Introduction to Clinical Research Boot Camp 2019

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Welcome!

Tuesday, July 30-Wednesday, July 31

8:00am-4:30pm

UW Husky Union Building

Lyceum/250/145

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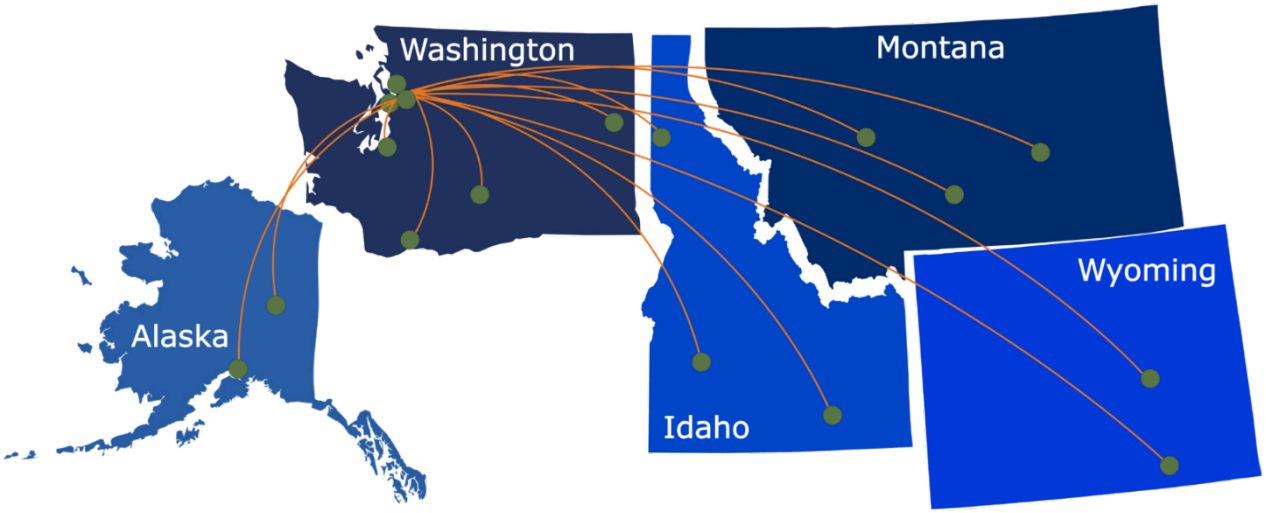

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What We Offer:

1. **Research Support Services:** Members gain access the different research services, resources, and tools offered by ITHS, including the ITHS Research Navigator.

2. **Community Engagement:** Members can connect with regional and community based practice networks

3. **Education & Training:** Members can access a variety of workforce development and mentoring programs and apply for formal training programs.

4. **Funding:** Members can apply for local and national pilot grants and other funding opportunities. ITHS also offers letters of support for grant submissions.

Contact our **Research Navigator**

- **Project Consultation**
- **Strategic Direction**
- **Resources and Networking**

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Introduction to Clinical Research Boot Camp 2019

Keynote

Working toward a cure in Hemophilia;

Progress in Gene Therapy

Presented by Barbara Konkle, MD

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Working Toward a Cure in Hemophilia: Progress in Gene Therapy

Barbara A. Konkle, M.D.
Chief Scientific Officer
Associate Director, Washington Center for Bleeding Disorders
Director, Hemostasis, Platelet Immunology and Genomics Laboratory
Bloodworks Northwest
Professor of Medicine/Hematology
University of Washington
Seattle, WA USA

UNIVERSITY of WASHINGTON

ITHS 7.30.19

Bloodworks Northwest

Disclosures

Shareholder	No relevant conflicts of interest to disclose
Grant / Research Support	Octapharma, Pfizer, Spark, Takeda/Shire, Uniqure, Sanofi
Consultant	BioMarin, Pfizer, Roche/Genentech, Sanofi
Employee	No relevant conflicts of interest to disclose
Paid Instructor	No relevant conflicts of interest to disclose
Speaker bureau	No relevant conflicts of interest to disclose
Other	No relevant conflicts of interest to disclose

Outline

- Brief history of gene therapy
  - Advances and setbacks
- Hemophilia as a target for gene therapy
- Ethical issues in gene therapy research/commercialization

Gene Therapy

- Definition: *Products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses or genetically engineered microorganisms*[1]
- Approaches:[2]
  - Somatic gene therapy
    - Change is not passed along to the next generation
    - Current approved approach
  - Germline gene therapy
    - Therapeutic or modified gene will be passed on to next generation[3]

Gene-edited babies: What went wrong and what could go wrong

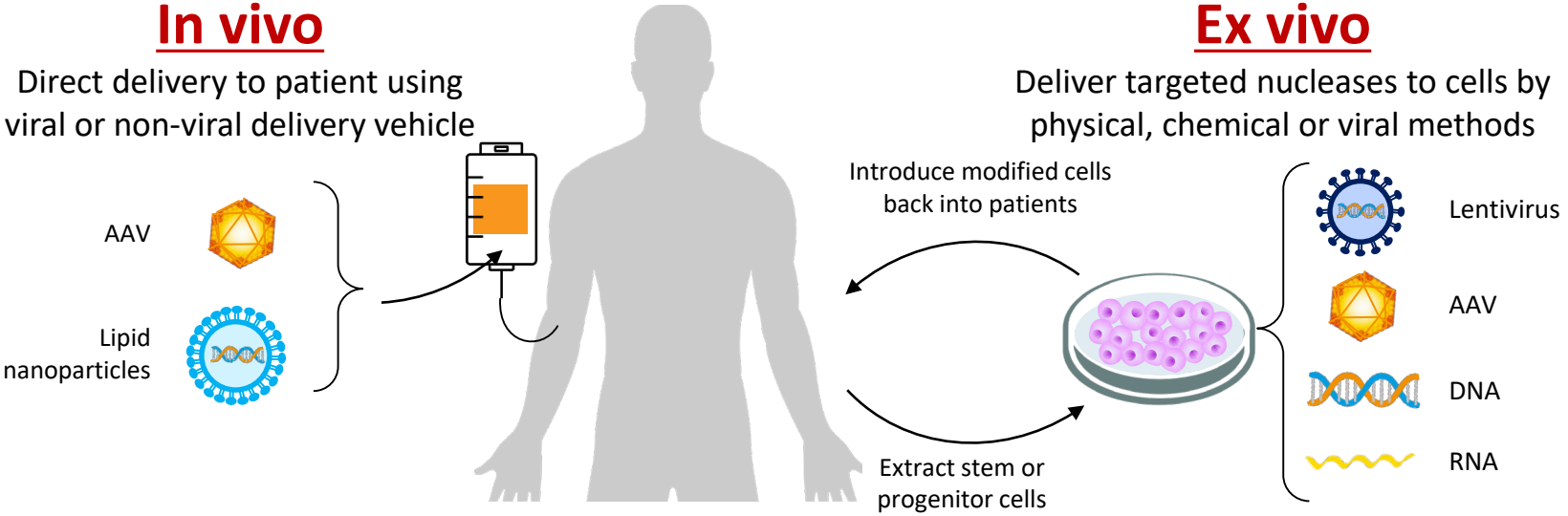
Haoyi Wang, Hui Yang

Published: April 30, 2019 • https://doi.org/10.1371/journal.pbio.3000224

PLOS BIOLOGY FIFTEENTH ANNIVERSARY

1. US FDA. https://www.fda.gov/media/81682/download (Accessed June 2019). 2. Wirth T, et al. *Gene* 2013;525:162. 3. Wang H, Yang H. *PLoS Biol* 2019;30;17(4):e3000224.

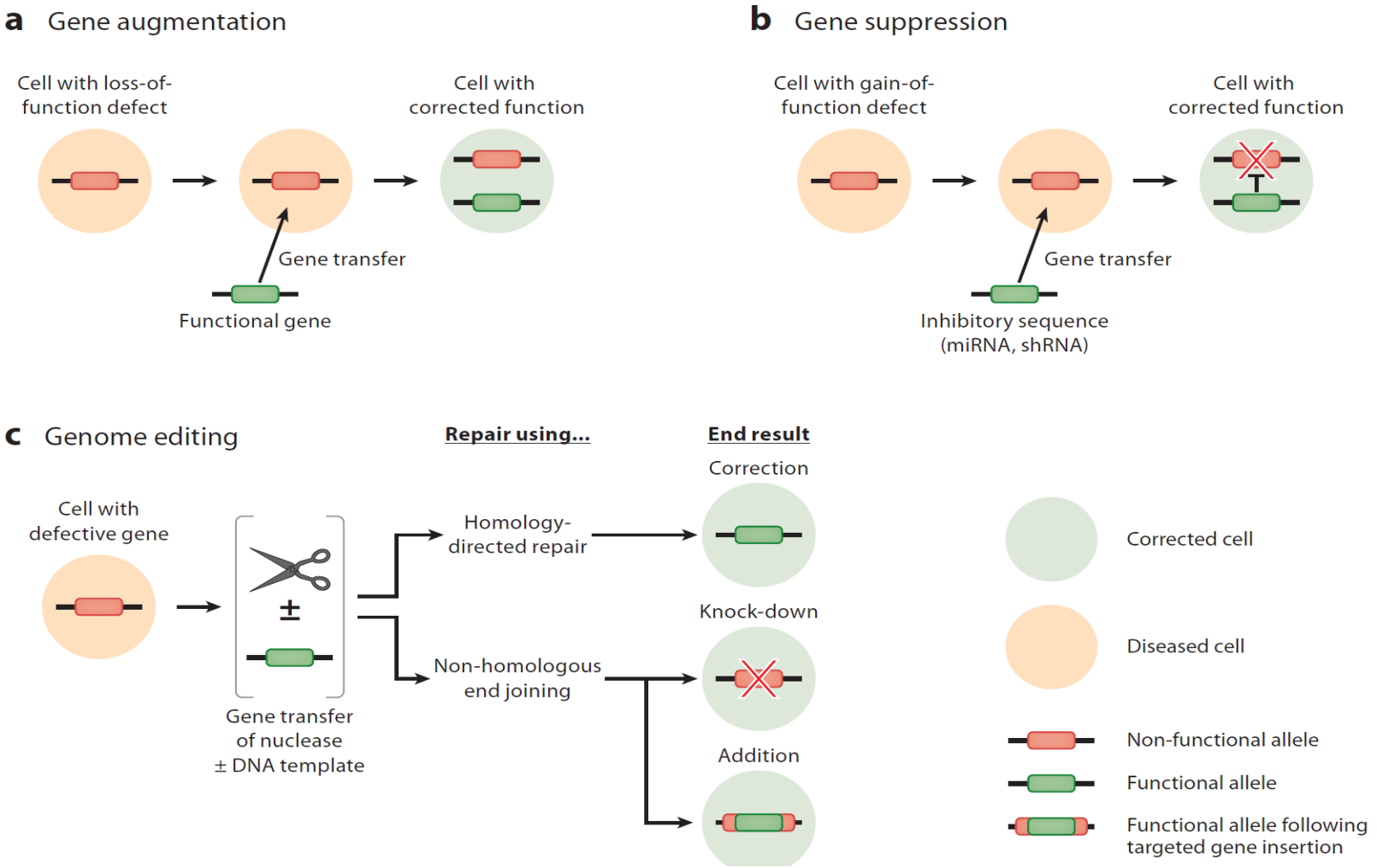
Approaches to Gene Therapy



- Common therapeutic strategies[1]
  - Lentivirus for *ex vivo* gene transfer into hematopoietic and other stem cells[2,3]
  - AAV for *in vivo* transfer into postmitotic tissues[2,4]

Image adapted from US FDA – What is gene therapy.[1]
AAV: Adeno-associated virus.
1. US FDA. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy (Accessed June 2019). 2. Mingozzi F, High KA. *Nat Rev Genet* 2011:12:341. 3. Milone MC, O'Doherty U. *Leukemia* 2018;32:1529. 4. Colella P, et al. *Mol Ther Methods Clin Dev* 2018;8:87.

Approaches to Gene Therapy - 2



Anguela and High. Ann Rev Med. 2019;70:273-88.

Milestones in Gene Therapy

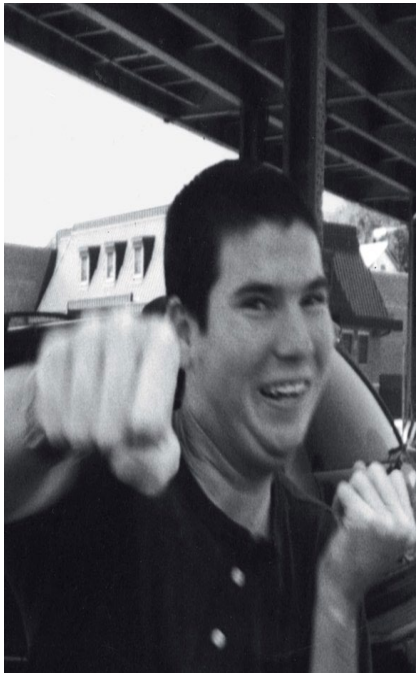
- Early studies with advances, but also setbacks
- First therapeutic ex-vivo gene therapy in 1990s
  - X-linked severe combined immune deficiency (SCID)
    - First generation γ-retroviral vectors with gene expressed under the control of viral regulatory elements
    - Positive response, however 5/20 developed leukemia due to insertional mutagenesis
  - Adenosine deaminase deficiency (ADA-SCID)
    - Retroviral transfer of ADA gene into HSCs
    - Early partial response, now with efficacy comparable to enzyme replacement
    - Approved by EMA in 2016
    - No leukemia
- Lentiviral vectors thought to be less genotoxic than retroviral vectors
  - Vectors under clinical development without viral regulatory elements

ADA-SCID: Adenosine deaminase severe combined immunodeficiency; EMA: European Medicines Agency; US FDA: U.S. Food and Drug Administration.

1. Wirth T, et al. *Gene* 2013;525:162. 2. Mingozzi F, High KA. *Nat Reviews: Genetics* 2011;12:341. 3. Anguela XM, High KA. *Annu Rev Med* 2019;70:273.

Major Setback in Gene Therapy in 1999

- Death of Jesse Gelsinger from adenoviral-mediated gene therapy for partial ornithine transcarbamylase deficiency
  - Major systemic reaction
  - Death from multi-organ failure
- Issues raised
  - Did subject meet inclusion criteria?
    - Milder disease
  - Conflict of interests
    - Involvement of investigator who developed vector in clinical trial
  - Did they underplay potential immune response?



JG 3 months before death

1. Wirth T, et al. *Gene* 2013;525:162. 2. Mingozzi F, High KA. *Nat Reviews: Genetics* 2011;12:341. 3. Anguela XM, High KA. *Annu Rev Med* 2019;70:273.

Continued Progress in Gene Therapy

- Steady progress in 21st century resulting in drug approvals
  - 2012, EMA approves first gene therapy Alipogene tiparvovec, for lipoprotein lipase deficiency
  - 2018, US FDA and EMA approve Voretigene neparvovec for RPE65 mutation-associated retinal dystrophy


SCIENTIFIC AMERICAN

The Most Expensive U.S. Medicine Now Has an Official Sticker Price

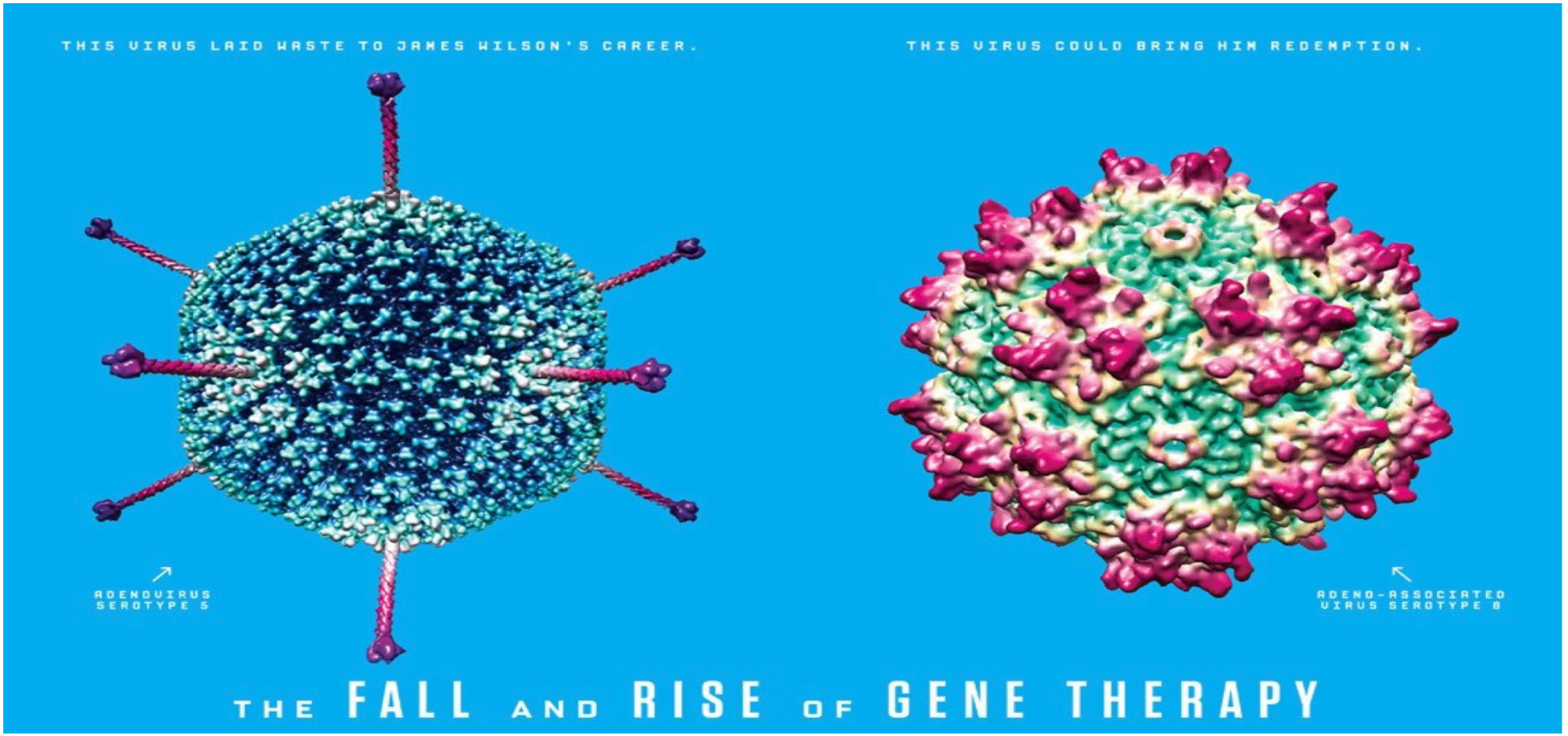
This gene therapy for vision loss will initially cost $850,000

- On June 9, 2019:
  - 3985 gene therapy studies on ClinicalTrials.gov

1. Mingozzi F, High KA. *Nat Reviews: Genetics* 2011;12:341. 2. Anguela XM, High KA. *Annu Rev Med* 2019;70:273.
3. https://clinicaltrials.gov/ct2/results?cond=&term=gene+therapy&cntry=&state=&city=&dist= (Accessed June 2019).

CARL ZIMMER SCIENCE 08.13.13 06:30 AM

GENE THERAPY EMERGES FROM DISGRACE TO BE THE NEXT BIG THING, AGAIN



AAV-Mediated *in-vivo* Gene Therapy

- Most common approach for *in vivo* gene transfer into post-mitotic tissues
- Can be targeted with tissue-specific regulatory elements
- Native virus is not known to cause disease and virus is replication defective
- Mostly non-integrating

1. Mingozzi F, High KA. *Nat Rev Genet* 2011:12:341. 2. Colella P, et al, Molec Ther Method Clin Develop 2018;8:87.

Gene Therapy for Hemophilia

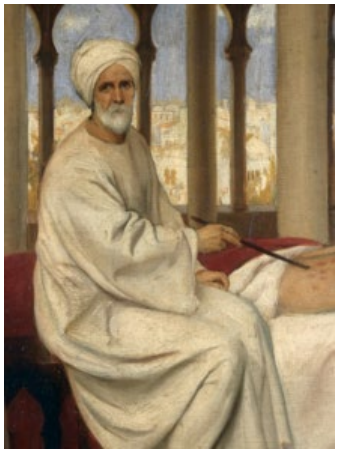
- Recognised early as good target
  - Single gene disorder[1]
  - Wide range of levels can produce therapeutic effect without safety concerns for factor activity[1]

- Early trials confirmed
  - Factor VIII and IX can be synthesized and undergo post-translational modification in cells that are not the normal site of production[2–4]
  - Functional factor activity can be secreted into the blood stream[2–4]

1. Lheriteau E, et al. *Blood Rev* 2015;29(5):321–8. 2. Murphy SL, High KA. *Br J Haematol* 2008;140:479–87. 3. Nathwani AC, et al. *N Engl J Med* 2011;365:2357–65.
4. Nathwani AC, et al. *N Engl J Med* 2014;137(21):1994–2004.

