Data and Safety Monitoring Board

Tamsin Knox, MD, MPH

Associate Professor of Medicine
Tufts University School of Medicine

tamsin.knox@tufts.edu
617-636-3558

Tufts | CTSI
Tufts Clinical and Translational Science Institute

Questions

- Why do we have DSMBs ?
- What is the function of a DSMB ?
- Whose side are they on ?
- Which studies need a DSMB ?
- How do DSMBs work ?

  And what work do they do?
- How do DSMBs monitor safety ? Data ?
- How do DSMBs respond to problems ?

Why do we have DSMBs ?

- Greenberg report (1967) from the National Heart Institute recommended an advisory group of experts to review a study protocol, conduct of the study and advise the Institute
- NIH 1979 – “Every clinical trial should have provision for data and safety monitoring.”
- NIH 1998 - Requires DSMBs for Phase III multicenter trials
- 2006 FDA “Guidance for Clinical Trial Sponsors”

Names

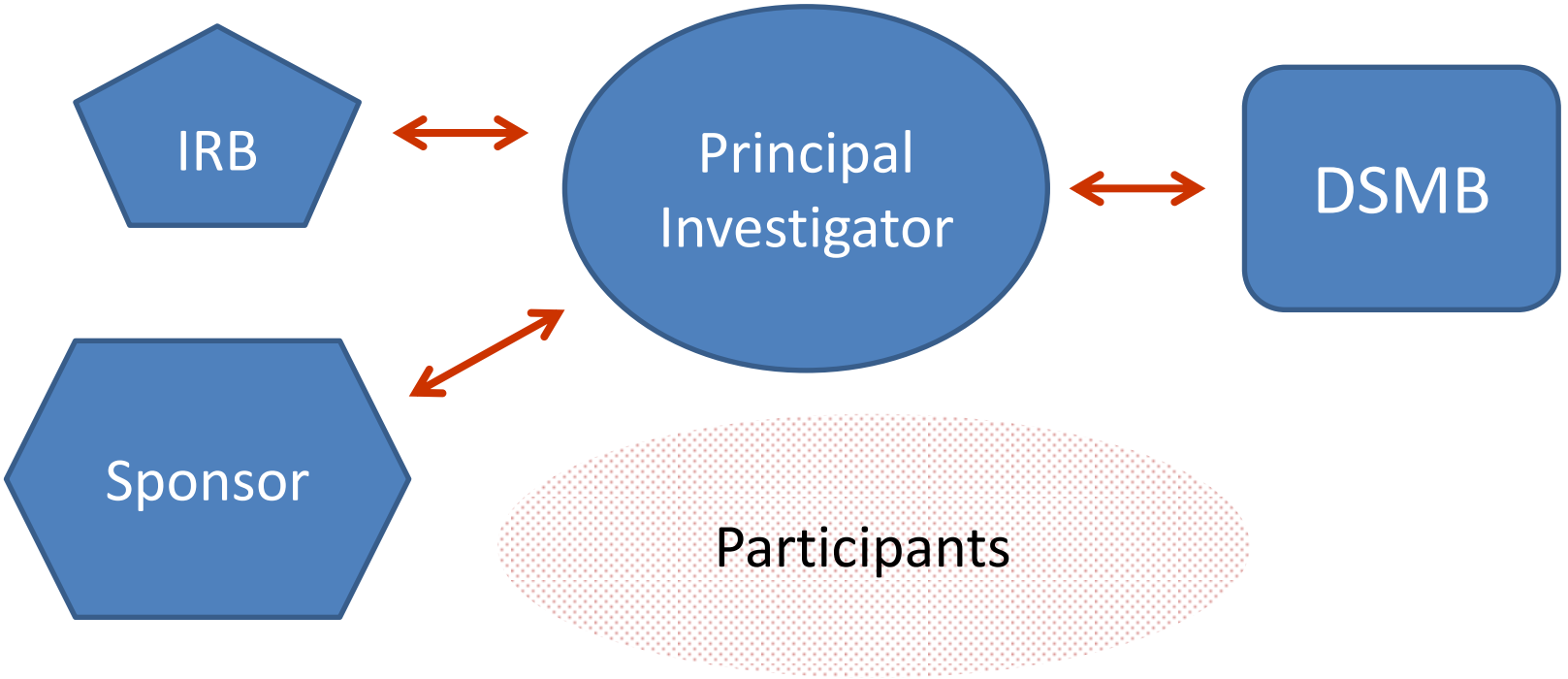
- DSMB: Data (and) Safety Monitoring Board
- DMC: Data Monitoring Committee
  - Used by the FDA
- Other monitoring options:
  - Defined by a study's Data Monitoring Plan
  - Medical monitor
  - Independent safety officer
  - Safety monitoring committee
  - External DSMB
  - Institutional DSMB

