problems)
- Processing issues (ie tissue deterioration due to residual moisture)
- Ill-defined deterioration as FFPE blocks age
- Inhibitors generated by original fixation/embedding process or by extraction
- Significant variation in “standard procedures” for FFPE tissue processing

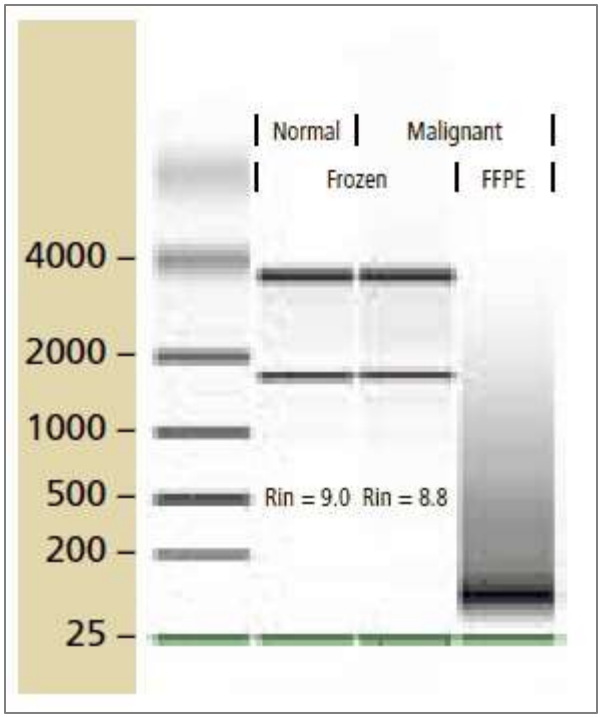
CAP/ASCO standards for processing breast tissue specimens used for ER, PR and HER2 testing

- begin the fixation quickly (within 1 hour) to minimize cold ischemic time
- grossly section the tissue at 5-mm intervals and fix in 10% neutral buffered formalin for 6 to 72 hours (recommended volume of fixative 10 fold greater than volume of specimen)
- record excision and fixation times
- tissue processing, staining and/or IHC must follow according analytically validated protocols



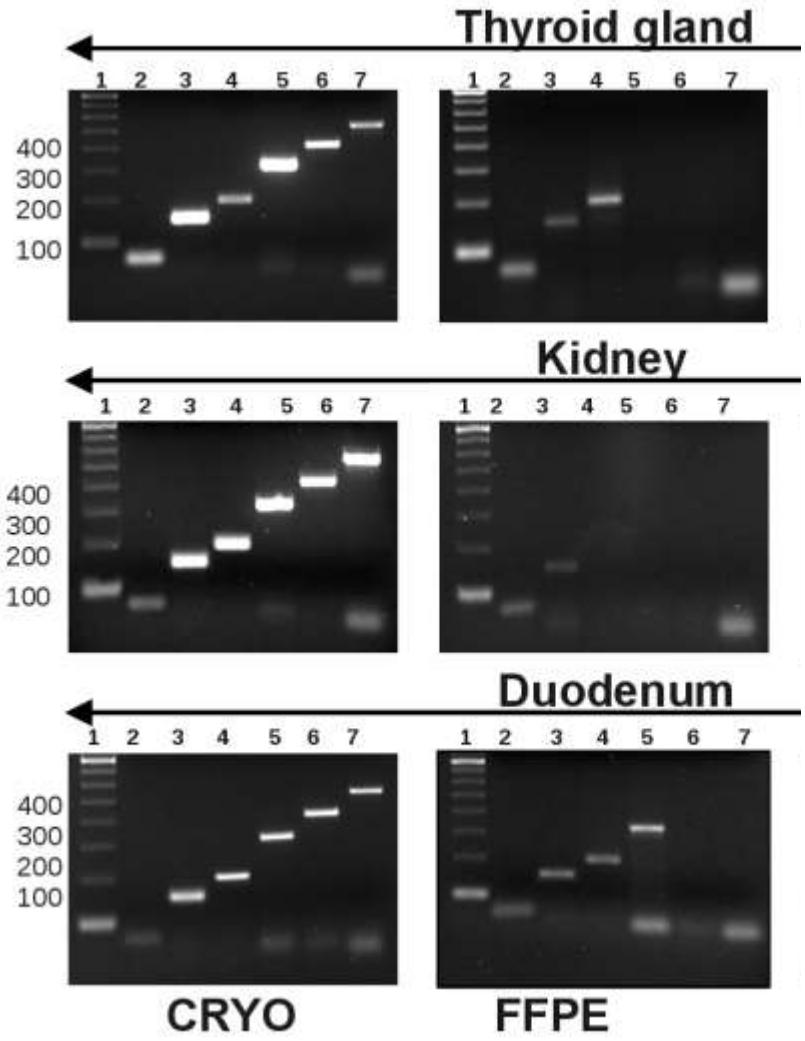
Visualization of overall RNA integrity Using Microcapillary Electrophoresis