History of Hemophilia

- Talmud – 2nd century
  - Recognition of bleeding with circumcision
- Al-Zahrawi, renowned 10th-11th century Arab physician
  - Described families with hemorrhagic disorder in males
- John Otto, physician in Philadelphia, USA
  - In 1803, published a description of X-linked bleeding disorder.
- Queen Victoria – 19th century
  - Descendants spread hemophilia through Europe

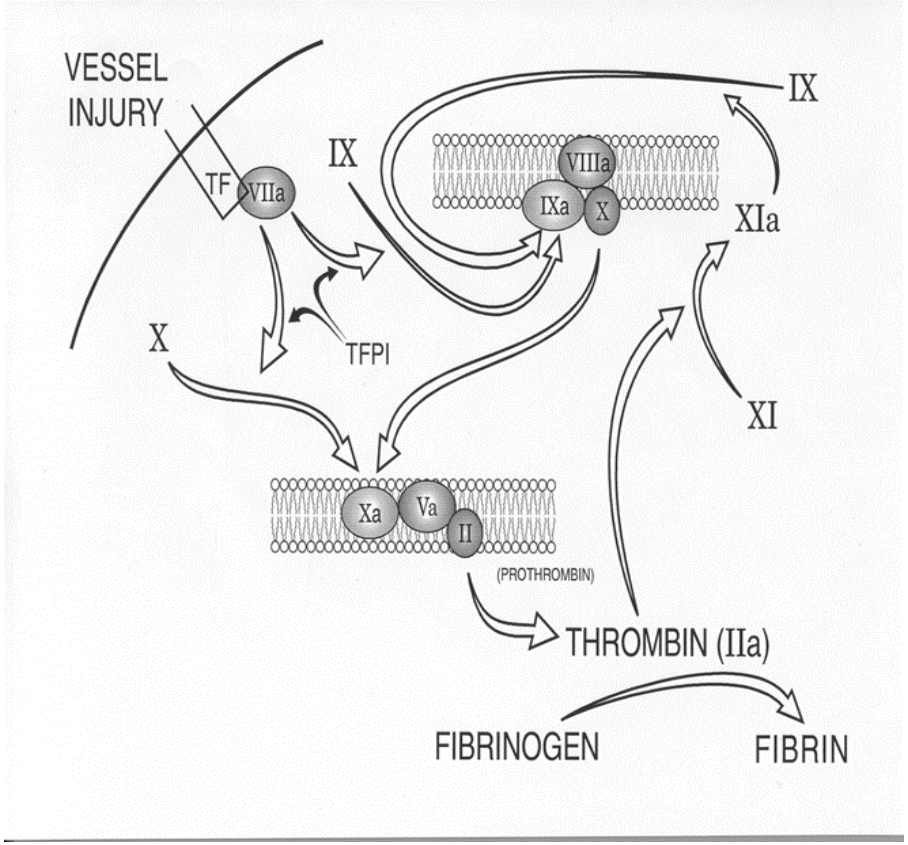


Hemophilia: Recognition

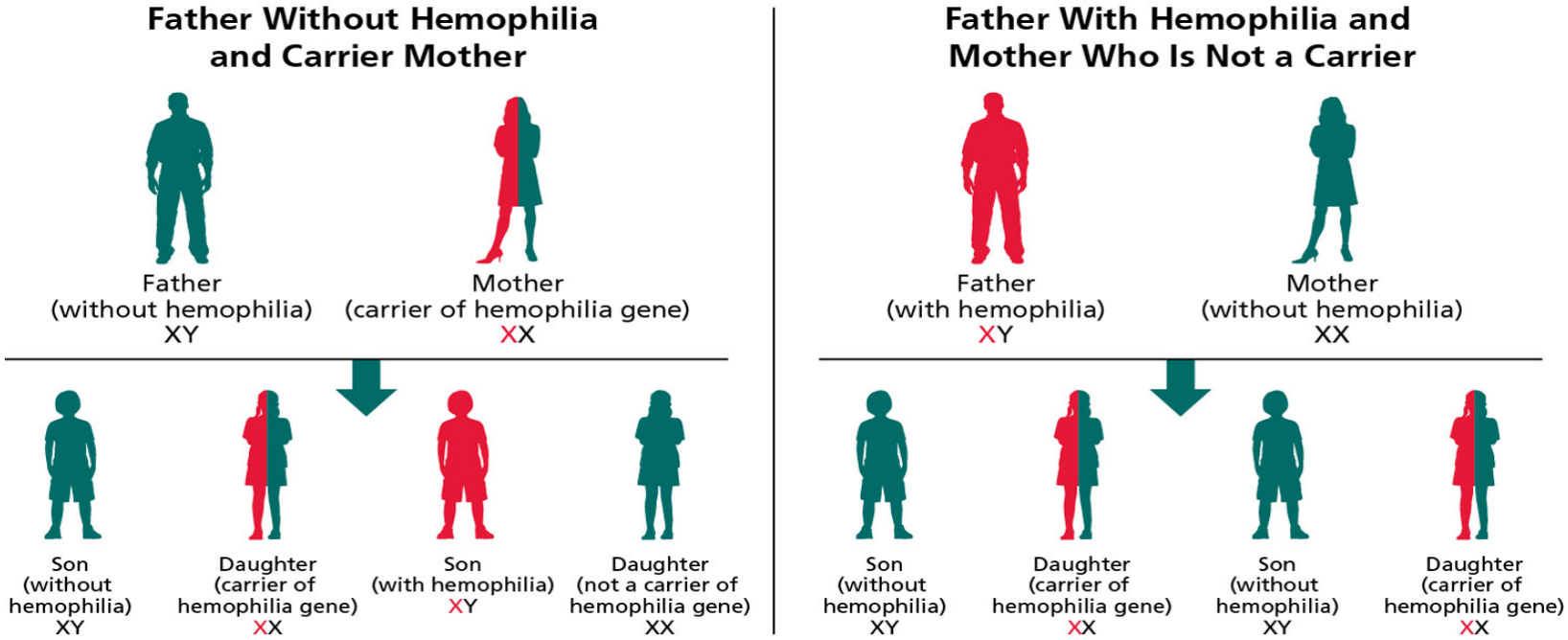
- Worldwide: At least 1/5000 male births
- New mutation rate ~ 30%
  - Thus hemophilia seen in all racial groups
  - First presentation may be bleeding symptoms in a female genetic carrier
- Hemophilia A - ~ 80% of cases
- Hemophilia B - ~ 20% of cases
- Presentation and diagnostic approach the same with A and B
  - Overall hemophilia B may be milder, but not useful on an individual patient level

Hemophilia: Pathophysiology

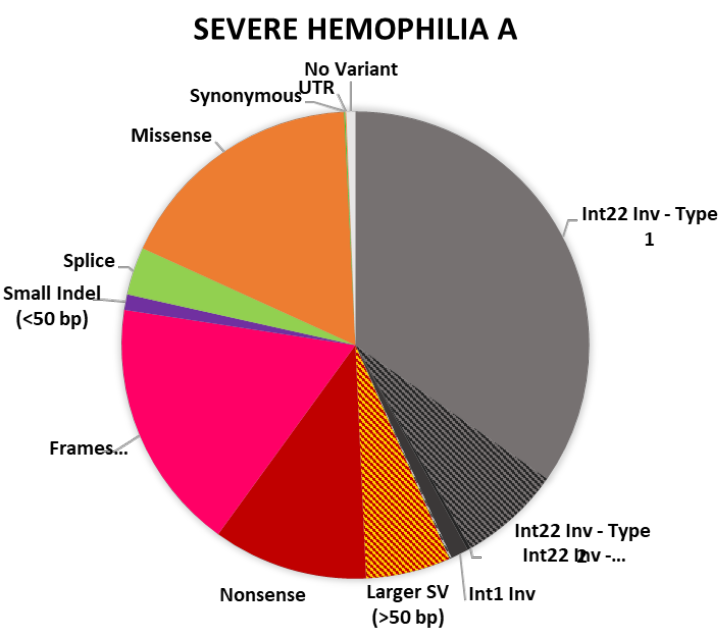
- FVIII accelerates the rate of FX activation by FIXa, eventually leading to the generation of thrombin (FIIa) and subsequent formation of the fibrin clot
- Deficiency of either FVIII or FIX predisposes to spontaneous and trauma-induced hemorrhage

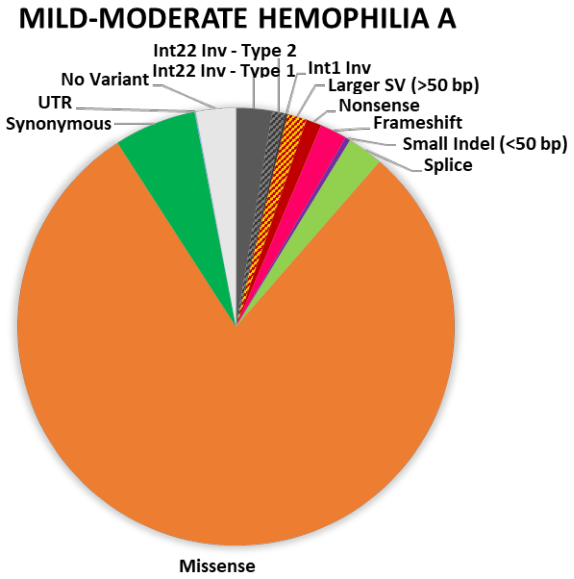


Inheritance of Hemophilia



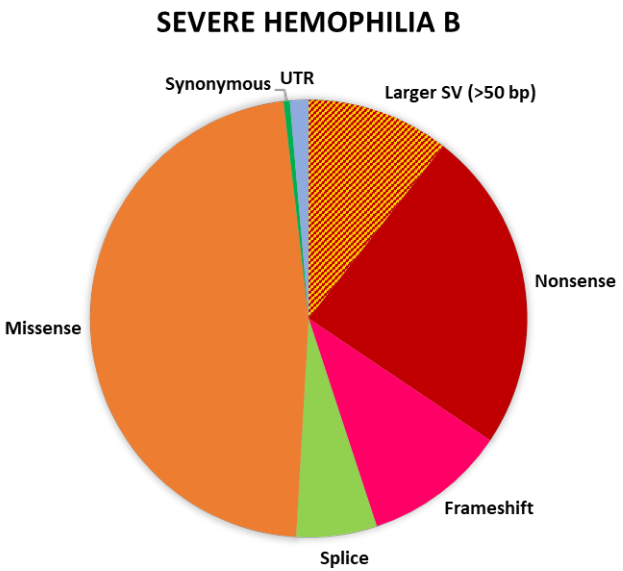
Genetics of Hemophilia A

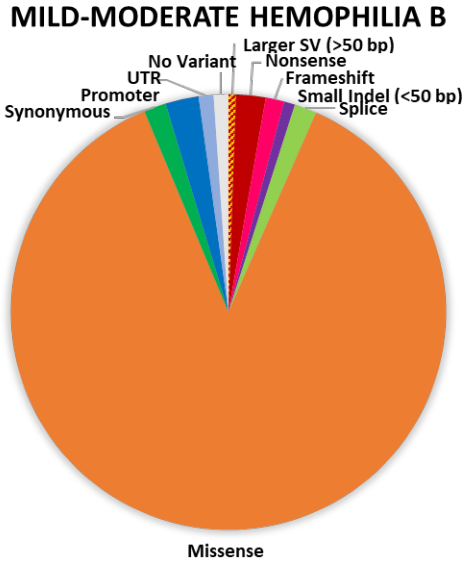




Johnsen JM, et al. *Blood Advances* 2017;1:824-834

Genetics of Hemophilia B





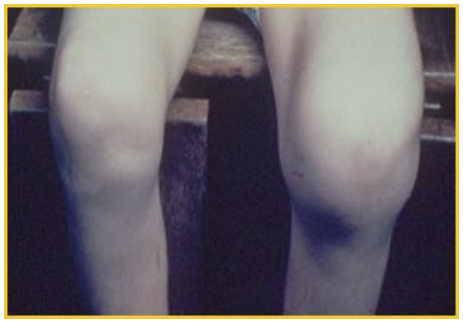
Johnsen JM, et al. *Blood Advances* 2017;1:8

Presentation of Hemophilia

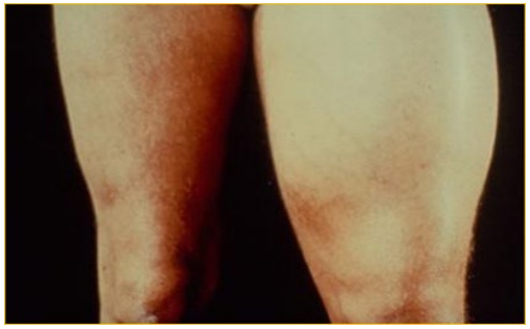
- Average onset of clinical symptoms
  - Severe: 1.5 years (many will present at birth)
  - Moderate: 3 years
  - Mild: 5 years
- Initial presentation:
  - Early postnatal procedures
  - With intramuscular injections
  - With dental eruptions/loss/tongue biting
  - Spontaneous hemarthroses after onset of walking

Sites of Bleeding

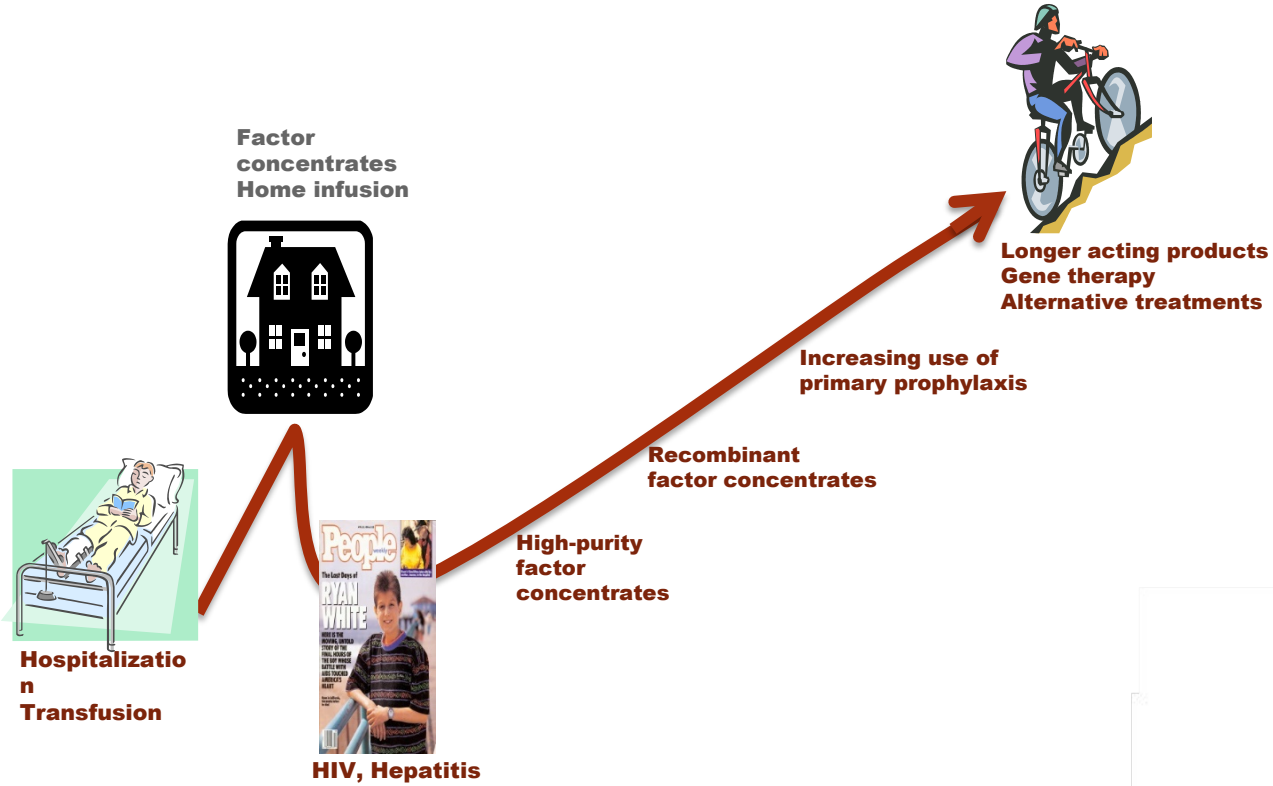
- Common
  - Mucous membrane
  - Soft tissue
  - Muscle
  - Joints (hemarthroses)



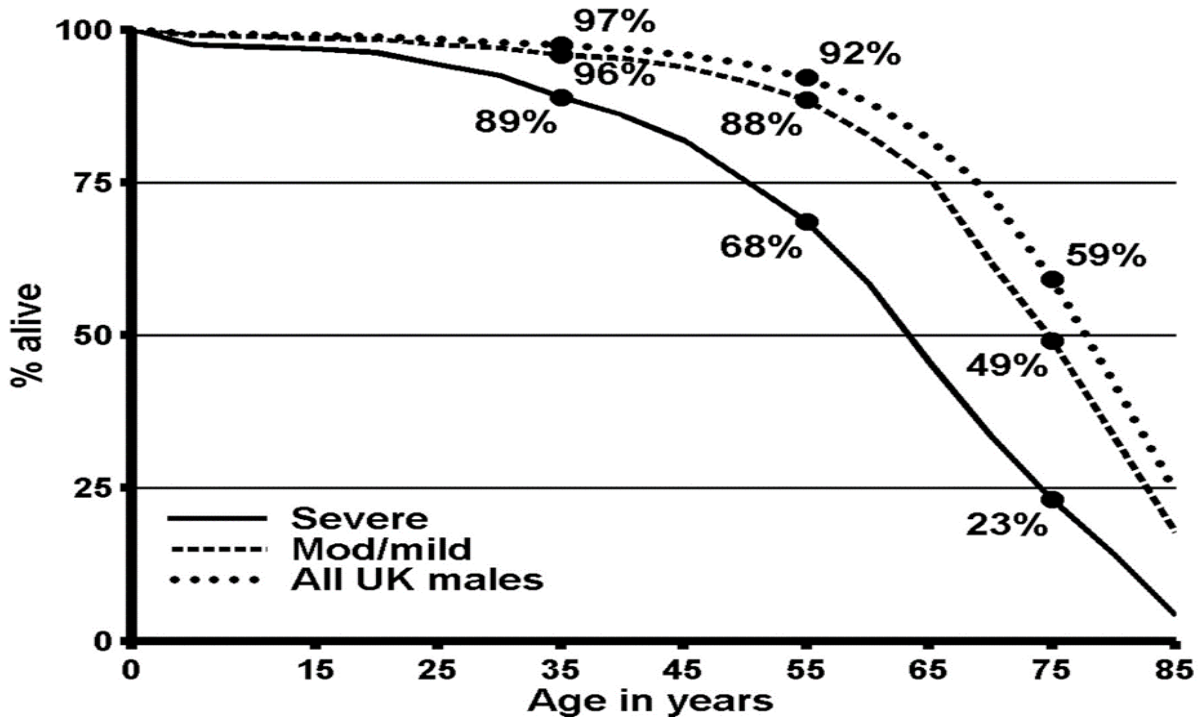
- Life-threatening
  - Central nervous system
  - Head
  - Neck and throat
  - Gastrointestinal
  - Retroperitoneal



Advances in Hemophilia Care: The Past Six Decades



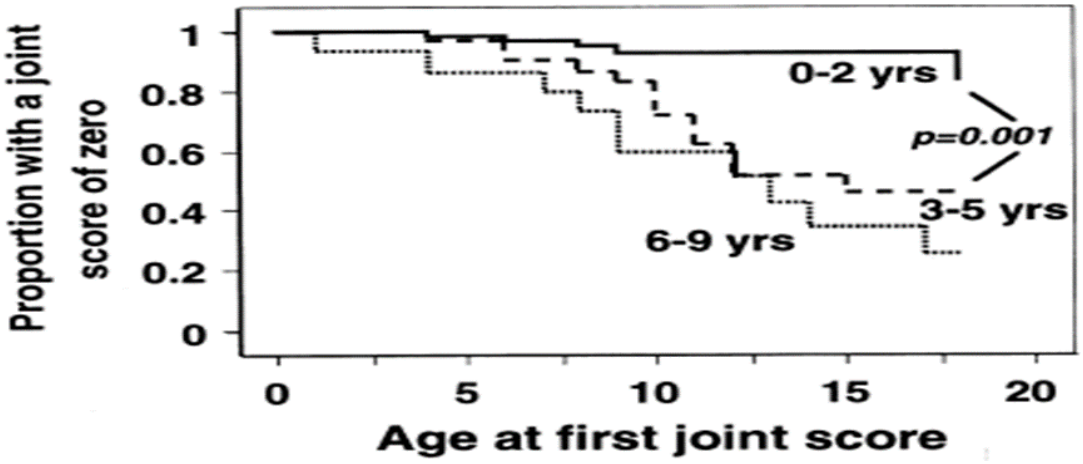
Effective therapy normalizes life expectancy



Darby et al, 2007

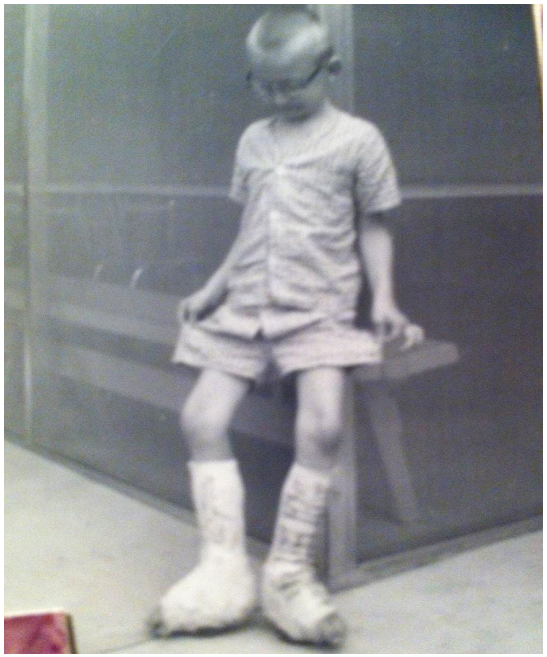
Joint Disease: Prevent by Primary Prophylaxis

- Prevents recurrent bleeding and chronic arthropathy
- Starting at an earlier age improves long-term outcomes
- Secondary prophy slows, but may not prevent, ongoing joint damage
- Low-dose primary prophylaxis can provide joint protection



Astermark J et al. *Br J Haematol.* 1999;105:1109-1113; Van den Berg HM et al. *Haemophilia.* 2006;12(suppl 3):159-168; Manco-Johnson MJ et al. *N Engl J Med*. 2007;357:535-544; Eshghi P et al. Clin Appl Thromb Hemost. 2018;24:513.; Wu RH, et al. Expert Rev Hematol. 2017;10:995.