What is the function of a DSMB ?

- Guiding principle:
  - To ensure the safety of subjects in the trial by monitoring serious adverse events (SAE), risk/benefit, and any clinically relevant trends
  - How does this differ from IRB functions?
- Other functions:
  - Trial and data quality (enrollment, randomization, follow-up, procedures, advice)
  - Early stopping for:
    - Safety
    - Efficacy
    - Futility

Relationships

- Principal investigator
- IRB
- Sponsor



Which studies need a DSMB?

- Risk assessment
  - Low risk: DSMPlan, Medical monitor, ISO
  - High risk:
    - DSMB
    - More frequent monitoring
- External review
  - Scientific Review Committee (SRC)
  - Investigational Review Board (IRB)
  - Sponsor: NIH, FDA, Industry

High Risk Features

Feature	Criteria with increased risk
Study type	• Phase I or II study • Phase III – Randomized controlled trial • Pilot study • Complex protocol (e.g., multiple intervention arms, different sequential treatments) • Multi-site study • International studies (drug or device) • Complex data collection or use of new technologies for data collection
Study population	• Co-morbidity in the study population (e.g., cancer, cirrhosis, or other conditions which may have a higher risk for poor outcomes) • Vulnerable populations (e.g., children, prisoners, women of child-bearing potential, decision-impaired) • Other risk to participants (e.g., HIV testing with loss of confidentiality, language barriers)
Study intervention	• Gene transfer studies • Known risk of a study agent or procedure (e.g., known risk of anaphylaxis with administration, major surgery) • Novel technologies • Study with high public scrutiny
Investigator	• Inexperienced investigator (< 2 previous clinical trials) • Investigator held IND / IDE • Institution faculty developed the agent, device, or process • Other conflict of interest by the investigator or institution

How do DSMBs work ?

- PI (or sponsor) forms a DSMB
  - Impaneled DSMB for a cancer center
  - Standing and ad hoc members
- PI and Chairperson write a DSMB Charter
- Start-up meeting
  - Review study protocol, charter, expected safety issues, early stopping (if applicable) with biostatistician
- Regular meetings
  - By calendar, by enrollment (# or cohort), interim analysis
  - Additional *ad hoc* meetings for safety events
  - Frequent e-mail or phone communication, if needed
- Close-out meeting at the end of the study

DSMB Members

- Experts in field of disease & patient population
  - Experience in clinical research
  - No conflicts of interest
- Biostatistician
- Pharmacist
- Patient advocate
- Others: Geneticists, lawyers, engineers, etc.

The DSMB Charter

- The Charter guides the actions of the DSMB
- It covers:
  - **DSMB responsibilities**: safety, efficacy, stopping rules
  - **PI responsibilities**: provide data, timeliness, convey recommendations to the IRB and sponsor
  - **DSMB membership**: COI, confidentiality
  - **Meetings**: frequency, structure (open / closed), quorum and voting, *ad hoc* meetings
  - **Reports** to the PI: Minutes, Recommendations

DSMB Responsibilities

- Review all the data from a trial
  - Enrollment, randomization, follow-up
  - Safety events (as they happen and cumulative at meetings)
  - Current literature on treatment
- Consider whether the trial should be modified or enrollment stopped due to safety, efficacy, or futility
- Report recommendations to PI