Bioanalyzer Virtual Gel Image
RNA Isolated from Frozen and FFPE Prostate Tissues



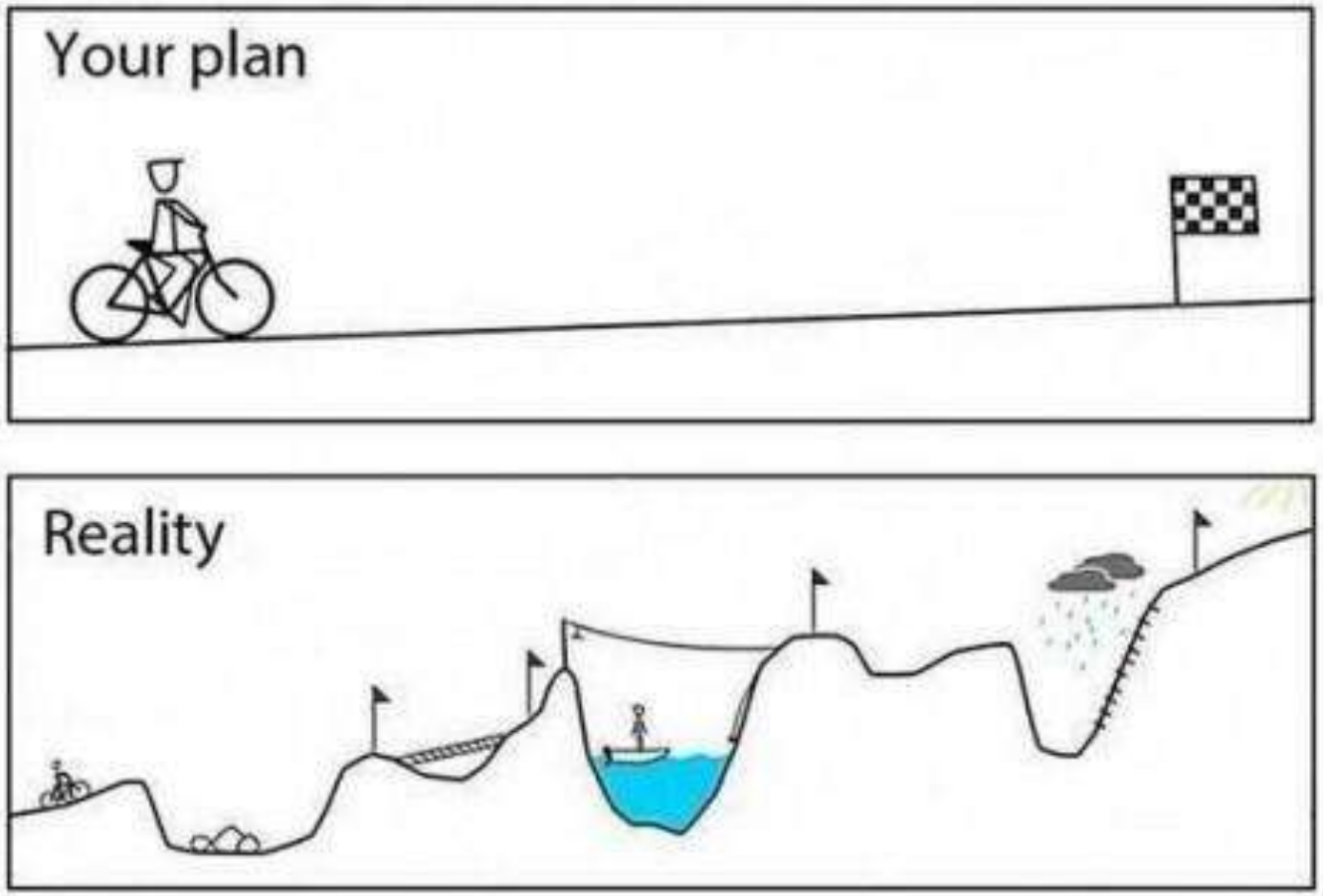
Lanes (l-r): reference ladder, frozen normal prostate, frozen malignant prostate, FFPE malignant prostate.

250 ng total RNA applied to each non-marker lane.



Amplicon length based assay of RNA quality (GAPDH amplicons)

Kashofer et al. PLoS One. 2013



- Getting the right biospecimens for your clinical trial may be more challenging than you anticipate at first glance but it can be done.
- Talk to the folks who have “been there - done that” right from the start!

Thank You

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