Goal in Hemophilia Care



WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

WBDR
WFH World Bleeding Disorders Registry

Why gene therapy for hemophilia ?

- Factor therapy is very labor intensive and expensive
  - Breakthrough bleeding still occurs
- ~30% of patients with severe hemophilia A develop neutralizing antibodies (inhibitors) to treatment
- To date, alternative therapies do not normalize hemostasis
- Concern about treatment availability
- Patient desire to be cured of disease
- Most of the world without treatment

For prophylaxis with FVIII: Infusions every other day to twice weekly

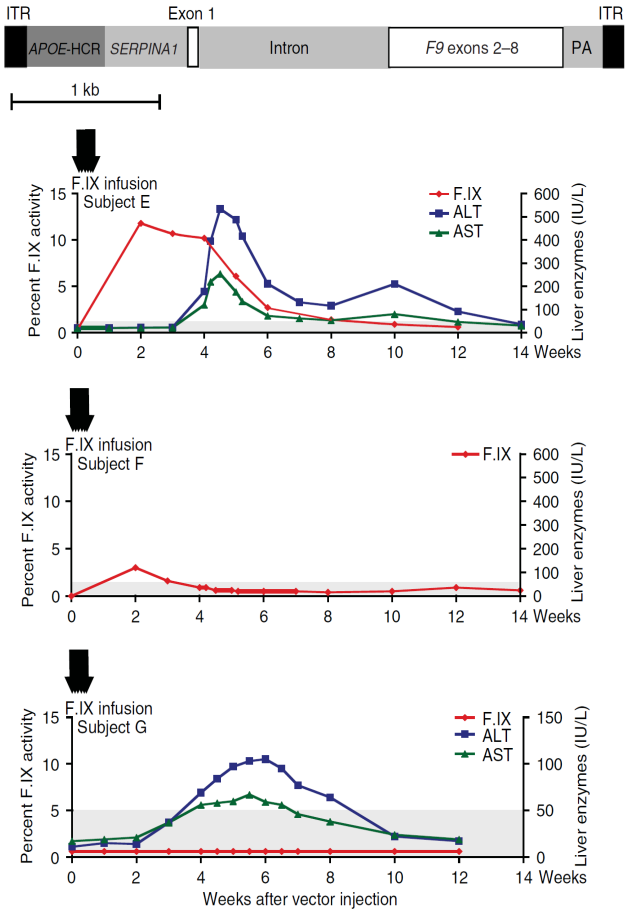
Gene Therapy Approaches in Hemophilia

Approach	Comments
Ex vivo F8 transfected fibroblast	• Implanted 100–400 million cells in peritoneal cavity • Small, transient increase in FVIII in 4/6 subjects
MoMLV-BDD-F8 IV	• Some evidence of vector in PBMCs • At most, small transient increases in FVIII
Adenovirus-F8	• Phase I trial stopped for inflammatory response in subject
Lentivirus	• In preclinical studies • Integrating vector, but risk of insertional mutagenesis decreased with improved vector design • Potential for use in liver-directed therapy in children • Ex vivo and in vivo HSC transduction to result in FVIII expression in megakaryocytes and platelets
AAV	• Vector used in current human trials • Wild-type virus is non-pathogenic • Predominantly non-integrating • Loss in dividing cells • Used for targeted integration into albumin locus

AAV: Adeno-associated virus; BDD: B-domain deleted; HSC: Hematopoietic stem cell; IV: Intravenous; MoMLV: Moloney murine leukemia virus; PBMC: Peripheral blood mononuclear cell.
Roth DA, et al. *N Engl J Med* 2001;344:1735. Powell JS, et al. *Blood* 2003;102:2038. Kelley et al. *Haemophilia* 2002;8:261-267. Evens H, et al. *Haemophilia* 2018;24(Suppl 6):50. Shi Q. *Molec Ther Methods Clin Dev* 2018;9:100. George L. *Blood Adv* 2017;1:2591.

AAV-Mediated Therapy in Hemophilia

- 1st in human
  - Intramuscular injection of *F9* construct into muscle[1]
    - Very low systemic expression with multiple muscles injected
      - Persistent expression in muscle[2]
- 1st liver infusion (AAV2-*F9*; CHOP/Stanford)[3]
  - Expression in high dose (2×10^{12}) subject
    - But unexpected hepatic inflammation and loss of transgene
      - Viral capsid T-cell immune response
  - Subject at same dose with anti-AAV2 antibodies
    - Limited expression
    - Study not continued

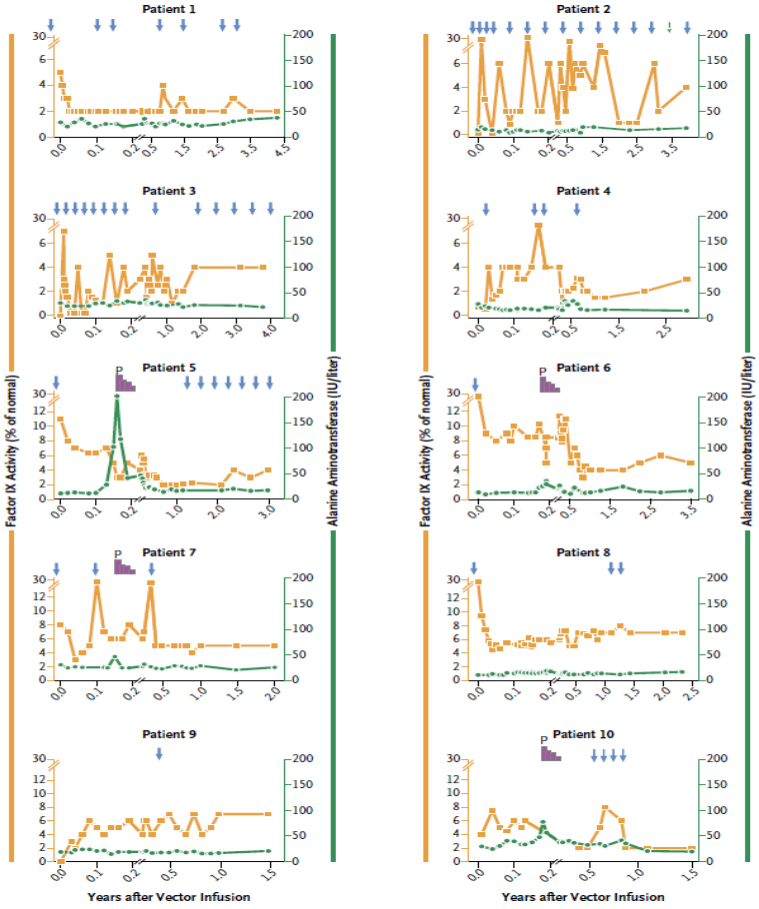


This slide contains information about a product that has not been approved by the Therapeutic Goods Administration.
Image from Manno *et al*.[3]
AAV: Adeno-associated virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.
1. Kay MA, et al. *Nat Genet* 2000;24:257. 2. Buchlis G, et al. *Blood* 2012;119:3038.3. Manno CS, et al. *Nat Med* 2006;12:342.

First study with long-term expression

Subsequent haemophilia B trial (St. Jude/UCL)

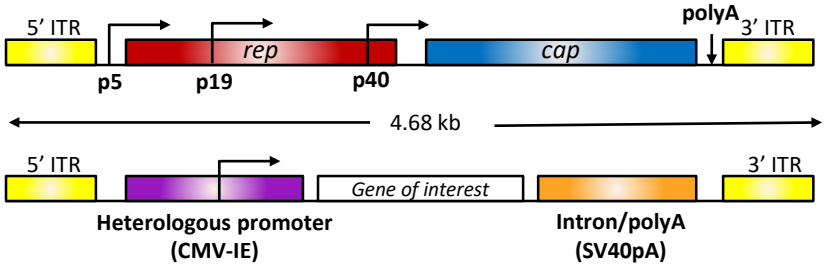
- Persistent FIX activity reported to date
  - Marked decrease in factor consumption
- Loss of transgene associated with transaminitis responsive to steroid therapy
- Study in long-term follow up



This slide contains information about a product that has not been approved by the Therapeutic Goods Administration.
Image from Nathwani *et al*.[2]

1. Nathwani AC, et al. *N Engl J Med* 2014;371:21. 2. Nathwani AC, et al. *Hematol Oncol Clin N Am* 2017;31:853.

Optimizing AAV Vectors



- Decrease in empty capsids
- Use of different AAV serotypes
- Optimization of liver-specific promoter/regulatory regions
- Codon optimization of *F8* and *F9* expression cassettes
- Use of optimized B-domain deleted *F8*
  - Size to allow optimal use of AAV
- Increase specific activity of *F9* insert through use of Padua variant (R338L)

Mingozzi F, High KA. *Nat Rev Genet* 2011;12:341. Evens H, et al. *Haemophilia* 2018;24(Suppl 6):50. George L. *Blood Adv* 2017; 1:2591. Pierce GF, Iorio A. *Haemophilia* 2018;24(Suppl.6):60. Colella P, et al. *Mol Ther Methods Clin Dev* 2018;8:87.

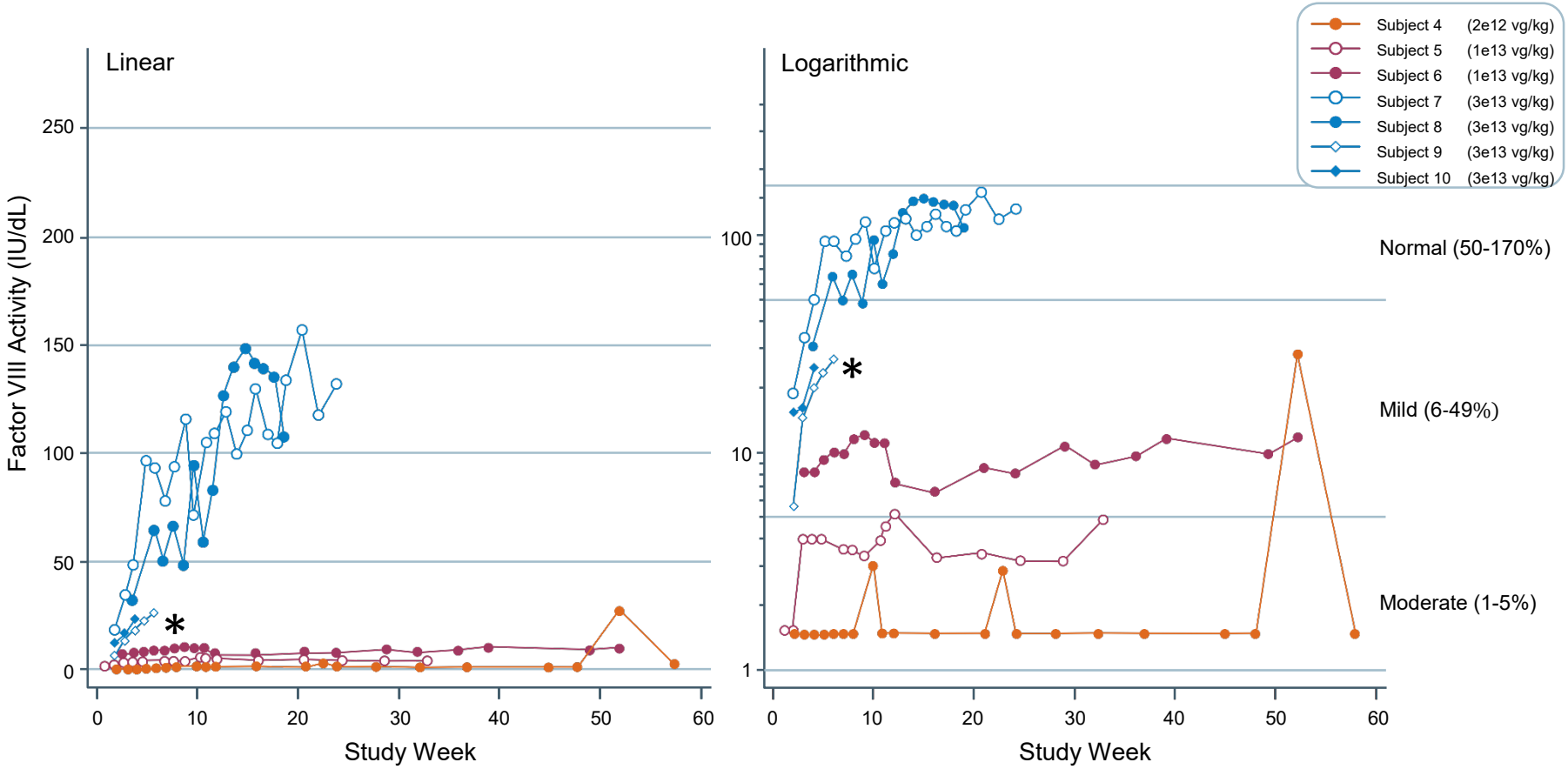
Successes in Haemophilia Gene Therapy

- Haemophilia B gene therapy may provide stable FIX levels for >8 years
- Now, both for haemophilia A and haemophilia B initial responses are being achieved to within or near normal factor levels
- Minimal short-term toxicity to date
- Patients with marked decrease in bleeding and use of factor replacement therapy
- Patients report feeling normal

This slide contains information about a product that has not been approved by the Therapeutic Goods Administration.

Nathwani AC, et al. *N Engl J Med*. 2014;371:21. https://hemophilianewstoday.com/2019/04/03/sb-525-shows-promise-hemophilia-a-phase-1-2-trial (Accessed June 2019)

Sangamo Phase I/II Trial: Factor VIII activity



* Subsequent to the data cut used for the ISTH presentation, Subject 9 attained normal levels at week 7

Questions in Haemophilia Gene Therapy

- Why is there such variability in expression between subjects?
  - Role of vector capsid, vector production, host immune repertoire, transgene construct, etc?
- Which factor assay methodology is relevant to bleeding risk?
  - One stage versus chromogenic
- Will factor activity levels be sustained?
  - Will that be different for haemophilia A and B?
  - Does site of vector transfection make a difference?

- If not sustained, will re-dosing be feasible?
- Can manufacturing be scaled up for commercialization?
- When will approaches allow gene therapy in young children and other populations, not included today?
- Can we modulate known and unknown risks of therapy?
- What will it cost and how will it be paid for?

Risks with AAV Gene Therapy

Some knowns

- Short-term liver toxicity
- Development of anti-AAV antibodies
- Wide inter-individual expression
  - Partially explained by anti-capsid T-cell immune response

Some unknowns

- Long-term liver toxicity
  - Impact of prior HCV infection unknown
- Risk of insertional mutagenesis
  - AAV integration estimated at 0.1–1%
    - Becomes real risk with current number of viral genomes infused
- Germline transfer
  - Animal models do not demonstrate AAV-infection of germ cells
  - In human studies vector has cleared from semen

AAV: Adeno-associated vrisu; HCV: Hepatitis C virus.

Pierce GF, Iorio A. *Haemophilia* 2018;24(Suppl.6):60. Nathwani AC, et al. *Hematol Oncol Clin N Am* 2017;31:853. Colella P, et al. *Mol Ther Methods Clin Devel* 2018;8:87. Perrin GQ, et al. *Blood* 2019;133:407.

Looking to the Future: My View

- Gene therapy will successfully decrease bleeding and factor consumption
- Some patients may not need factor infusion post-gene therapy
- Sustainability may depend on vector, achieved level and site expressed
- There will be gradual uptake in the community
- New approaches, including new vectors, will allow treatment and re-treatment of children and other patient groups
- An option for low-resource countries

Speaker's personal opinion.

That being said….we proceed with caution

- Ethical Issues
  - Consent for potential long-term unknown risks
  - Many patients excited about possibility of cure
    - How to be sure patient understands risks
    - Consent is a process
      - Current trials with initial observation period before vector infusion
  - What risks are acceptable when standard of care is very good?
  - In current trials with AAV
    - No or loss of response prevents re-dosing
      - In hemophilia can revert to prior therapy
  - How will price influence access?

Introduction to Clinical Research Boot Camp 2019

Faculty Track -Tuesday, July 30

UW Husky Union Building

Room 250

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Physician vs. The Physician-Investigator

Presented by Paul Martin, MD

9:30am-10:30am

UW Husky Union Building

Physician vs. the Physician Investigator:

Is There A Difference?

Paul Martin, MD
Member, Fred Hutch

FRED HUTCH
UNIVERSITY OF WASHINGTON
CANCER CONSORTIUM

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ACCELERATING RESEARCH. IMPROVING HEALTH.

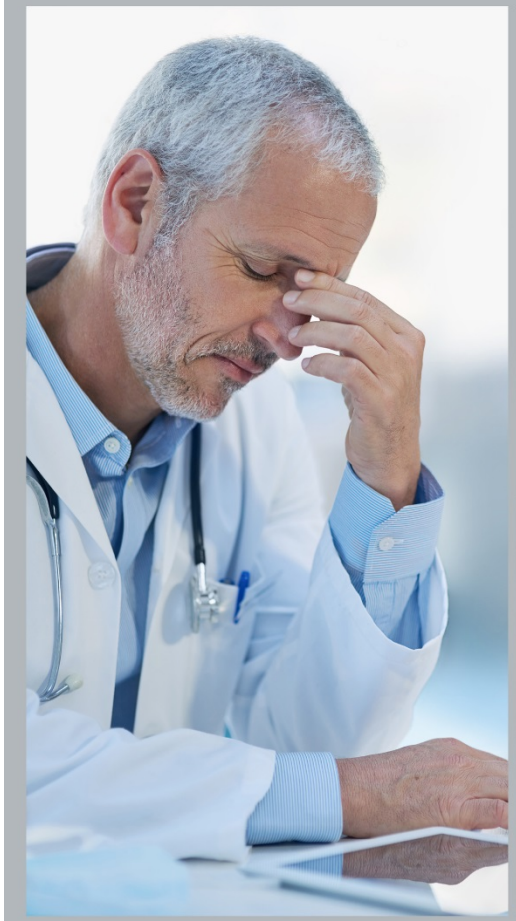
Learning Objectives

By the end of the session, you will be able to:

- Describe how participation as an investigator in a clinical trial differs from usual clinical care
- Assess whether your temperament is well suited for a career with a major focus on clinical trial research

EXPERIMENT

FAIL



LEARN

REPEAT

Dimension	Physician	Physician-Investigator
Patient care decisions		
Interventions, procedures		
Accountability		
Documentation		
Team		
Management		

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	

Dimension	Physician	Physician-Investigator
Patient care decisions	**Clinical practice guidelines, experience, scientific literature, patient beliefs/values**	

re·search

ˈrēˌsərCH,rəˈsərCH/

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	

re·search

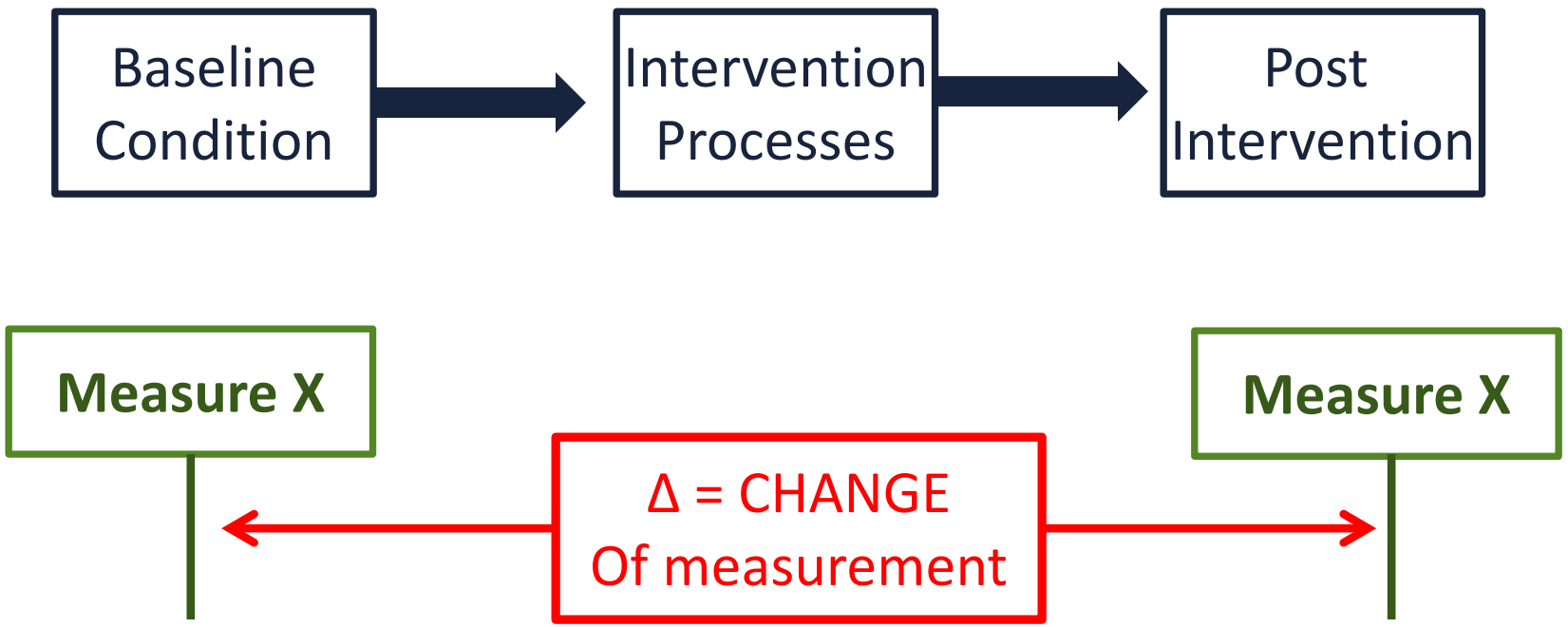
ˈrēˌsərCH,rəˈsərCH/

Noun

1. **<u>Diligent</u> and <u>systematic</u> inquiry or investigation into a subject in order to discover or revise facts, theories, applications, etc.**