A DSMB Meeting

- Open meeting
  - DSMB Committee
  - PI, research staff, study biostatistician
  - Study updates, protocol deviations, review of enrollment, SAE reviews
- Closed meeting
  - DSMB Committee only
  - Review study data and SAEs again
  - May request data by treatment arm or unblinded data from the study biostatistician
  - Prepare recommendations

Safety Review

- Individual SAE review
- Look for patterns
- Consider safety events in the context of the disease and the population being studied
- IF needed:
  - Review data by treatment arm (A or B)
  - Request unblinded data
- Resist the urge ….

SAEs – Example

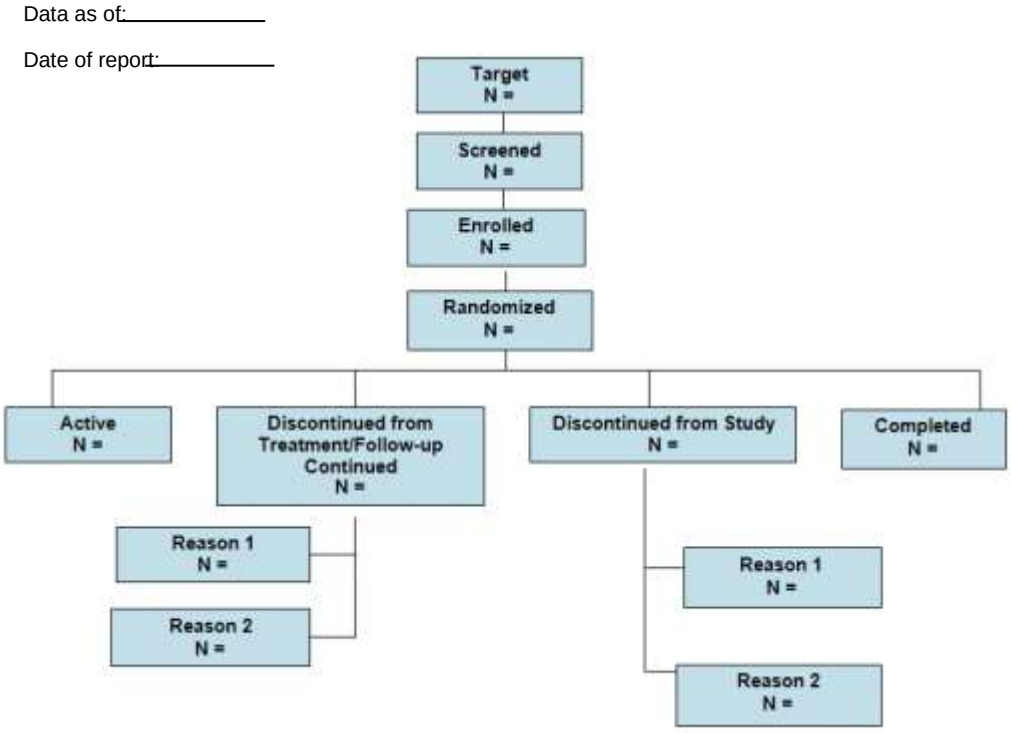
	[redacted]	# Current Trial (n=21)		
Gestational Age		24 0/7 – 27 0/7 wks	27 1/7 – 29 0/7 wks	Total
Pneumonia		0	0	0/21
Grades III,IV IVH or PVL **Interventricular hemorrhage** **Peri-Ventricular Leukomalacia**		0	0	0/21
Late Onset Infection		3	0	3/21 (14%)
NEC **Necrotizing Enterocolitis**		0	0	0
Death		1	0	1/21 (5%)
BPD **Bronchopulmonary Dysplasia**		3	0	3/21 (14%)