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	**Care necessary for quality study data as dictated by study protocol**, patient safety

Clinical Research – basic plan



Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	**Care necessary for quality study data as dictated by study protocol**, patient safety

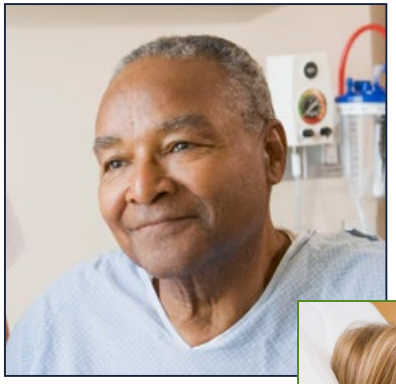
- Study protocol
  - Objectives
  - Eligibility criteria
  - Required procedures and assessments
  - Contraindicated medications
  - AE review reporting requirements
  - Stopping rules
  - Outcome criteria

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	**Care necessary for quality study data as dictated by study protocol**, patient safety

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	Care necessary for quality study data as dictated by study protocol, **patient safety**

Human volunteers

- Protect rights, safety and welfare



Dimension	Physician	Physician-Investigator
Interventions, tests, procedures	Standard of care	

Dimension	Physician	Physician-Investigator
Interventions, tests, procedures	Standard of care	Additional interventions and/or testing at specific time points

Example Time and Events Schedule

	Screen Day –28 to –1	CRU Admission (Baseline)	Day 1			Day X to X	Prior to Discharge (Day X)	Follow-up ≥3 days and ≤5 days after Discharge
			Pre-dose	Dosing	Post-dose	Post-dose		
Informed Consent Form Signed	X							
Eligibility Review and Confirmation	X	X	X					
Medical History	X							
Physical Examination	X	X					X	X
Height Assessment	X							
Weight Assessment	X	X	X				X	
Urine Drug Test	X	X						
HIV & Viral Hepatitis Screen	X							
Vital Signs	X	X	X		X	X	X	X
12-lead ECG	X	X	X		X	X	X	
Clinical Laboratory (Blood) and Urinalysis	X	X	X		X	X	X	
Prior Medication Assessment	X	X	X					
Serum Pregnancy Test	X							X
Urine Pregnancy Test		X						
CRU Admission		X						
Randomization			X					
Administer Study Drug				X				
Pharmacokinetic Sampling (Blood)			X		X	X	X	
Pharmacokinetic Sampling (Urine)			X		X	X	X	
Treatment-Emergent Adverse Events				X	X	X	X	X
Concomitant Medication Assessment				X	X	X	X	X
CRU Discharge							X	X

Dimension	Physician	Physician-Investigator
Accountability	Patient and family, Institutional policies, state laws and licensing board, Medicare guidelines	

Dimension	Physician	Physician-Investigator
Accountability	**Institutional policies, state laws and licensing board, Medicare guidelines**	**Cancer Consortium entities, Study Sponsor, IRB, ICH GCP, state and federal regulations (FDA, HHS, etc.)**

- Rules and Standards Governing Clinical Research
  - Study Protocol
  - Cancer Consortium/Institutional policies
  - IRB requirements
  - ICH Guidelines for Good Clinical Practice (GCP)
  - FDA – Title 21 CFR Parts 11, 50, 54, 56, 312, 314, and 812
  - HHS – Title 45 CFR Part 46

Dimension	Physician	Physician-Investigator
Accountability	Institutional policies, state laws and licensing board, Medicare guidelines	Cancer Consortium entities, Study Sponsor, IRB, ICH GCP, state and federal regulations (FDA, HHS, etc.)

Text from an actual FDA Warning Letter:

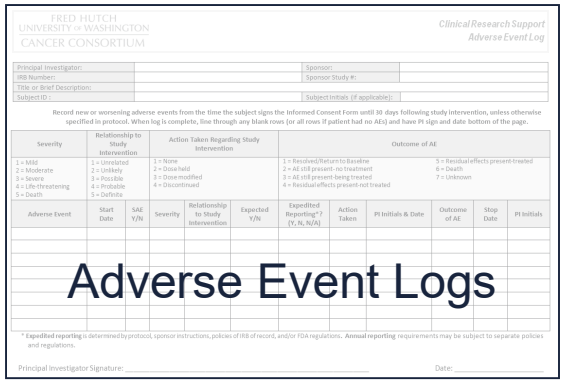
3. Failure to ensure that the investigation was conducted according to the signed agreement, investigational plan, and applicable FDA regulations…

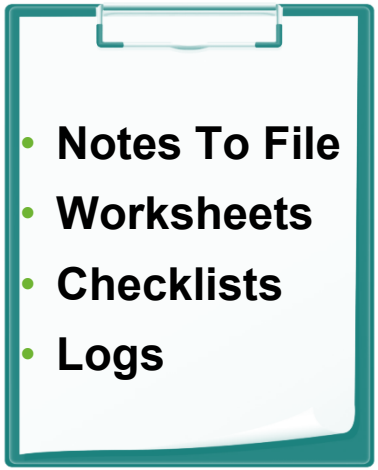
As a clinical investigator, you are responsible for ensuring that an investigation is conducted in accordance with the investigational plan, the signed agreement, and applicable FDA regulations…

You failed to follow the Clinical Investigation Plan, Protocol RAL 1. In addition, the study changes were not reported to the IRB, nor was prior approval obtained from the IRB. Examples of your failure include, but are not limited to, the following:

Dimension	Physician	Physician-Investigator
Documentation	EMR / patient charting, consents for care	

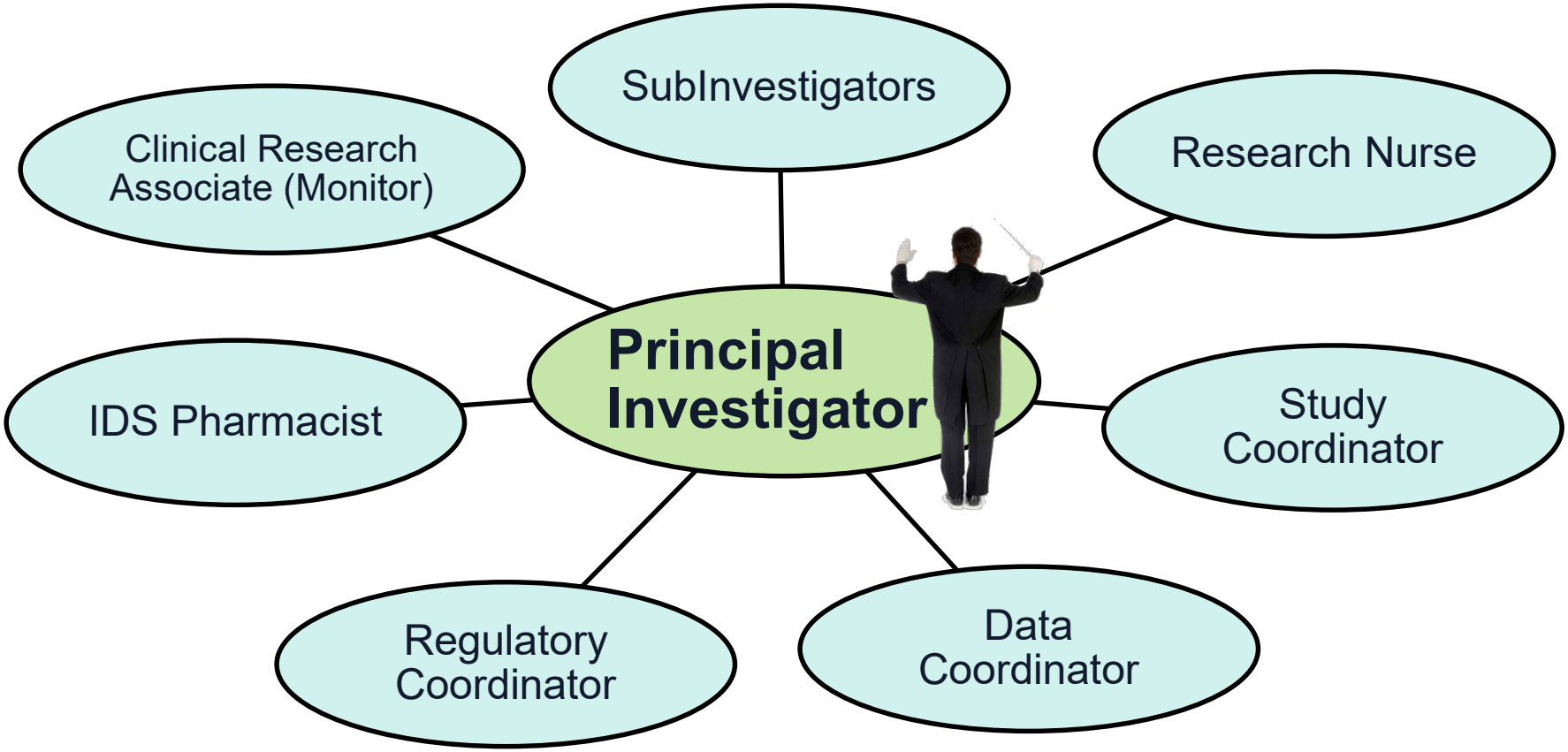
Dimension	Physician	Physician-Investigator
Documentation	EMR / patient charting, consents for care	Research chart, informed consent documents, CRFs/database, tracking tools, other reg docs





Dimension	Physician	Physician-Investigator
Team	PAs, ARNPs, RNs, MAs, ancillary services	

Dimension	Physician	Physician-Investigator
Team	PAs, ARNPs, RNs, MAs, Dental, ancillary services	Clinical Research Team



Dimension	Physician	Physician-Investigator
Management	Orders, patient visits, chart and lab review, medical rounds, continuing education	

Dimension	Physician	Physician-Investigator
Management	Orders, patient visits, chart and lab review, medical rounds, continuing education	Study operations, compliance, recruitment, budget and contracts, patient billing, personnel training

- Organized
- Detail-oriented
- Flexible
- Collaborative
- Manage time wisely
- Passionate
- DRIVE in continuing research education

Knowledge Base

Clinical Research Regulations

Human Subjects Protection

Protocol Design & Development

Protocol Review & Approval Process

Informed Consent Elements / Process

Clinical Research Documentation

Budget Development

Patient Billing Procedures

Medical Background

Trial Monitoring & Auditing Procedures

Learning Objectives

- Describe how participation as an investigator in a clinical trial differs from usual clinical care
- Assess whether your temperament is well suited for a career with a major focus on clinical trial research

Credits

Kersten Brinkworth
Stacey Long Genovese

“What is the Difference between 14 Days and 15 Days?”

Case No. 1: Carl Steubing

- 1985—diagnosed with colon cancer, successfully treated
- Jan 2001—diagnosed with stomach cancer
- Feb 2001—offered participation in clinical trial

Study Design

- Randomized prospective trial
- Experimental arm: Docetaxel plus Cis-platinum or Docetaxel plus 5-fluorouracil
- Standard treatment: Cis-platinum plus 5-fluorouracil

Steubing Evaluation

- Feb 13—lab tests done
- Feb 15—date of lab tests in CRF
- Feb 22—started study treatment
- Protocol requirement $\leq$ 8 days from lab test to start of treatment
- Exclusion criteria
  - Previous malignancy
  - Creatinine clearance < 60 mL/min
- Steubing creatinine clearance 49.5 mL/min

Steubing Outcome

- July, 2001—completed 6 cycles of treatment per protocol
- March, 2002—died after further treatment with Docetaxal and Xeloda

Medical Considerations

- All three agents approved by FDA
- 5-FU—not given if WBC is low or if bilirubin > 5.0
- Cis-platinum—dose reduced by 50% if creatinine clearance is 30 – 60 mL/min
- Docetaxel—not given if bilirubin is $\geq$ 1.5

Medical Assessment

- Any of the agents could have been used “off study”
- Possible harm if cis-platinum was given at 100% dose with creatinine clearance < 60 mL/min
- Protocol treatment did not cure the cancer

Regulatory Assessment

- Patient not eligible for at least two reasons
  - Prior cancer
  - Renal impairment
- Patient not eligible because lab tests not done within required time-frame
- Intentional misrepresentation of test dates in CRF

Case No. 2: James DiGeorgio

- Gastric cancer
- Phase II study of
  - α-difluoromethylornithine (DFMO) plus
  - Cis-platinum and
  - 5-fluorouracil
- DFMO is an investigational irreversible inhibitor of ornithine decarboxylase, which is needed for synthesis of polyamines

Eligibility Assessment

Test	Protocol Exclusion	5/25/01 Results	CRF
Creatinine	> 1.75	1.9	1.3
Cr Clearance	< 60	41	60.3
AST	> 85	99	39
Bilirubin	> 1.0	1.9	0.9
Alk. Phos.	> 340	378	208

DiGeorgio Outcome

- Completed treatment on June 6, 2001
- Died on June, 11, 2001
- Death reported to sponsor on June 14, 2001

Medical Assessment

- Nephrotoxic study drug likely contributed to death
- Neither DFMO or 5-FU is known to cause renal toxicity
- Death was most likely caused by administration of cis-platinum at an inappropriately high dose, relative to the baseline level of renal function

Regulatory Assessment

- Subject not eligible for at least 5 reasons
- Intentional misrepresentation of test results in CRF
- Delayed reporting of death

Albany Stratton VA Hospital

- 1993—complaints by hospital pharmacist and pharmacy manager
- Mid 90's—internal investigation, no significant changes implemented
- Dec, 2001—routine monitoring visit by drug company. Findings led to formal audit.
- 2002—Drug company audit led to notification of FDA about problems. FDA was aware of problems from a prior notification.

FDA Investigation and Consequences

- Nov, 2002 to Jan, 2003—51-day investigation by FDA
- Report of FDA Inspectional Observations
- Protocol investigator and research assistant dismissed
- Mrs. DiGeorgio filed $20 million law suit for wrongful death against US Department of Veterans Affairs
- Mrs. Steubing also sued Veterans Administration

Paul Kornak

- Attended medical school in Grenada
- 1990—New Jersey medical license application denied because of falsified documents
- 1991—Iowa medical license revoked because of false information on application
- 1993—convicted for mail fraud in Pennsylvania after falsifying information on an application for a medical license, resulting in 3 years of probation and $2500 fine

Career at Albany Stratton VA Hospital

- 1999—Hired as research assistant, later promoted to Chief Research Assistant
- VA business card identified as M.D.
- Passed exam covering informed consent and clinical fraud
- “Inherited” by Dr. James Holland, who was medical investigator for protocols and was later appointed Chief of Oncology
- Jan, 2001—fired by VA after FDA inspection

Legal Actions Against Kornak

- March, 2003—Mrs. Steubing filed class action law suit
- Oct, 2004—indicted on 48 felony counts, including fraud, manslaughter and criminally negligent homicide of James DiGeorgio
- Jan, 2005—pled guilty to 3 counts, including fraud, making false statements, and criminally negligent homicide
- May, 2005—will go to jail, possibly 4 to 20 years

Dr. Holland
Inspectional Observations by FDA

- Failed to personally conduct or supervise the clinical investigations
- Failed to protect the rights, safety and welfare of subjects
- Repeatedly or deliberately submitted false information to the sponsor
- Failed to conduct studies or ensure they were conducted according to the protocol
- Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual

False Information

- In most cases, misrepresentation was designed to make subjects eligible for studies
- One protocol required EKG within 14 days of enrollment
  - 3 subjects had EKG > 14 days before enrollment (dates falsified in CRF)
  - 4 subjects had no study-related EKG before enrollment (EKG after enrollment or long before enrollment with dates falsified in CRF; in one case, EKG was from a different subject)
  - 2 of the above subjects had EKG abnormalities deleted from the CRF

Dr. James Holland—Epilog

- Jan, 2003—fired by Albany Stratton VA after FDA inspection
- March, 2003—Mrs. Steubing filed class action law suit
- Hired by an oncology center in Georgia
- Investigation by Georgia Medical Board found no evidence of misconduct
- Sept, 2004—FDA issued NIDPOE
- Possibly facing federal criminal indictment

FDA Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

"FDA asserts that you have failed to protect the rights, safety and welfare of subjects under your care, repeatedly or deliberately submitted false information to the sponsor and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator in a written response or at an informal conference in my office."

“What is the Difference Between 14 Days and 15 Days?”

- Depends on the “hat” you’re wearing
- If a “medical” hat—no difference
- If an “investigator” hat—Protocol Violation

Research Budget Oversight

Presented by Nora Disis, MD & Lauren Corulli

10:40am-11:40am

UW Husky Union Building

Research Budget Oversight:

Tips for Responsible Financial Management

Nora Disis, MD
Lauren Corulli, MPM
UW Medicine Cancer Vaccine Institute

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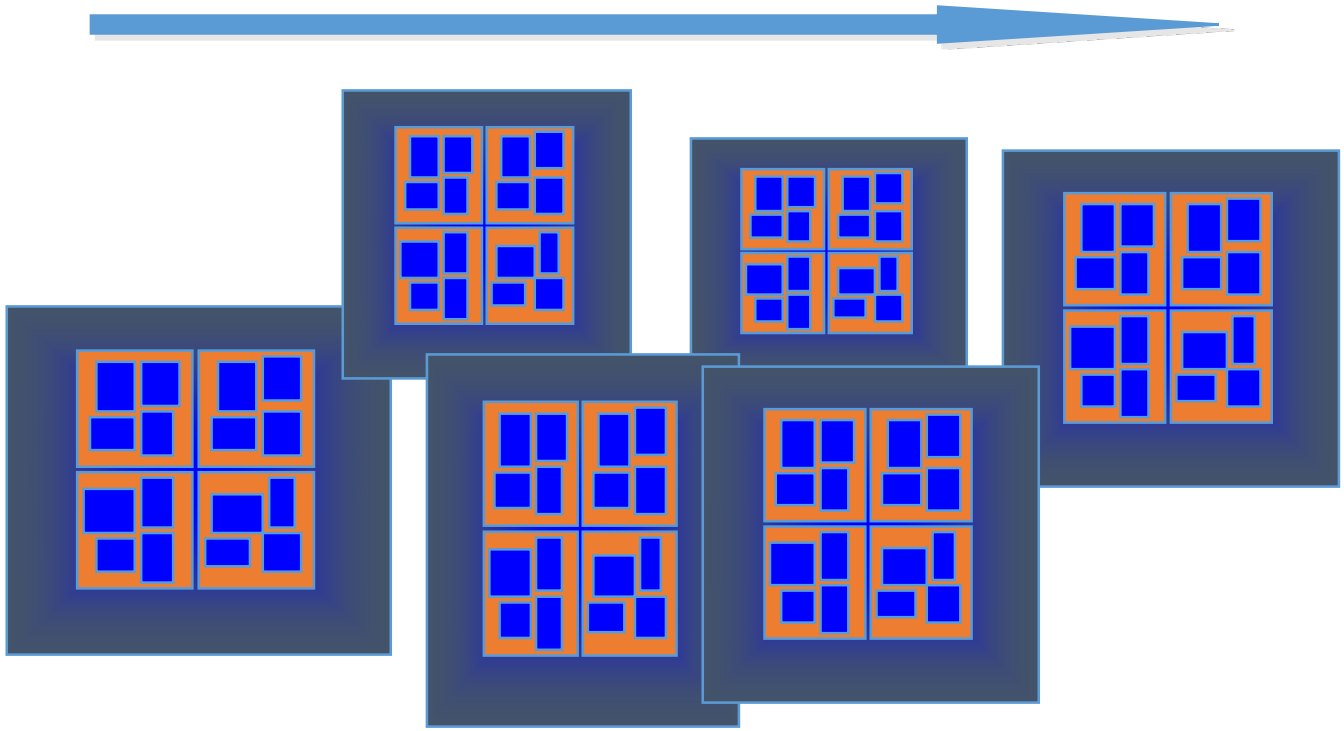
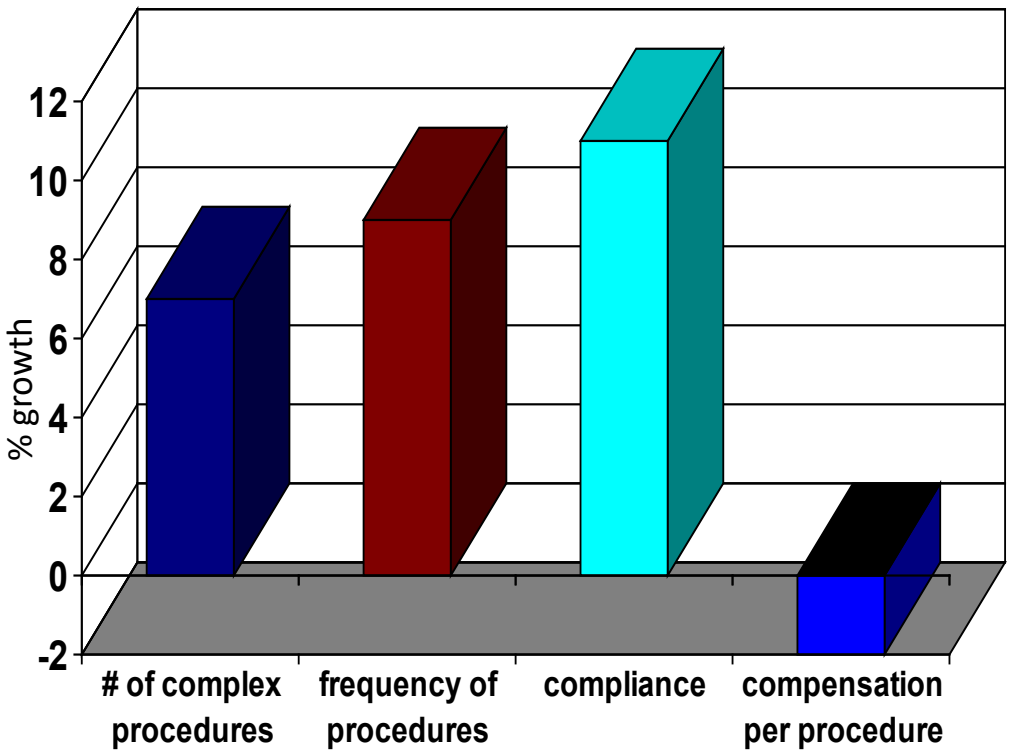
Your Career is a Series of Interrelated Projects



Success is many projects being conducted simultaneously- team development

The Reality for all Research, Including Clinical Research, is:

- Sites are required to perform at a higher level at lower cost differentials
- Functions required have become more complex; contract/budget negotiation, recruitment, logistics, and regulatory
- A JUGGLING ACT!



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Source: Tufts Center for the Study of Drug Development

Impossible Role of the Principle Investigator

- Clinician
- Researcher
- Fundraiser
- Recruiter
- Data analyst
- Creative genius
- HR manager
- Fiscal specialist
- Regulatory expert
- Significant other
- …Parent

At the End of the Day- YOU'RE the One Responsible

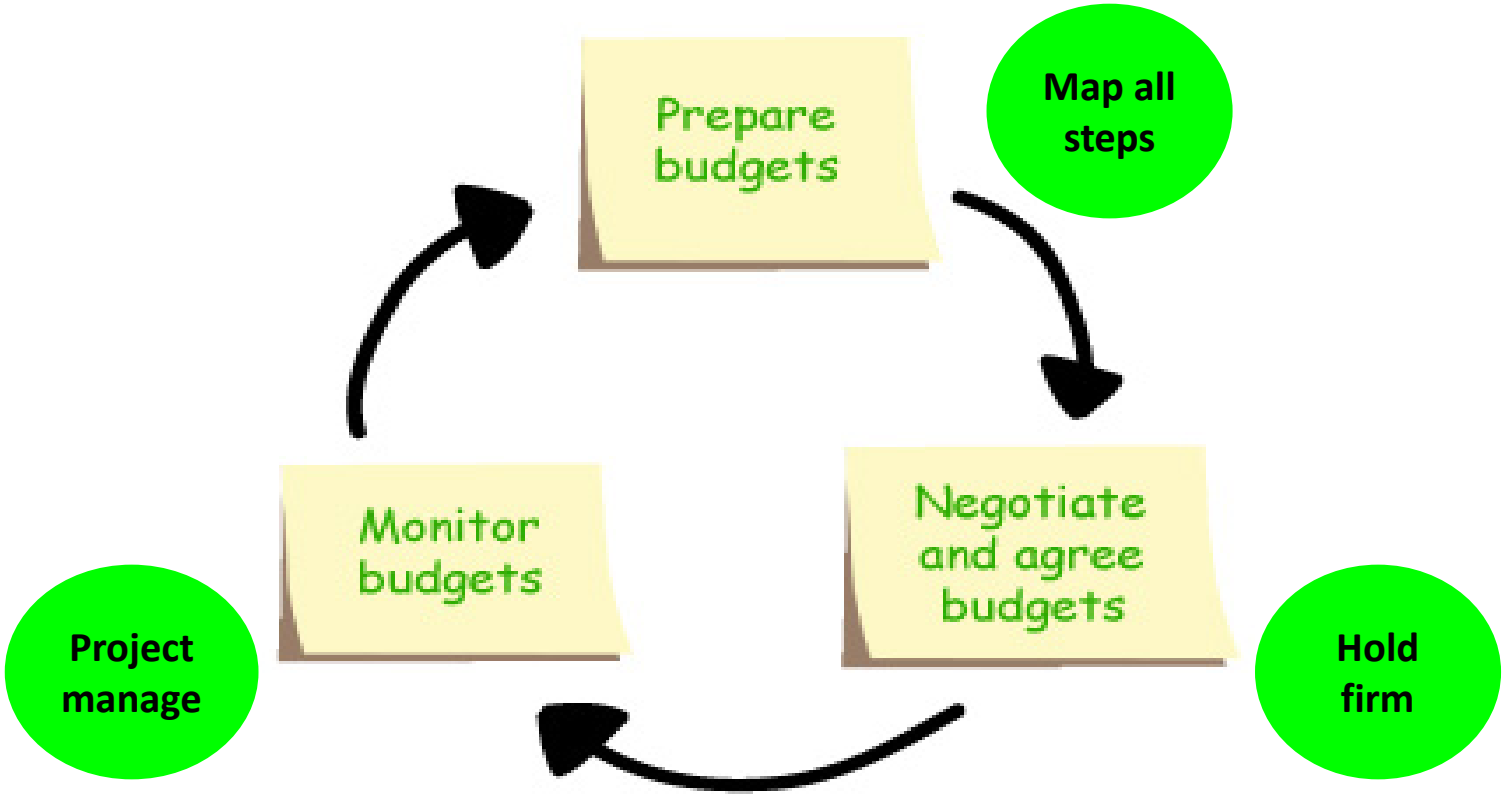
- To the FDA…
- To the IRB…
- To the NIH…
- To the trial sponsor
- To your department
- To OSP
- To your team members
- TO THE PATIENTS!

What happens when you go broke?

Budget Management IS Project Management

- A strong project management plan will keep you afloat fiscally
- Prevents or mitigates unanticipated problems

Your Budget Will Never Be Perfect- But You Can Perfectly Prepare for Shortfalls



Before You Start the Budget Planning for Your Trial Ask:

- Are the scientific value and ethical quality of the study acceptable?
- Would I enroll my mother in this study?
- Do I have an adequate pool of potential subjects?
- If from a company, does the proposed budget support the work described in the protocol?

- If the answer to any of these questions is no, <u>decline the trial</u>

Trial Costs

Study Period				Double-blind Treatment Period						
Visit		1	2	3	4	5	6	7	8	
PROCEDURES:	**Cost**	-21	-14	1	7	14	28	42	56	**Totals**
Informed Consent	**$75**	$75								$75
Inclusion/Exclusion Criteria	**$25**	$25	$25	$25						$75
Taper AntiHyp Meds	**$40**	$40								$40
Medical History	**$85**	$85								$85
Height/ Weight	**$15**			$15						15
Waist Circumference	**$15**			$15						$15
BP and Pulse	**$25**	$25	$25	$25	$25	$25	$25	$25	$25	$200
Screening PE	**$125**	$125								$125
Complete PE	**$175**			$175					$175	$350
EKG	**$63**	$63		$63					$63	$189
EKG Interpretation	**$37**	$37		$37					$37	$111
Collect Labs	**$25**	$25		$25			$25		$25	$100
Lab Interpretation	**$25**	$25		$25			$25		$25	$100
Pharmacogenetic Consent	**$25**			$25						$25
Adverse Events	**$20**		$20	$20	$20	$20	$20	$20	$20	$140
Concomitant Medications	**$15**	$15	$15	$15	$15	$15	$15	$15	$15	$120
Drug Accountability	**$25**			$25	$25	$25	$25	$25	$25	$150
IVRS	**$40**		$40	$40	$40				$40	$160
Screening Log	**$25**	$25								$25
Randomization	**$25**			$25						$25
Dispense Study Meds	**$20**		$20	$20	$20					$60
Echocardiagram	**$40**								$40	$40
Pt Reimbursement for Travel	**$25**	$25	$25	$25	$25	$25	$25	$25	$25	$200
Coordinator Fee:	**$60**	$60	$60	$60	$60	$60	$60	$60	$60	$480
Total per procedure		$650	$230	$660	$230	$170	$220	$170	$575	$2,905
Institutional overhead	26%	$169	$60	$172	$60	$44	$57	$44	$150	$755
Total w/ overhead		$819	$290	$832	$290	$214	$277	$214	$725	**$3,660**
								9	Patients:	**$32,942.70**

STUDY LEVEL COSTS:										
Screen Failures	Maximum of		**6**	Failures at		$1,108.80				$6,652.80
Electronic Data Capture Support	24	hours at		$40.00	per hour					$960.00
Advertising/Recruitment										$3,000.00
Study Initiation										$3,250.00
IRB Fee										$2,000.00
Unscheduled Visits	13	sits per patient, up to			9	patients at		$85.00	per visit	$9,945.00
Pharmacy Set Up Fee										$500.00
Storage Fee										$450.00
TOTAL INVOICED COSTS:										**$26,757.80**
								Total Requested		**$59,700.50**

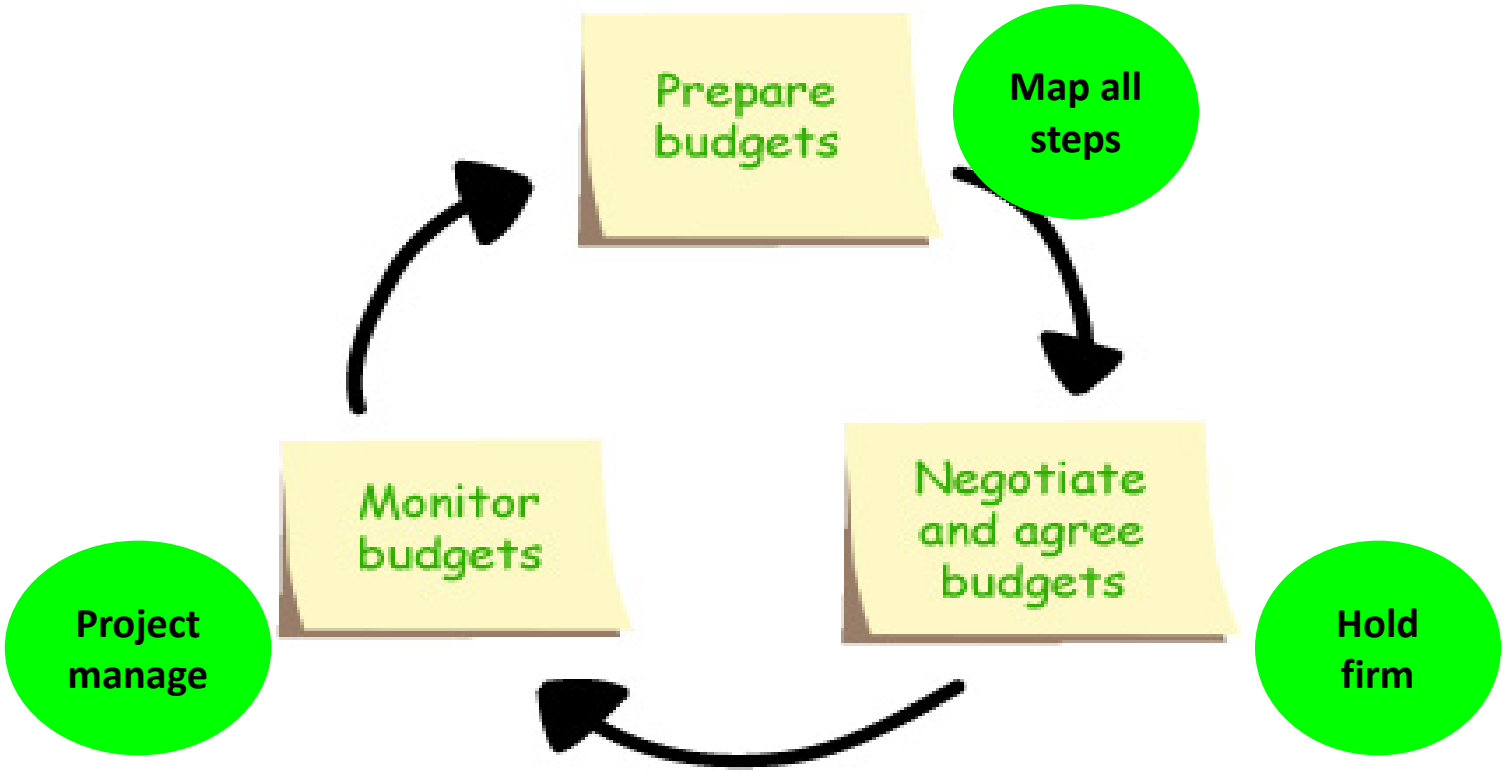
- Staff costs (estimated)
- Physician costs
- Clinical research unit
- Labs
- Imaging
- Drug delivery

X number of patient visits…

Are you Capturing Additional Costs?

- RC time for prep and attending sponsor monitoring visits (days)
- Time dealing with screen failures (4 or more screens for one patient)
- Start-up fees
- IRB/DSMB fees
- Electronic data capture (Redcap/CTMS)
- Investigational drug pharmacy, drug storage fees
- Time an administrator or the RC spends invoicing and billing
- Additional FTE: biostatistician, consultant
- Document translation fees
- Effort spent with PROTOCOL AMENDMENTS
- Anticipated trial enrollment delays

Your Budget Will Never Be Perfect - But You Can Perfectly Prepare for Shortfalls

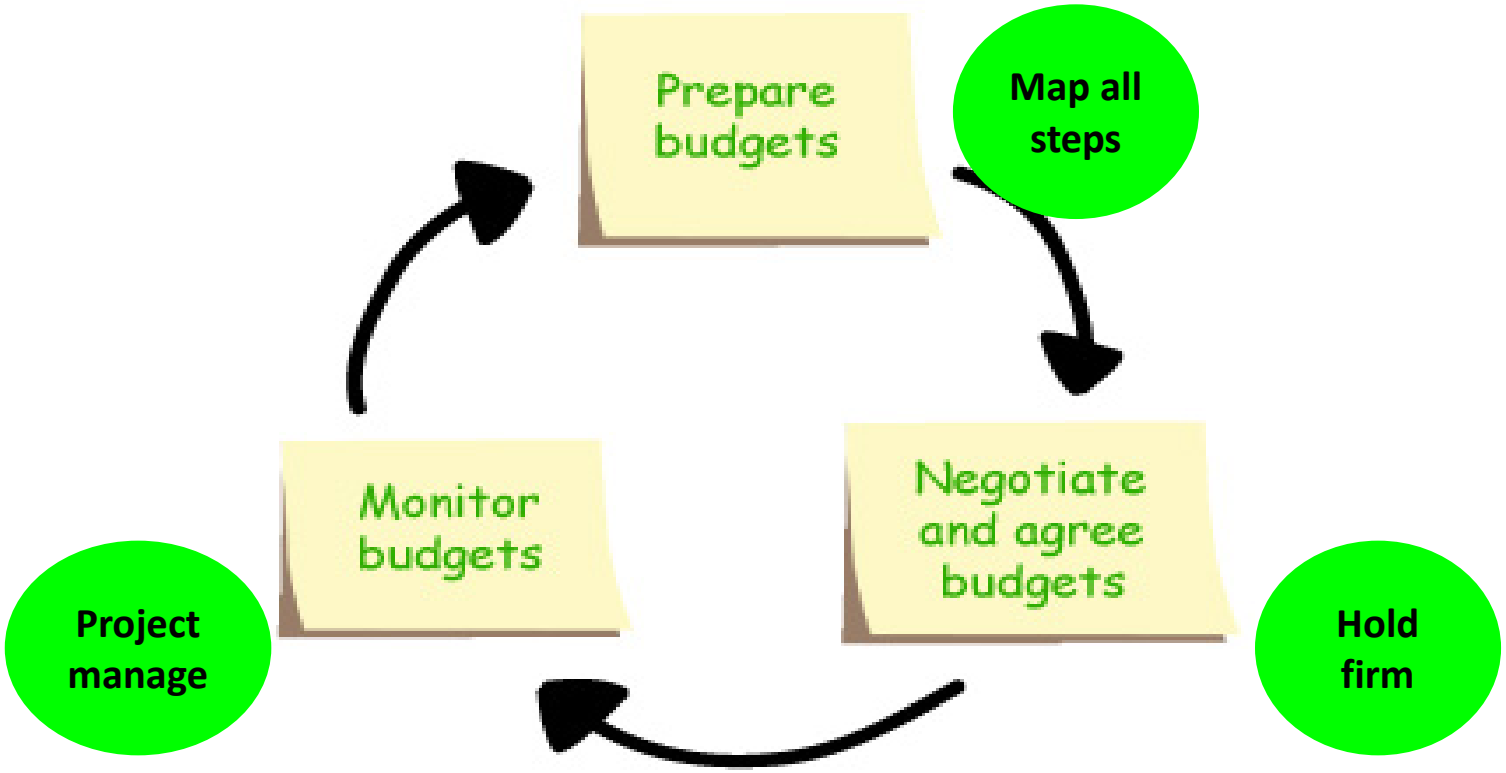


Sponsor's Budget

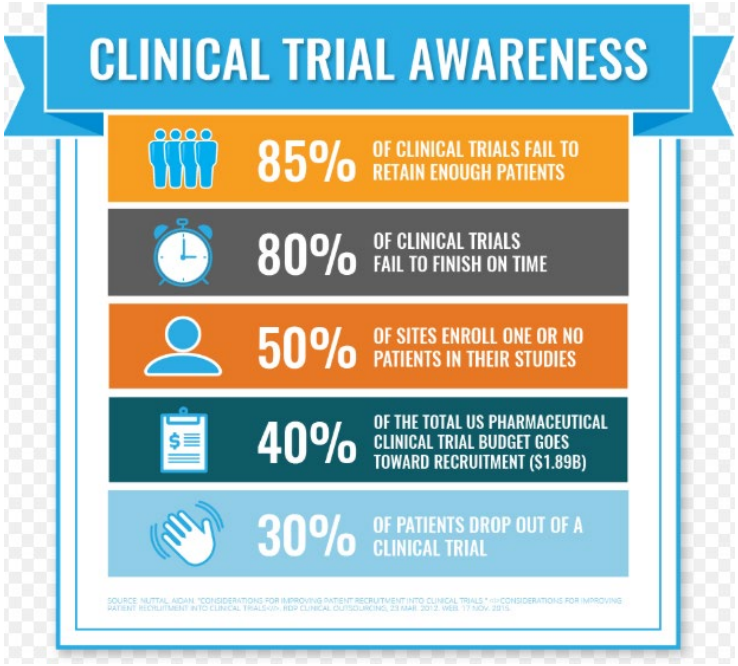
- Compare with your budget
- Is the per subject cost equivalent?
- Is overhead accurately represented?
- Any missing items?
- Are costs at the study level comparable?
- Review
- Negotiate-be sure to provide flexibility for re-negotiation

Don't back down!!!!!!

Your Budget Will Never Be Perfect - But You Can Perfectly Prepare for Shortfalls



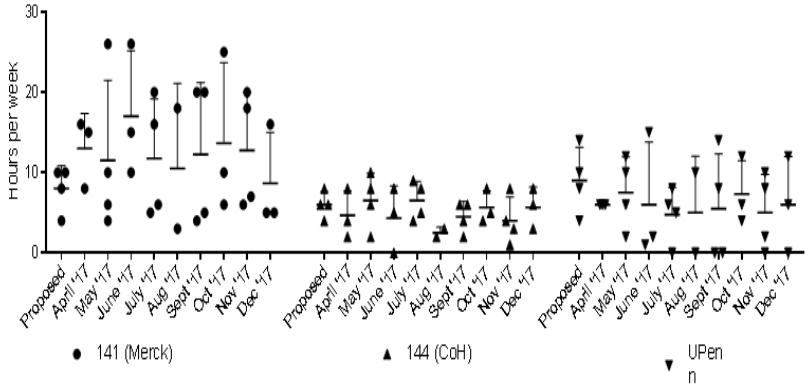
Your Budget Will NOT Be Accurate - But You Can Minimize Variance With Active Management

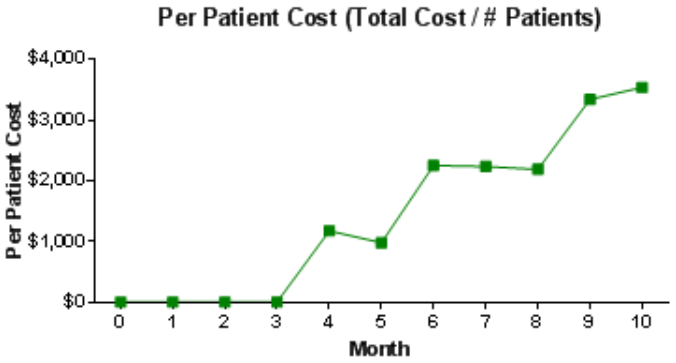


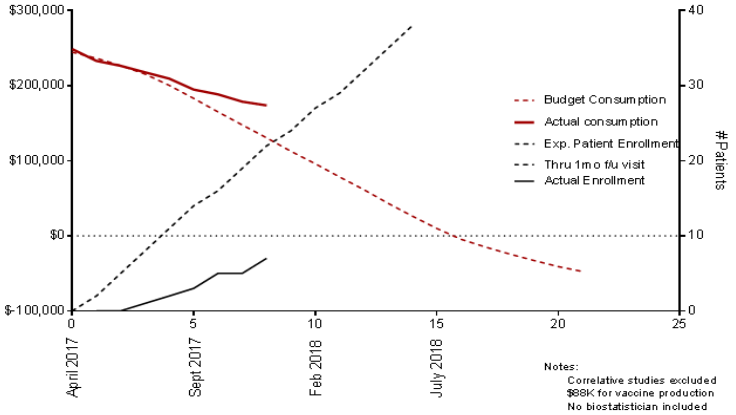
Make a Plan

- Use process mapping to make your budget
- Map budget to patient enrollment - better yet, use a budget tool!
- Remember- staff costs are the most often underestimated (keep track for a month)
- Outsource small projects or parts of projects - usually cheaper
- Decide what you can and cannot live with if you have to cut out parts of your protocol (never mess with the primary endpoint or number of patients enrolled)
- Negotiate with vendors
- Continuous monitoring and finding root cause of any variance

Lots of Different Ways to Manage Projects, Find What Works For You!