SAEs in Context

	% Stop BPD Trial			% Vermont-Oxford Data			# Current Trial (n=21)		
Gestational Age	24 0/7 – 27 0/7 wks	27 1/7 – 29 0/7 wks	Total	24 0/7 – 27 0/7 wks	27 1/7 – 29 0/7 wks	Total	24 0/7 – 27 0/7 wks	27 1/7 – 29 0/7 wks	Total
Pneumonia	10	2	6	8	4	6	0	0	0/21
Grades III,IV IVH or PVL **Interventricular hemorrhage** **Peri-Ventricular Leukomalacia**	8	5	6	11	6	9	0	0	0/21
Late Onset Infection	15	11	13	17	11	14	3	0	3/21 (14%)
NEC **Necrotizing Enterocolitis**	15	7	10	5	7	6	0	0	0
Death	7	5	6	16	7	11	1	0	1/21 (5%)
BPD **Bronchopulmonary Dysplasia**	47	28	37	42	16	28	3	0	3/21 (14%)

Data

- Accrual
  - Overall
  - By site
- Demographics
- Randomization
- Follow-up
- Missing data
- Clean data



Problems

- Enrollment is slow
  - Site issues, field moved on, inclusion/exclusion criteria are too strict, local culture
- Safety
  - Modify protocol
  - Place a hold on enrollment
  - Stop study
  - Need clearly defined parameters to stop a study (DeMets)
- Data
  - Data monitoring (PI's responsibility; help from a CRO or the Cancer Center)
  - 10% missing data = warning, 20% = may shut down

DSMB Meeting Report

Study Title: Wearing Rabbit Ears in Boston
To: Jonathan Hare, MD
Principal Investigator

Meeting Date: 4/1/2016

Meeting Attendees:

- ☐ Knox
- ☐ Bunny
- ☐ Squirrel
- ☐ Goldfinch

Recommendations:

- ☐ Continue the trial
- ☐ Continue the trial with suggestions
- ☐ Continue the trial with mandatory changes
- ☐ Suspend further enrollment in the trial

Comments:

Chairperson (initials and date):_____

Summary

- A DSMB is an independent review board for the participants and the PI.
- It reports to the PI
- It monitors safety and data quality
  - More risk, more monitoring
- Helps in all aspects of study function
- Plan ahead – budget for a DSMB, work with the chair to plan meetings and data presentation

DSMB Policies

- NIH Policy for Data and Safety Monitoring at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html
- FDA: Guidance for Clinical Trial Sponsors at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf
- FDA: Guidance for Industry at: *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*
- NIAID Policy on DSMB Operations at: http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Documents/dsmbpolicyv3.pdf
- List of NIH policies on DSMBs at: http://grants.nih.gov/grants/policy/hs/data_safety.htm
- NIH research tool-kit at: http://www.nidcr.nih.gov/Research/toolkit/

Thank You

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Budgeting for Clinical Trials

Doug Reichgott, MS

Director, Financial and Regulatory Operations/Policy
Tufts Medical Center

Tufts | CTSI
Tufts Clinical and Translational Science Institute

Goals

- Identify issues related to clinical trial budgeting
- Understand the process of creating a budget

Which is the Better Budget?

$5,000 per pt	$1,000 per pt
5 Visits 300 page CRF	1 visit 10 page CRF

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Distinguish Between Research and Usual and Customary Care

- Utilize Protocol
  - Chart of Events/Procedures Descriptions
- Usual and Customary vs. Research Only
- Coordinator/Nurse Time
- Physician Time

Example

Procedures	V1	V2	V3	V4
Consent	X			
Inc./Exc.	X			
Physical	X			X
CBC	X	X	X	X
MRI		X		
Coordinator	X	X	X	X
PI	X	X	X	X
Subject	X	X	X	X

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Determine Time Per Activity

- Based on Protocol
- Start Standard, but Be Flexible
- Be Careful With your Estimates

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Determine Who Will Complete These Activities

- MD?
- Nurse?
- Non-Nurse Coordinator?
- Research Assistant?
- Fellows?
- Combination?