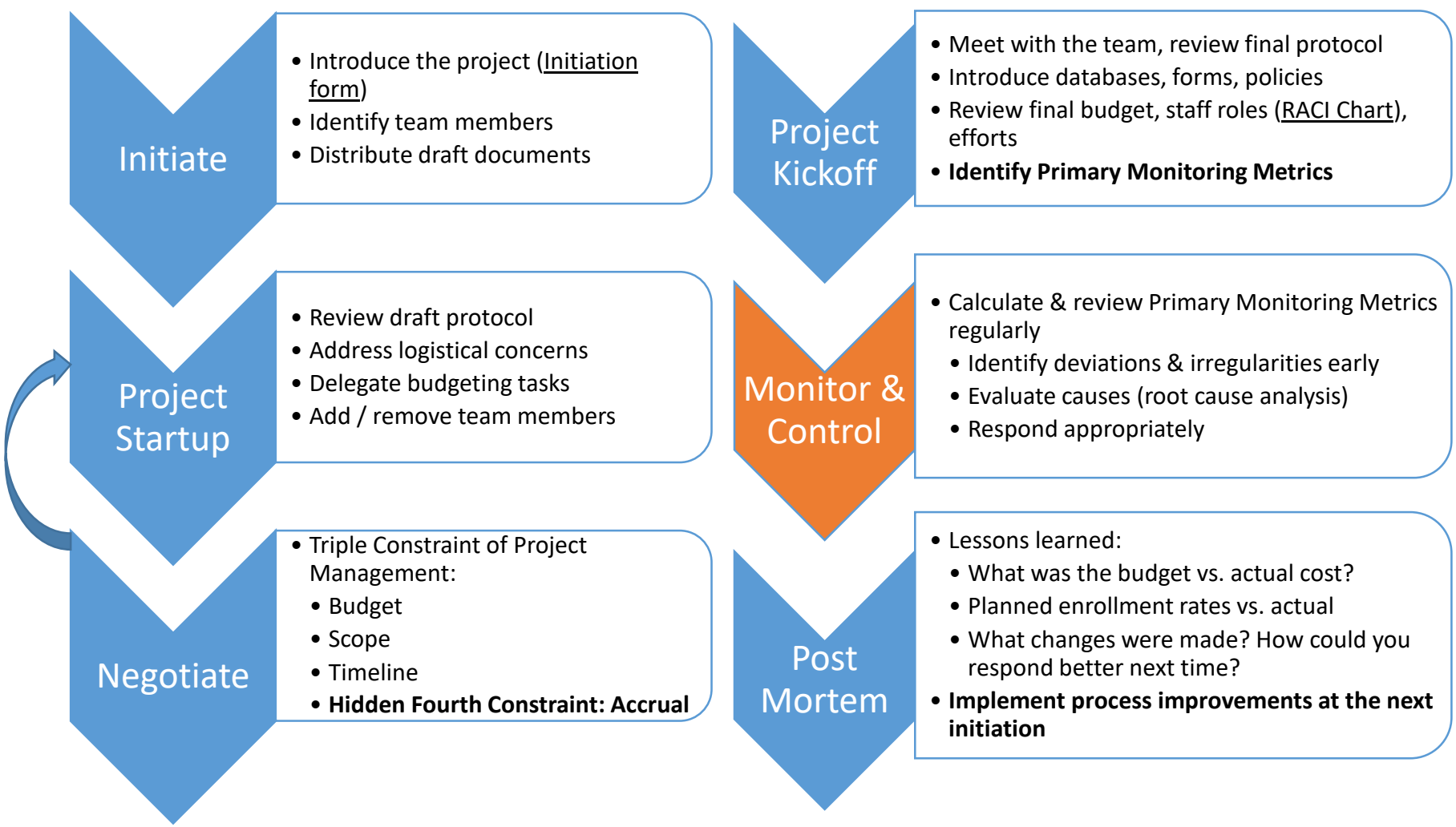






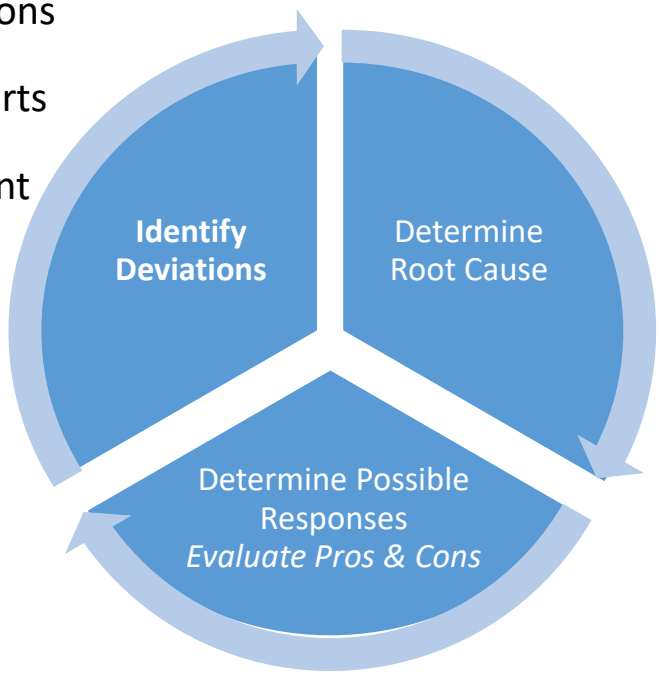
ACTIVITY

CVI Clinical Project Lifecycle



Clinical Budget Monitoring & Controlling

- Per Patient Cost Calculations
- Budget Consumption Charts
- Earned Value Management



Per Patient Cost Calculations: Example

- Phase I/II Trial of immune therapy drug X
- Patients with triple negative breast cancer
- Statistical Design: 25 patients
- Primary Objective Measures:
  - Progression free survival (PFS) as determined by CT scan every other visit
- Secondary Objective Measures:
  - PD-L1 expression of primary tumor by IHC
  - Serum expression of various markers
- 2.5 year (30mo) project with expected enrollment rate of 1 patient per month
- Historically, the CT scans & major patient costs hit the budget about 2 months after-the-fact

Per Patient Cost Calculations: Example

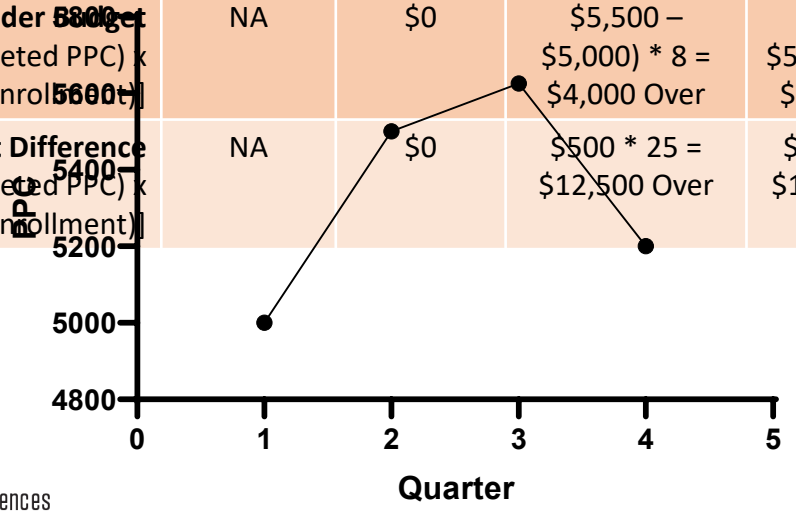
Cost Calculations	Month 2	Month 4	Month 6	Month 8	Month 10	Avg
Staffing Costs	**$20,000**	**$40,000**				
Total Patient Care Costs	**$0**	**$10,000**	**TBD**			
Actual Enrollment (of 25)	**2**	**5**				**1.25/mo**
Budgeted PPC			$5,000 per patient			
Planned Enrollment	2	4	6	8	10	1/mo
Actual PPC [Total Care Costs / Actual Enrollment]	NA	$5,000	TBD	TBD	TBD	--
Amount Over/Under Budget [(Actual PPC – Budgeted PPC) x Actual Enrollment)]	NA	$0	TBD	TBD	TBD	--
Projected Trial Cost Difference [(Actual PPC – Budgeted PPC) x Planned Enrollment)]	NA	$0	TBD	TBD	TBD	--

Per Patient Cost Calculations: Example

Cost Calculations	Month 2	Month 4	Month 6	Month 8	Month 10	Avg
Staffing Costs	**$20,000**	**$40,000**	**$60,000**			
Total Patient Care Costs	**$0**	**$10,000**	**$27,500**			
Actual Enrollment (of 25)	**2**	**5**	**8**			**1.33/mo**
Budgeted PPC	$5,000 per patient					
Planned Enrollment	2	4	6	8	10	1/mo
Actual PPC [Total Care Costs / Actual Enrollment]	NA	$5,000	$5,500	TBD	TBD	--
Amount Over/Under Budget [(Actual PPC – Budgeted PPC) x Actual Enrollment)]	NA	$0	$5,500 – $5,000) * 8 = $4,000 Over	TBD	TBD	--
Projected Trial Cost Difference [(Actual PPC – Budgeted PPC) x Planned Enrollment)]	NA	$0	$500 * 25 = $12,500 Over	TBD	TBD	--

Per Patient Cost Calculations: Example

Cost Calculations	Month 2	Month 4	Month 6	Month 8	Month 10	Avg
Staffing Costs	**$20,000**	**$40,000**	**$60,000**	**$80,000**	**$100,000**	
Total Patient Care Costs	**$0**	**$10,000**	**$27,500**	**$45,000**	**$62,400**	
Actual Enrollment (of 25)	**2**	**5**	**8**	**12**	**16**	**1.6/mo**
Budgeted PPC	$5,000 per patient					
Planned Enrollment	2	4	6	8	10	1/mo
Actual PPC [Total Care Costs / Actual Enrollment]	NA	$5,000	$5,500	$5,625	$5,200	--
Amount Over/Under Budget [(Actual PPC – Budgeted PPC) x Actual Enrollment)]	NA	$0	$5,500 – $5,000) * 8 = $4,000 Over	($5,625 – $5,000) * 12 = $7,500 Over	($5,200 – $5,000) * 16 = $3,200 Over	--
Projected Trial Cost Difference [(Actual PPC – Budgeted PPC) x Planned Enrollment)]	NA	$0	$500 * 25 = $12,500 Over	$625 * 25 = $15,625 Over	$200 * 25 = $5,000 Over	--



Per Patient Cost Calculations: Case Study

- Phase II Trial of Vaccine Y given with immune therapy Z
- Patients with platinum resistant ovarian cancer
- Statistical Design: 50 patients
- Primary Objective Measures:
  - Responses measured by PET at each visit, up to 6 times total per patient
  - Toxicity by patient reports (nurse to trains patients on self-reporting)
- Secondary Objective Measures:
  - Immune response to vaccine Y antigens by ELISPOT
  - IHC of tumor
- 3 year project (36mo) with full enrollment achieved within first 30mo
- Budget: $350,000 patient care costs, $360,000 salaries/benefits, & $150,000 for ELISPOT and IHC
- The clinic we are using is SLOW to invoice! Patient care costs are taking almost 3 full months to hit the budget.

Per Patient Cost Calculations: Case Study

Cost Calculations	Month 3	Month 6	Month 9	Month 12	Month 15	Avg
Staffing Costs	**$30,000**	**$60,000**	**$90,000**	**$120,000**	**$150,000**	**--**
Total Patient Care Costs	**$0**	**$9,000**	**$32,000**	**$42,500**	**$67,200**	**--**
Actual Enrollment (of 50)	**1**	**4**	**5**	**8**	**10**	**0.67/mo**
Budgeted PPC	$7,000 per patient					
Planned Enrollment	5	10	15	20	25	1.67/mo
Actual PPC [Total Care Costs / Actual Enrollment]						--
Amount Over/Under Budget [(Actual PPC – Budgeted PPC) x Actual Enrollment)]						--
Projected Trial Cost Difference [(Actual PPC – Budgeted PPC) x Planned Enrollment)]						--

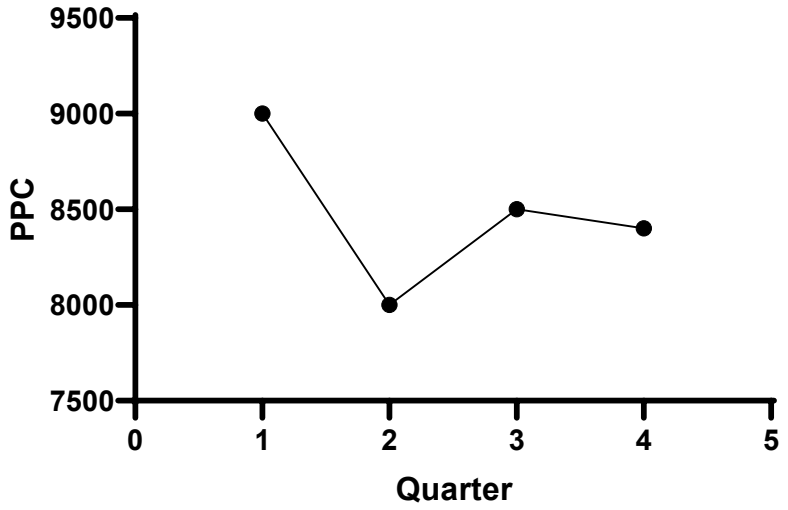
*Patient charges take, on average, 3 months to hit the budget

Per Patient Cost Calculations: Case Study Results

Cost Calculations	Month 3	Month 6	Month 9	Month 12	Month 15	Avg
Staffing Costs	**$30,000**	**$60,000**	**$90,000**	**$120,000**	**$150,000**	--
Total Patient Care Costs	**$0**	**$9,000**	**$32,000**	**$42,500**	**$67,200**	--
Actual Enrollment (of 50)	**1**	**4**	**5**	**8**	**10**	**0.67/mo**
Budgeted PPC	$7,000 per patient					
Planned Enrollment	5	10	15	20	25	1.67/mo
Actual PPC [Total Care Costs / Actual Enrollment]	TBD	$9,000	$8,000	$8,500	$8,400	--
Amount Over/Under Budget [(Actual PPC – Budgeted PPC) x Actual Enrollment)]	TBD	$2,000 * 4 = $8,000	$1,000 * 5 = $5,000	$1,500 * 8 = $12,000	$1,400 * 10 = $14,000	--
Projected Trial Cost Difference [(Actual PPC – Budgeted PPC) x Planned Enrollment)]	TBD	$2,000 * 50 = **$100,000**	$1,000 * 50 = **$50,000**	$1,500 * 50 = **$75,000**	$1,400 * 50 = **$70,000**	--

Assume that patient charges take, on average, 3 months to hit the budget

Per Patient Cost Calculations: Case Study Results



Considerations – and why they matter!

- Failure to consider delays in actual charges can lead to panic – or worse – failure to panic when necessary.
- Don't celebrate too early – and don't panic too late!
- Had we NOT considered the 3 month delay in the last case…

Cost Calculations	Month 6	Month 9	Month 12	Month 15	Month 30	Month 33
Staffing Costs	**$60,000**	**$90,000**	**$120,000**	**$150,000**	**$300,000**	**$330,000**
Total Patient Care Costs	**$9,000**	**$32,000**	**$42,500**	**$67,200**	**$360,000**	**$385,000**
Actual Enrollment (of 50)	**4**	**5**	**8**	**10**	**50**	**50**
Budgeted PPC	$7,000 per patient					
Planned Enrollment	10	15	20	25	50	50
Actual PPC	$2,250	$6,400	$5,313	$6,720	$7,200	$7,700
Amount Over/Under Budget	$-4,750 * 4 = $-19,000	$-600 * 5 = $-3,000	$-1,687 * 8 = $-13,496	$-280 * 10 = $-2,800	$200 * 50 = $10,000	$700 * 50 = $35,000
Projected Trial Cost Difference	$-4,750 * 50 = **$-237,000 UNDER**	$-600 * 50 = **$-30,000 UNDER**	$-1,687 * 50 = **$-84,350 UNDER**	$-280 * 50 = **$-14,000 UNDER**	**$10,000 OVER!** (now you have $140k for assay work)	**$35,000 OVER!** (now you have $115k for assay work… uh oh!)

Considerations – and why they matter!

- Case studies did not factor in the added complexity of STAFFING LEVELS.
  - Enrolling too slow? Staffing will need to increase or be covered for longer duration to complete enrollment
  - Enrolling faster than anticipated? Be sure your staff are covered for the extra work, and you aren't letting other grants "cover" for this trials work.
- Remember: Invoicing delays will vary from study to study – or may not exist at all! Don't worry if it takes a few months to figure out the pattern.

Clinical Budget Monitoring & Controlling

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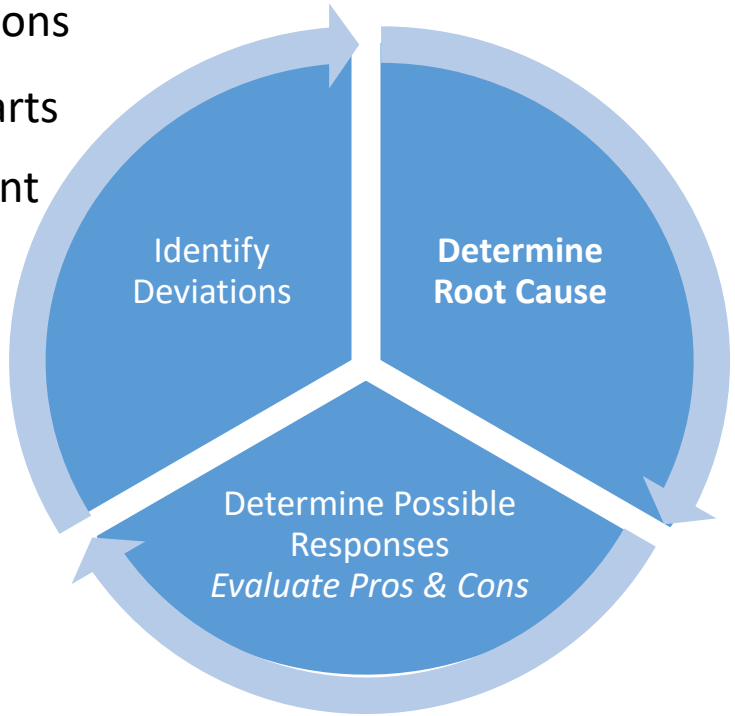

- **Project Team Brainstorming**
- **Direct comparison to budget**
- **Staff time tracking**
- **Enrollment Rates**

Clinical Budget Monitoring & Controlling

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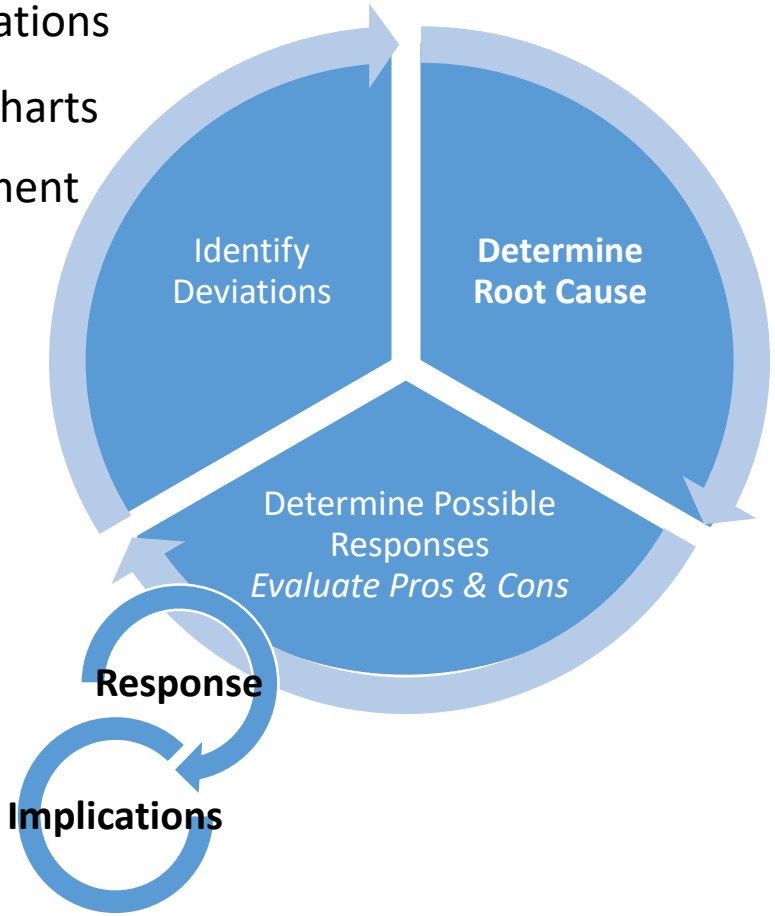

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Budgeted PPC	$7,000 per patient					
Planned Enrollment	5	10	15	20	25	1.67/mo
Actual PPC [Total Care Costs / Actual Enrollment]*	TBD	$9,000	$8,000	$8,500	$8,400	--
Amount Over/Under Budget [(Actual PPC – Budgeted PPC) x Actual Enrollment)]	TBD	$2,000 * 4 = $8,000	$1,000 * 5 = $5,000	$1,500 * 8 = $12,000	$1,400 * 10 = $14,000	--
Projected Trial Cost Difference [Patients remaining * (Actual PPC – Budgeted PPC) + Amount Over/Under Budget]	TBD	$2,000 * 46 + $8,000 = **$100,000**	$1,000 * 45 + $5,000 = **$50,000**	$1,500 * 42 + $12,000 = **$75,000**	$1,400 * 40 + $14,000 = **$70,000**	--

Assume that patient charges take, on average, 3 months to hit the budget

Brainstorm Responses / Pros & Cons

The situation:

It is the end of month 15. We are currently 20% enrolled, with 21mo left on the project. Upon comparing budgets to invoices, we discovered that the hospital where we run this trial has recently increased PET scan costs by $300 per scan. Further root-cause analysis also showed that we underestimated the cost of several other line items.

Our latest realized PPC of $8,400 seems to be rather accurate when comparing invoices (remember: our budgeted PPC was only $7000). Worse, we still have 40 more patients to enroll AND we are enrolling quite slowly.

As of today, we expect to be 70k overspent.

Brainstorm with your tables: What can we do?

Brainstorm Responses / Pros & Cons

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As of today, we expect to be 70k overspent.

Shout out your ideas – What can we do?

Response	Pros	Cons
Enroll fewer patients or do fewer scans	• We certainly won't overspend budget…	• Our trial is no longer powered, and primary measures of responses can't be changed • **Not a viable option**
Decrease staff efforts or cut staff from the project	• May be more fitting given actual enrollment rates are slower • Decreases overall spending each month	• Likely to result in over-worked staff / underpaid for the amount of work • Let's assume we decreased efforts by 60% ($6k/month savings). However, at 0.67 patients/mo x 21mo, we would only enroll about 14 more patients. • A 60% FTE decrease actually increases our overspending by another $30k, and ensures a >2x longer project period. Sponsor will likely never work with you again! • **Not a viable option**
Ask sponsor for more money	• Depending on contract type, this may be an option…	• You may never get another contract with this sponsor again! • Sponsor could pull the plug entirely, and your staff now has no job • **Not a viable option**
Dip into the $150k you have held for secondary endpoints or find cheaper assays	• You'll have extra funds to spend on patient care costs	• Possible you'll get less data in the end for your secondary time points. Consider whether or not to address this with the sponsor. • You still need to improve your enrollment rates – at this rate, you won't finish by month 36. • **Potentially improves outlook, but needs more. What about enrollment?**
Dip into the $150k you have held for secondary endpoints AND increase your staff efforts to speed up enrollment	• Enroll faster • More likely for you to finish on time	• You'll get less data in the end for your secondary time points. Consider whether or not to address this with the sponsor. • Your staff may not have any extra available time to give • **This is a good option.**
If appropriate: Modify eligibility criteria (simplify)	• Might improve enrollment rates • May simplify screening	• Amendments are a large cause of cost overruns • Consider combining this with rearranging or revising secondary endpoint • **This is a good option.**

Other Potential Problems (Relating to Budget)

Personnel Related Problems:

- Unbudgeted state mandated raises or merit raises
- Actual efforts mis-estimated: staff unavailable for high workloads

Trial Enrollment Problems:

- Concurrent/competing/co-located trials
- Limited patient population or overly restrictive enrollment criteria
- Anything that results in higher OR lower than anticipated enrollment rates

Institutional/Government Problems:

- Available research space
- Patient care cost/billing delays
- FDA clinical hold

Summary

- Determine **before starting** how you will monitor the budget. Develop tracking metrics: enrollment rates, staff efforts, per patient costs…
- Track metrics **regularly** (every other month). When you smell smoke…
- Decisions should not be made lightly! Talk to your project team in an open brainstorm session w/ pros & cons list before making changes.
- Remember: your stats and primary endpoints **cannot be changed** to fit your budget.
- Learn from it! Determine **what went wrong** (root cause analysis), how you responded, and whether you should have responded differently.

Return of Research Results

Presented by Ted Gooley PhD

1:00pm-2:00pm

UW Husky Union Building

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Considerations for CT.GOV

Ted A. Gooley
Fred Hutchinson Cancer Research Center
Seattle, WA

- Historically, results from clinical trials often not reported
  - Some estimates suggest only 25% of trials are published
- FDA Modernization Act of 1997 required NIH create and operate public information resource
  - ClinicalTrials.gov, tracking drug efficacy studies resulting from IND
  - Primary purpose to improve public access to clinical trials
    - Purpose of experimental drug
    - Subject eligibility
    - Location of trial sites
    - Point of contact for enrolling

- FDA Amendments Act of 2007
  - Mandated expansion of CT.gov for better tracking of basic results of trials
    - Expanded registration requirements
    - Legally defined timeline with specifics on reporting of results (within one year of completion)
    - Failure to report carried potential fine of up to $10,000 per day
- Study of trials conducted between 2008 and 2012 found roughly 50% of trials required to report had not been reported
- Another study found that 74% of industry trials were either not reported or reported late; 90% of academic studies!
  - No fines!!
- NEJM article from late 2016 cites 224,000 studies registered to CT.gov, with only 23,000 that display results
  - Perhaps due to ambiguity of requirements

- This led to the “Final Rule”, developed by HHS and made available September, 2016
- Rule took effect January 18, 2017
- NIH simultaneously issued policy requiring registration and reporting of results for all NIH-funded trials
- Goals
  - Enable funders to assess need for new trials
  - More complete listing of trials to inform medical evidence base
  - Better enable examination of overall state of clinical research as basis for quality-improvement efforts
  - Ethical and scientific obligation to report results, regardless of what happened

- Defined “applicable clinical trials”, i.e., trials required to report results
- Deemed “controlled” clinical trials included single-arm Phase II
  - “all interventional studies with pre-specified outcome measures”, excluding Phase I clinical trials
- Results need to be reported within one year of final data collection for purposes of evaluation of primary endpoint
- Requires results reporting for primary endpoint, secondary endpoints
  - Tertiary, Exploratory, Correlative endpoints do not need to be reported
- What information needs to be reported?
  - 4 components

- Participant flow
  - Information about number who started and completed trial, by group
- Demographics and baseline characteristics
  - Age, sex, race and ethnicity required; other measures encouraged
- Outcomes and statistical analyses
  - Results primary and all secondary outcomes, including statistical analyses if relevant
- Adverse event information
  - Anticipated and unanticipated AE's, as specified in protocol, exceeding 5% frequency within any group
  - All SAE's

Outcomes and statistical analyses

- Be sure to CLEARLY state primary and secondary objectives and the endpoints that make up these objectives
- Do not specify “too many” secondary endpoints
  - This is not only good clinical-trial practice, but reduces burden of reporting
    - This is not to say that you can/should ignore important endpoints!!
- Make sure that you collect all data relevant to primary and secondary endpoints, and do so in a manner that allows you to estimate/assess these endpoints/objectives.

- Difference between objective and endpoint
  - Objective of a trial is to address the scientific question by collecting appropriate data
  - Selection of endpoint is made to address the objective of the trial
    - Endpoint should be clinically relevant, interpretable, sensitive to effects of proposed intervention, practical (and affordable) to measure, measured in an unbiased manner, easy to observe
    - Endpoints are typically continuous (e.g., BP or pain on visual analogue scale), categorical (including binary, e.g., response vs. no response), or time-to-event (e.g., time to death)

- Objective is formulated as a question, goal, or an aim, and is a phrase or sentence
  - Key words: determine, estimate, evaluate, assess
- Endpoint is an outcome
  - Determined for each patient, quantitative measurement required by objective

- A “bad” objective: “Determine the difference in outcome in patients with breast cancer”
  - What is outcome?
  - What are the treatment groups?
  - All patients with breast cancer?
  - Way too vague

- A “good” objective: “Estimate the difference in time to breast-cancer progression between chemotherapy alone and chemotherapy plus trastuzumab in women with HER2-positive metastatic breast cancer who had not previously received chemotherapy for metastasized disease”
  - Wordy, yes; but defines population, treatment groups, and outcome

Adverse Events

- Be sure to collect adverse events on a per-patient basis, allowing for multiple AE's for each patient (same kind or different kinds)
- Use common terminology, list type of AE and site
- Distinguish between AE as defined in protocol and SAE; all SAEs must be reported

Primary Objective

- To assess the pathologic response rate in patients with operable breast cancer treated with a two part, neoadjuvant regimen consisting of complete hormonal blockade (CHB) for 2 weeks followed by four three-week cycles of Xeloda, Methotrexate and Navelbine with continuation of complete hormonal blockade.

Secondary Objectives

- To assess the clinical response rate in patients with surgically resectable breast cancer treated with complete hormormonal blockade and four three-week cycles of Xeloda, Methotrexate and Navelbine.
- To assess the toxicity associated with these regimens.
- To assess the relapse rate, overall and disease-free survival in patients with operable breast cancer when treated with neoadjuvant CHB and XMN + CHB followed by adjuvant treatment using XMN or Taxol.
- To assess whether the phenotype of breast cancer changes with treatment.
- To assess whether phenotypic changes in breast tumors predict outcome.

Primary Objective

- Proportion of patients achieving a complete response (CR), defined as no emesis and no rescue medications in the 0-24 hour time period following weekly intravenous doxorubicin.

Secondary Objective

- Proportion of patients achieving a complete response (CR), defined as no emesis and no rescue medications in the 24-120 hour time period following weekly intravenous doxorubicin.
- Proportion of patients achieving a complete response (CR), defined as no emesis and no rescue medications in the 0-120 hour time period following weekly intravenous doxorubicin.
- Number of emetic episodes daily and cumulatively for the 24-120, and 0-120 hour time periods
- Time to first emetic episode
- Time to first administration of rescue medication
- Time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first)
- Side effects of antiemetic medications used
- Severity of nausea
- Quality of life

Objectives

Primary: To estimate the maximally tolerated dose of 131I-BC8 (anti-CD45) that can be delivered prior to autologous stem cell transplantation for patients with relapsed/refractory B-NHL, T-NHL, or HL.

Secondary:

- 1) To optimize the protein dose (Ab) to deliver a favorable biodistribution in the majority of patients.
- 2) To assess the radiation dose delivered to tumor sites and normal organs by the above therapy.
- 3) To evaluate the dose-response relationship of radiation-dose to tumor and clinical response.
- 4) To estimate the overall and progression-free survival of the above regimen in such patients.
- 5) To evaluate the toxicity and tolerability of the above therapy.
- 6) To evaluate the feasibility of delivering high-dose 131I-BC8 and ASCT to B-Cell NHL, T-NHL, and HL patients.
- 7) To evaluate the ability to reduce infusion reactions via unlabeled BC8 preinfusion.

Objectives

- The primary objective of this study is to:
- Determine anti-tumor activity as assessed by disease-free survival (DFS). Estimate the two year DFS rate in mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

- The secondary objectives of this study are to:
- To estimate the overall survival rate and evaluate time to treatment failure/remission duration.
- To describe non-relapse death events and the toxicity profile.
- Evaluate the biological markers of mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

Objectives

Primary objectives

- To assess the feasibility of expanding HER2 specific T cells ex vivo for infusion into subjects who have advanced HER2 overexpressing cancer.
- To assess the toxicity associated with infusing autologous HER2 specific T cells into patients using either a single dose of cyclophosphamide or ONTAK prior to T cell infusion.

Secondary objectives

- To investigate to what extent HER2 specific T cell immunity can be boosted in individuals treated with a single dose of cyclophosphamide or ONTAK followed by infusion of autologous HER2 specific T cells.
- To investigate the potential anti-tumor effects of HER2 specific T cells in patients with HER2 overexpressing advanced-stage cancers.
- To evaluate how long tumor antigen specific T cell immune augmentation persists in vivo after a single dose of cyclophosphamide or ONTAK followed by infusion of autologous HER2 specific T cells.

- Hypothesis: We hypothesize that advanced MRI techniques incorporating DCE and DWI MRI characteristics at 3T will enable reliable prediction of DCIS risk, defined by nuclear grade and advanced pathologic variables (HER2/neu, p16, cox-2, Ki-67, and Oncotype DXTM DCIS score), and can identify the presence of invasive disease missed during needle core biopsy.
- Specific Aims:
- Aim 1: Measure DCIS lesion characteristics on DWI and DCE MRI at 3T. We will measure the 3T DWI and DCE MRI characteristics in 12 DCIS lesions, 6 diagnosed as high grade (HG) and 6 diagnosed as non-high grade (NHG) by means of core needle biopsy. We will characterize these DCIS lesions qualitatively and quantitatively on DWI obtained at multiple b values, calculating apparent diffusion coefficient (ADC) and contrast-to-noise ratio (CNR) values of each lesion. An experimental DCE-MRI sequence will also be obtained with high spatial and temporal resolution, and characterization will be performed utilizing experimental kinetics assessments as well as standard BI-RADS descriptors of morphology and size.
- Aim 2: Identify predictive MRI markers at 3T for discrimination of DCIS grade. We will confirm histopathological data for all lesions from surgical excision and assess the correlation of imaging characteristics with pathologic biomarkers of DCIS. Statistical analysis will be performed to validate predictive markers that had been identified in our prior studies and to identify additional markers that significantly differ between HG and NHG DCIS. Utilizing the specific imaging markers identified to be independently predictive of DCIS grade, multivariate statistical analysis will be performed to optimize in vivo DCIS grade characterization. In addition, we will characterize DW and DCE MR features that predict for the presence of invasive disease in vivo.

Primary objective

- To evaluate the feasibility of “early” allogeneic hematopoietic cell transplant (HCT) for patients with relapsed or refractory (R/R) high-grade myeloid neoplasms. The feasibility of this trial is defined in Section 12.1.

Secondary objectives

- Estimate relapse-free survival (RFS), acute GVHD, TRM, event-free survival (EFS), overall survival (OS), and complete remission (with or without measurable disease) among patients who receive early HCT, Endpoint applicable to patients who don’t receive early transplant (survival endpoints and remission) will be also be estimated for all patients enrolled on the study.
- Assess factors that distinguish patients who receive early HCT from those who do not
- Compare RFS, EFS, OS, acute GVHD, and TRM between patients in the feasibility study and matched patients who were transplanted with standard scheduling
- Demonstrate the feasibility of collecting patient-reported outcomes and resource utilization data for trial participants
- Describe the outcomes of patients enrolled who went on to allogeneic HCT off-study

12.1 We would consider this feasibility study a success and plan to launch a randomized trial if: 1) we were able to enroll 30 patients per year (1/3 of the anticipated 90 who present with R/R AML) 2) we transplant at least 15 of the 30 patients within 60 days of start of induction therapy, and 3) among patients who are transplanted the observed 6-month relapse-free survival after transplant is 40% or higher

Primary Objectives

- Compare the time to neutrophil engraftment (ANC >500) in patients receiving a standard-of-care myeloablative CBT augmented with an off-the-shelf pre-expanded and cryopreserved cord blood product to those who do not receive the product.

Secondary and Exploratory Objectives

- Provide initial data on clinical and economic benefit, such as time to platelet engraftment, duration of initial hospitalization, transplant-related mortality (TRM), death without engraftment, and incidence of severe infections in the first 100 days post transplant. The kinetics of immune system recovery will also be evaluated in both arms.

Primary Endpoint

Time to engraftment (ANC >500) in both arms (standard myeloablative CBT with and without off-the-shelf expanded cord-blood progenitors).

Secondary Endpoints

1. Platelet engraftment (20k)
2. Incidence of infectious complications in the first 100 days post transplant
3. Overall Survival
4. Non-relapse mortality
5. Acute and chronic GVHD.

Exploratory Endpoints

1. In vivo persistence of the ex vivo expanded cord blood product
2. Duration of initial hospitalization
3. Grade? 3 infusional toxicity
4. Graft failure: Primary and secondary (see protocol section 13.0 for definition of graft failure)
5. Immune reconstitution: TCR sequencing (see protocol section 10.9)

An Ethical Framework for Clinical Research

Presented by Ben Wilfond, MD

2:15pm-3:15pm

UW Husky Union Building

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An Ethical Framework for Clinical Research: Rethinking and Going Beyond Informed Consent

Benjamin Wilfond, MD

UW Department of Pediatrics
Seattle Children's Research Institute

Learning Objectives

By the end of the session, you will be able to:

- Describe the eight ethics benchmarks for ethical clinical research
- Discuss how empirical data illustrates challenges with informed consent
- Identify the role of researcher-participant interactions in the ethical conduct of research

Overview

- A framework for ethical clinical research (20 min)
- Case study: *A randomized study of financial incentives for hepatitis B vaccination in an immigrant community*
  - Small group discussion (15 min)
  - Large group discussion (15 min)
- Q&A (10 min)

What is the Value of Research Ethics?

- To prevent **exploitation** of human subjects
- To prevent unjustified or unnecessary **harm**
- To provide **guidance** to researchers who are unsure about their ethical obligations
- To ensure public **trust** in research and support for future research

“Born in Scandal”

- Guidelines for ethical research are largely responsive to research ethics scandals
  - Nuremberg Trials → Nuremberg Code (1947)
  - Tuskegee syphilis study and other research ethics scandals → Belmont Report (1979)

- “The voluntary consent of the human subject is absolutely essential.” – Nuremberg Code, 1st principle