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Determine Salary

- Institutional Fringe
  - 30%
- Potential for Increase
  - Inflation
- For corporate sponsored studies, use of specific salary is not required
- For NIH studies, salary limitations apply

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Do the Math! / Obtain Pricing

- Activities - *Staff/Investigator Time*
  - Time Required for a Task x Salary

- Ancillary Procedures - *Purchased Service*
  - Obtain Research Pricing from Ancillary Department (technical and professional fees, if applicable)
  - + Margin? Inflation factor, scheduling, etc.

- NIH studies MUST USE THE MEDICARE RATE for all Ancillary Procedures.
- Mark-up Margin/Infation are NOT allowed.

Procedures	V1	V2	V3	V4
Consent	X			
Inclusion/ Exclusion	X			
Physical	X			X
CBC	X	X	X	X
MRI		X		

Procedures				
Consent	PI $200 hr/0.5 hours			
Inclusion/ Exclusion	Coordinator $100 hr/0.5 hours			
Physical	PI $200 hr/0.5 hours			
CBC	Local Lab - $12			
MRI	Radiology $1200/Pro fee $450			

Example

Procedures	V1	V2	V3	V4
Consent	100			
Inc./Exc.	50			
Physical	100			100
CBC	15	15	15	15
MRI		1750		
Coordinator	100	100	100	100
PI	100	100	100	100
Subject	25	25	25	25

Procedures				
Consent	PI $200 hr/0.5 hours			
Inclusion/ Exclusion	Coordinator $100 hr/0.5 hours			
Physical	PI $200 hr/0.5 hours			
CBC	Local Lab - $12		PHLEBOTOMY	
MRI	Radiology $1200/Pro fee $450			

Example

Procedures	V1	V2	V3	V4
Consent	100			
Inc./Exc.	50			
Physical	100			100
CBC	35	35	35	35
MRI		1750		
Coordinator	100	100	100	100
PI	100	100	100	100
Subject	25	25	25	25

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Determine Institutional Charges

- Overhead
  - 30%
  - 75%
- Base?
  - Total Direct Cost vs. Modified Total Direct Cost
  - Location of the Majority of Research

Institutional Charges (Cont.)

- IRB Fees
- Pharmacy
- MCA
- Other?

Budget Development in 7 Steps

1. Determine Research Procedures and Activities
2. Determine Time Per Activity
3. Determine Who Will Complete These Activities
4. Determine Salary
5. Do The Math! / Obtain Pricing
6. Determine Institutional Charges
7. Determine Other Charges

Administrative/One Time Charges

- Activities related to the study but not related to specific patient care activities
- Can be accounted for as part of one time fees, or by invoice
- Sponsors are variable in their willingness to pay

- Recruiting
- Advertising
- Stipends
- Sample Processing
- Shipping Of Samples, Films
- Packing, Dry Ice
- Record Retention
- IRB Prep / Start-up
- IRB Maintenance
- Regulatory Document Collection
- Document Maintenance
- Protocol Amendments
- SAEs
- Safety Reports

Payment Schedules

- Invoicing vs. Milestones
  - Benefits/Problems
- Start-Up vs. Advanced Funds
  - Non-Refundable vs. Advanced Subjects
- Screen Failures
  - How Much?
  - How Many

Payment Schedules (cont.)

- Early Termination of Project
  - Due to Competitive Enrollment
  - Due to FDA Action
  - Due to Corporate Decision Making

- Chart Review
- Specimens
- Devices
- Multi-Center

- *There is no such thing as an unfunded study*

Pitfalls

- Underestimating required time
  - Its not just the time *with* the subject
- Not properly explaining need to sponsors

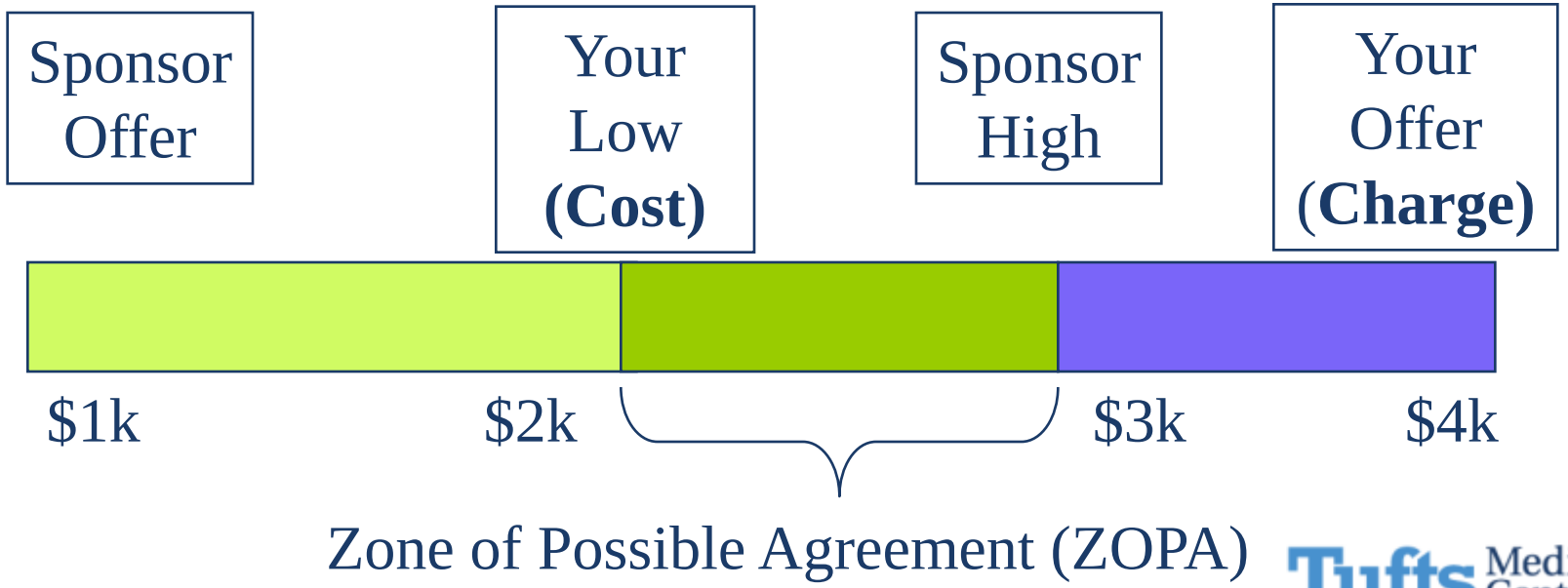
- AS A NOT-FOR-PROFIT WE SHOULDN'T BE SUBSIDIZING DRUG COMPANIES

Charges vs. Cost

- Cost is the low-end beneath which you cannot move
  - Physicians May Have Other Reasons
- Charge is where you would like to be and includes appropriate margin
- YOU NEED TO KNOW BOTH!

Final Thoughts

- Budget creation is a negotiation.
  - What is important for that study?
- Don't negotiate from ego
- Know your desires and requirements in advance



Contact Info

Douglas Reichgott

Director, Financial and Regulatory Operations

Director, NCCCR

617 636 5609

dreichgott@tuftsmedicalcenter.org

Thank You

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Overview of Next Session

February 10, 2017

8th Floor Conference Room

35 Kneeland Street

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Agenda

Meeting Agenda
Clinical Trials – From PI-Initiated to Collaborative Research

Registration	12:30 – 1:00 PM
Team Science *Bob Martell & Andy Evens*	1:00 – 1:45 PM
Engaging with Industry *Bob Martell & Andy Evens*	1:45 – 2:45 PM
Break & Snack	2:45 – 3:00 PM
Food and Drug Administration (FDA) *Andreas Klein & Bob Martell*	3:00 – 4:00 PM
Medicare Coverage Analysis *Doug Reichgott*	4:00 – 4:45 PM
Closing Remarks	4:45 – 5:00 PM

Pre-Work

No Pre-Work!

Tufts | CTSI

Tufts Clinical and Translational Science Institute