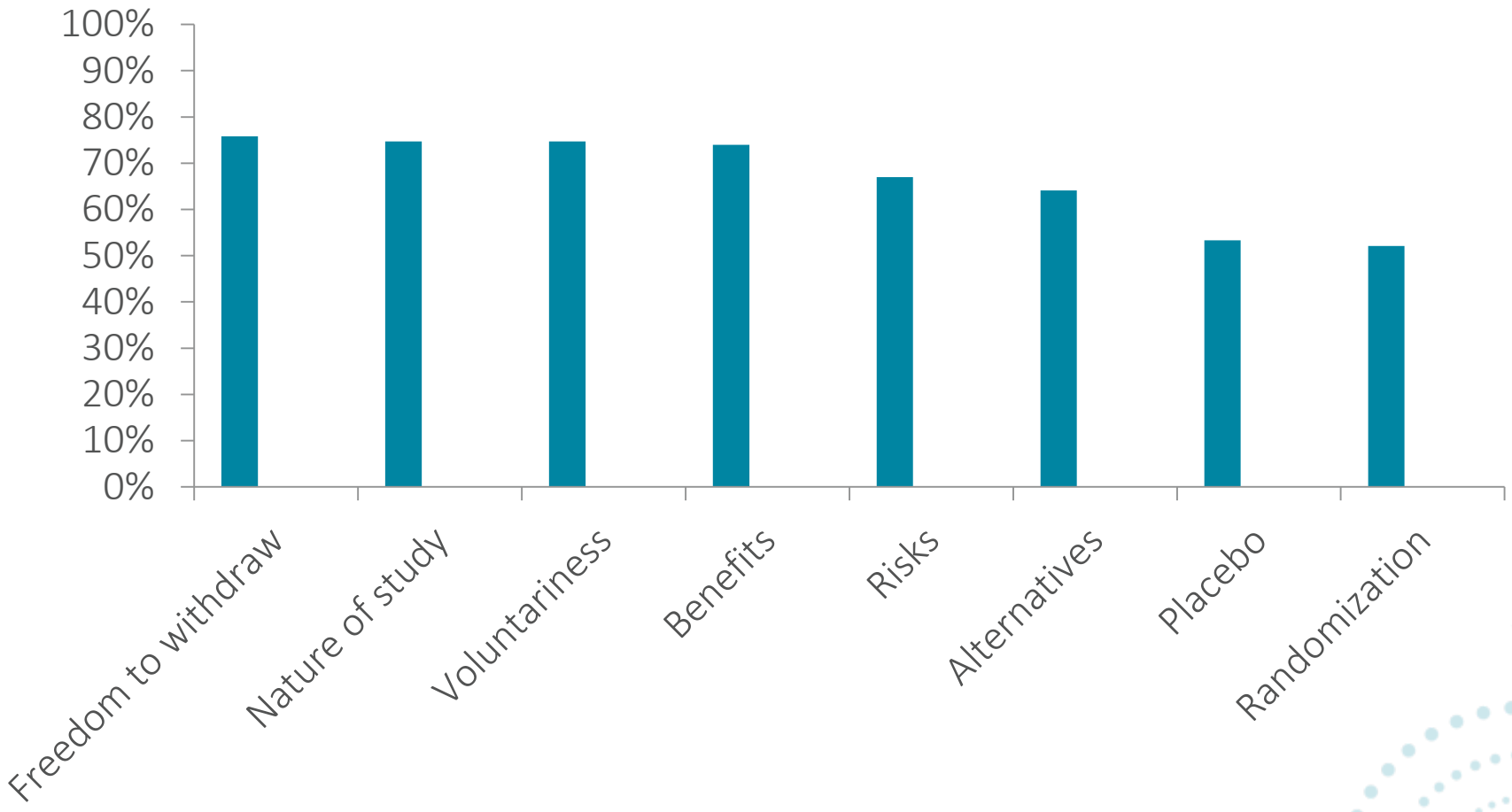
Elements of Informed Consent

- Capacity
- Disclosure
- Understanding
- Voluntariness
- Authorization

Elements of Informed Consent – Empirical Data

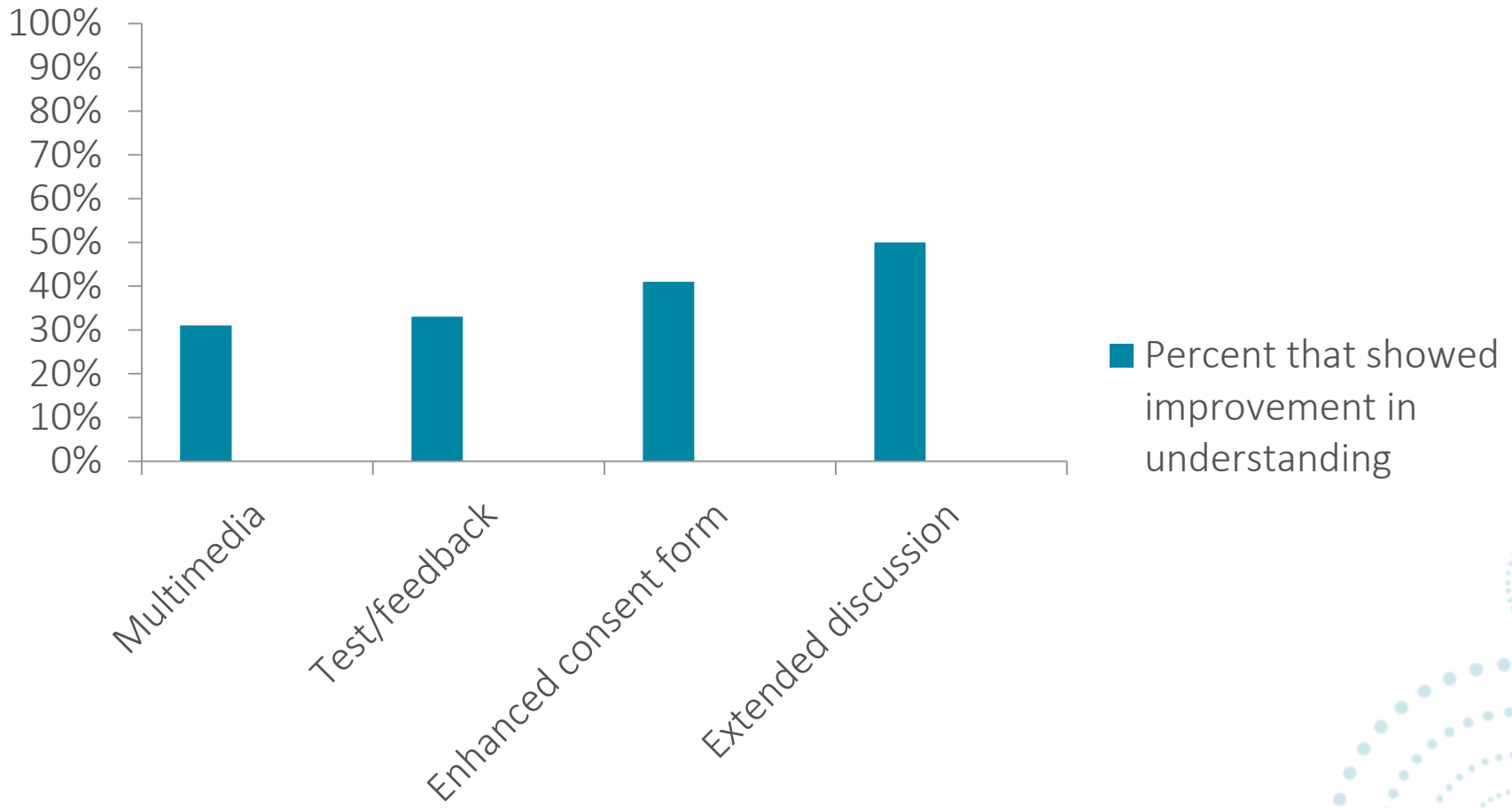
- Capacity
- Disclosure
- Understanding
- Voluntariness
- Authorization

Systematic Review of Participant Understanding of Consent Elements



Nguyen TT et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. *Bull WHO* 2015.

Meta-analysis of Interventions to Improve Understanding



Nishimura et al. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Med Ethics* 2013.

The Enduring Challenges of Informed Consent

- Understanding is limited and hard to improve
- Empirical social science research is important but challenging
  - Better metrics for understanding, voluntariness, satisfaction, and other outcomes are needed
- Easy to study a form; harder to study the whole recruitment, enrollment, and study process
  - When do people actually make decisions about research?
  - What else informs their decisions?

→ Conceptual research to develop a systematic, comprehensive ethics framework can contextualize the role of informed consent

Eight Benchmarks to Balance

1. Collaborative partnership
2. Social value
3. Scientific validity
4. Fair subject selection
5. Favorable risk/benefit ratio
6. Independent review
7. Informed consent
8. Respect for participants and communities

Emanuel et al. What makes clinical research ethical? *JAMA* 2000;283:2701-11; *JID* 2004;189:930-37.

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1. Collaborative Partnership

Collaborative Partnership

- Clinical researchers should partner with the community in which or with which the research occurs
  - Community engagement in planning, conducting, and overseeing research (e.g., community advisory boards)
  - Sharing benefits with the community
- Many reasons for community consultation:
  - Transparency
  - Buy-in
  - Assessing risks and ensuring benefits are actually beneficial
- Challenges:
  - Different reasons may warrant different forms of engagement
  - Different definitions of community

Wendler & Shah. Involving communities in deciding what benefits they receive in multinational research. *J Med Phil* 2015.

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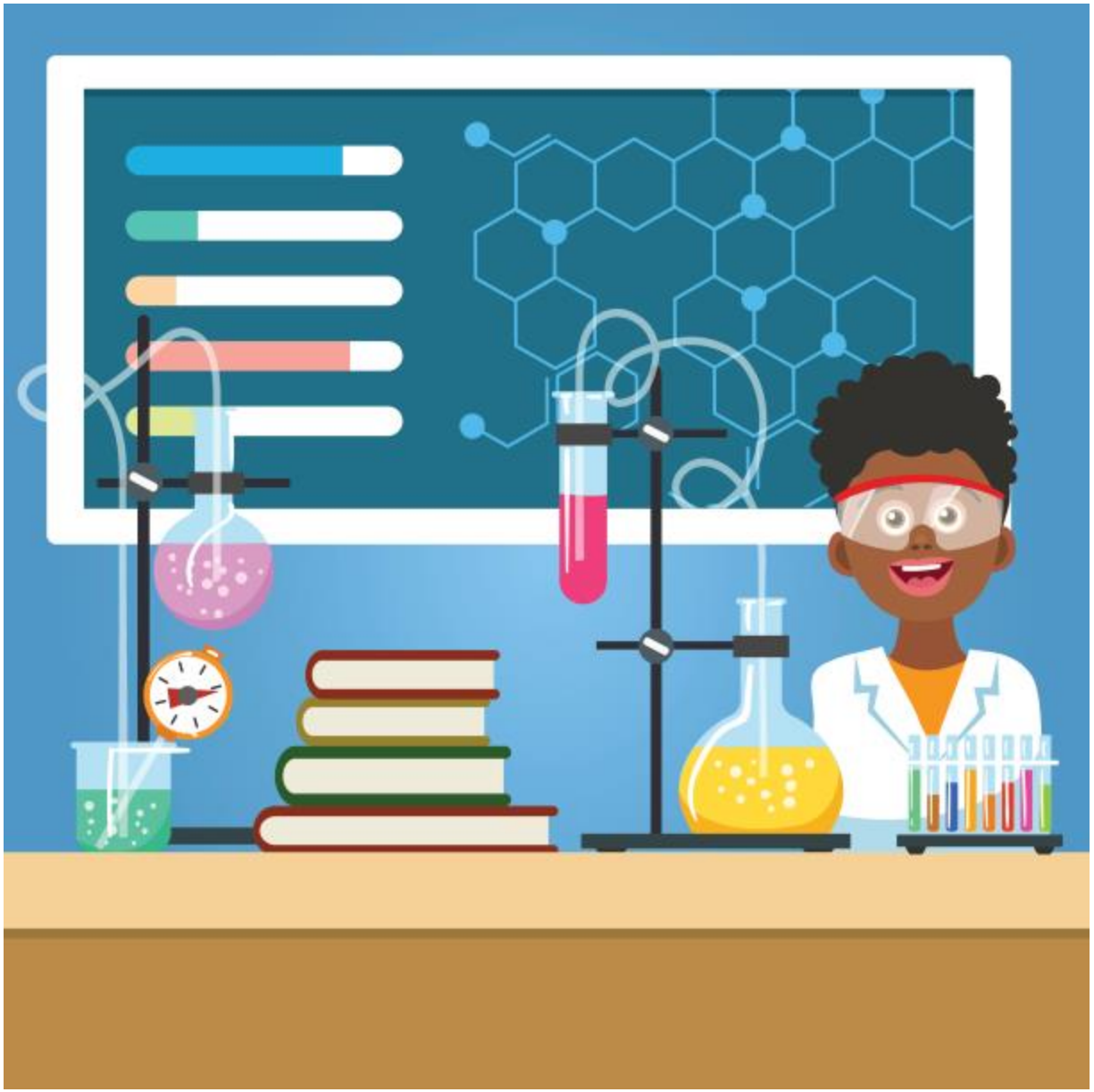
2. Social Value

Social Value

- Clinical research should lead to improvements in health or generalizable medical knowledge for:
  - Participants
  - Communities
  - Future patients

- Research with limited social value:
  - Unimportant questions
  - Limited advancement in knowledge
  - Non-generalizable studies
  - Non-disseminated research



3. Scientific Validity

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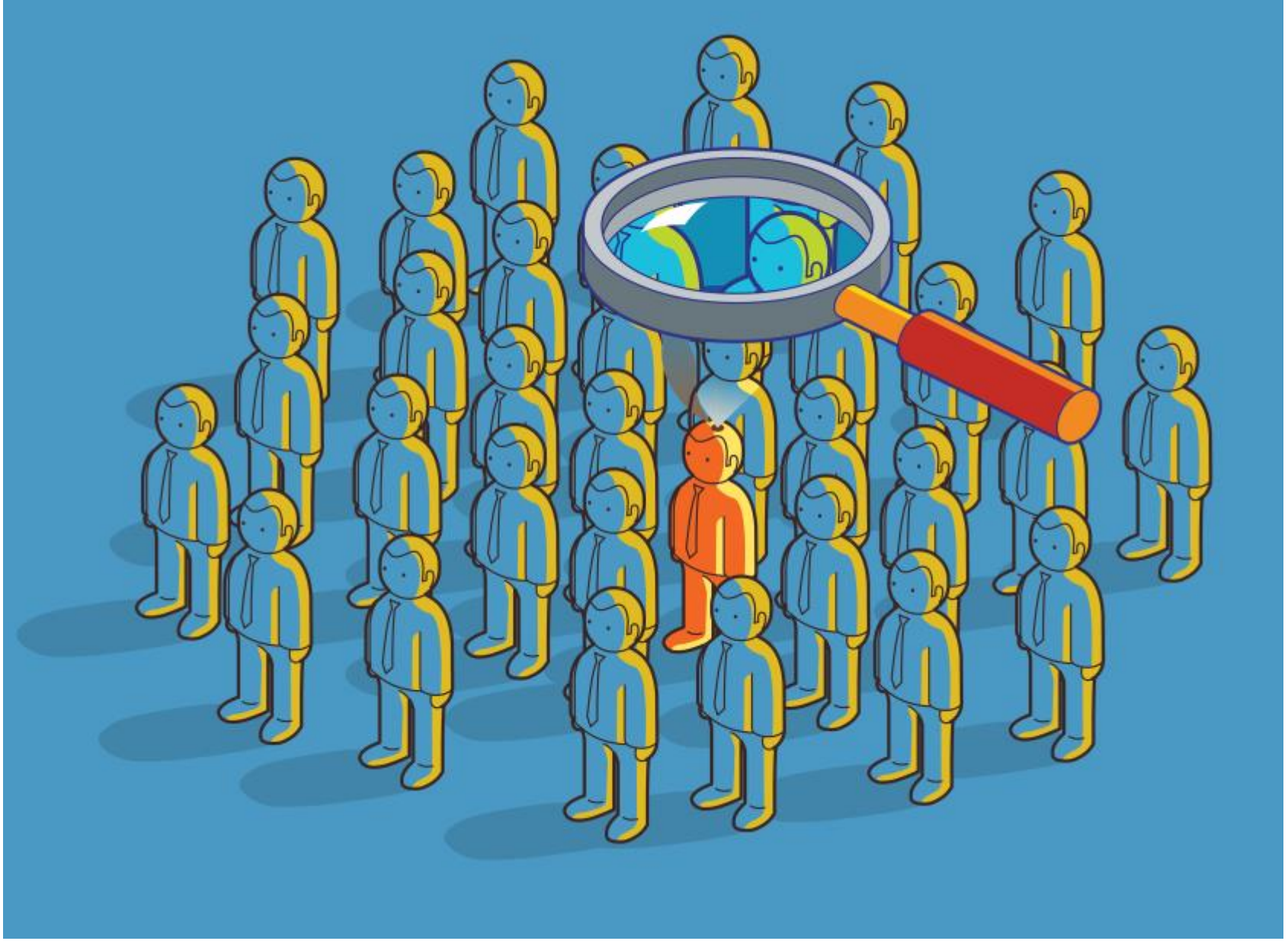
Scientific Validity

- Must be a reasonable possibility that research will produce valid scientific results
- If a study is not valid, there is no basis to justify:
  - Resources used to generate knowledge and promote health
  - Risks and burdens undertaken by participants
- Invalid research includes:
  - Underpowered studies
  - Studies with biased endpoints, instruments, or statistical tests
  - Studies that cannot enroll sufficient subjects

Wertheimer A. Non-completion and informed consent. *J Med Ethics* 2014.



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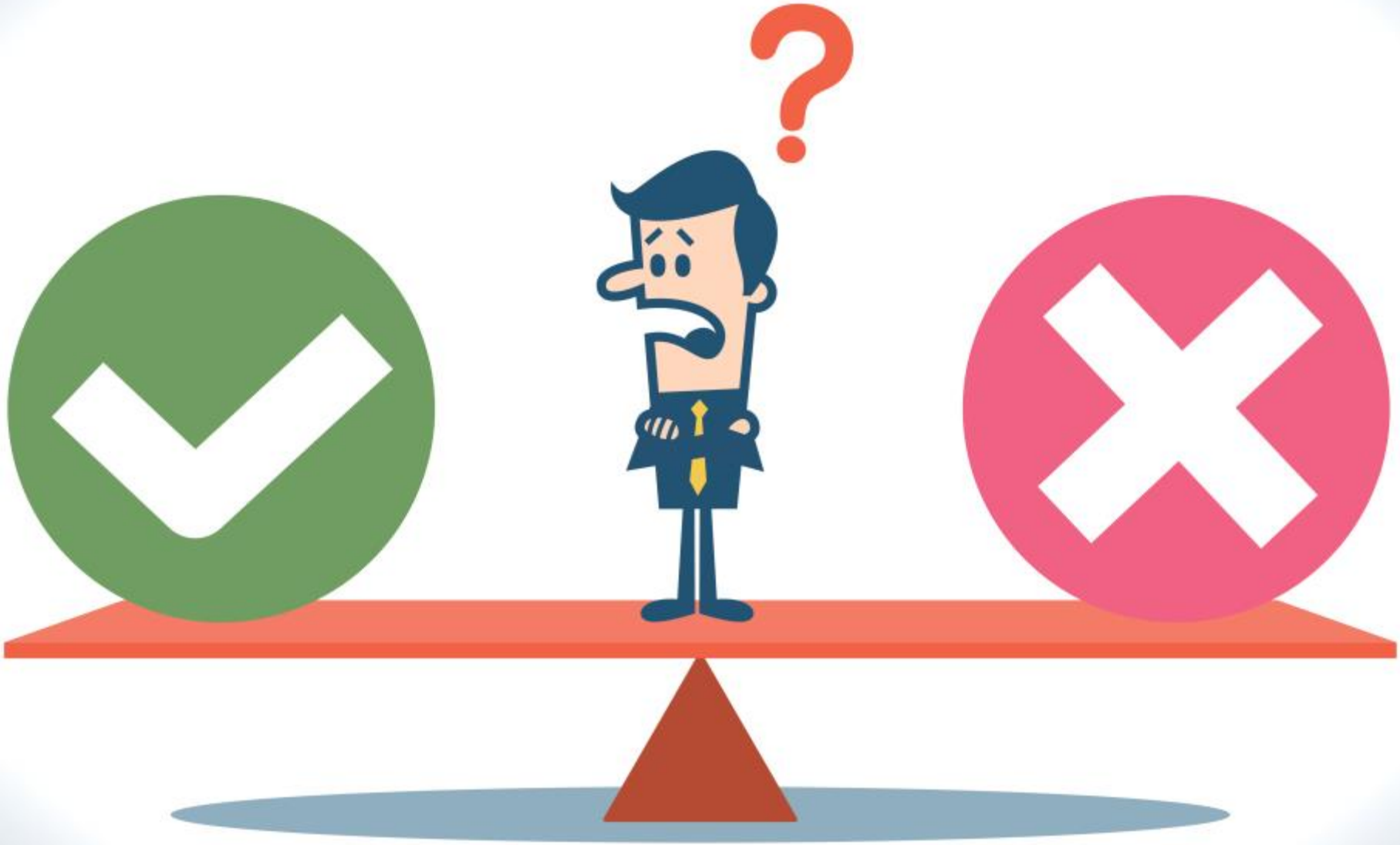
4. Fair Subject Selection

Fair Subject Selection

- Scientific objectives of the study, not vulnerability or privilege, should guide inclusion criteria and targeted populations
  - Vulnerability = decreased ability to protect one's own interests
- May be good reason to exclude certain groups (e.g., higher risk or unable to consent)
- Consider distribution of burdens and benefits of research
  - Research as burden: participants need protection
  - Research as benefit: participants need access



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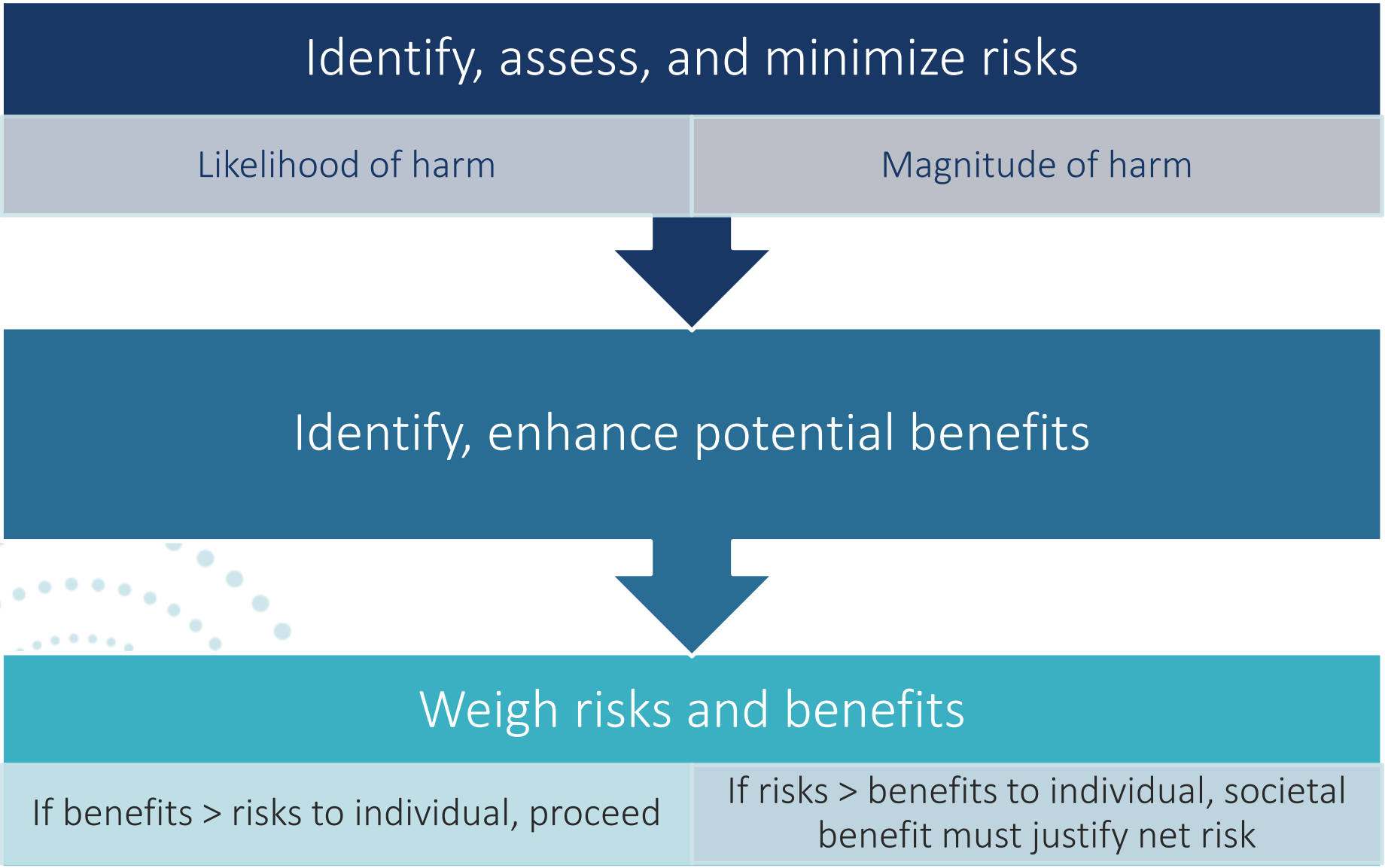
5. Favorable Risk/Benefit Ratio

Favorable Risk/Benefit Ratio



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6. Independent Review

Independent Review

- Investigators have multiple legitimate interests
- Can lead to conflicts of interest
- Independent review:
  - Minimizes the impact of conflicts of interest
  - Assures society that research is ethically appropriate and demonstrates trustworthiness

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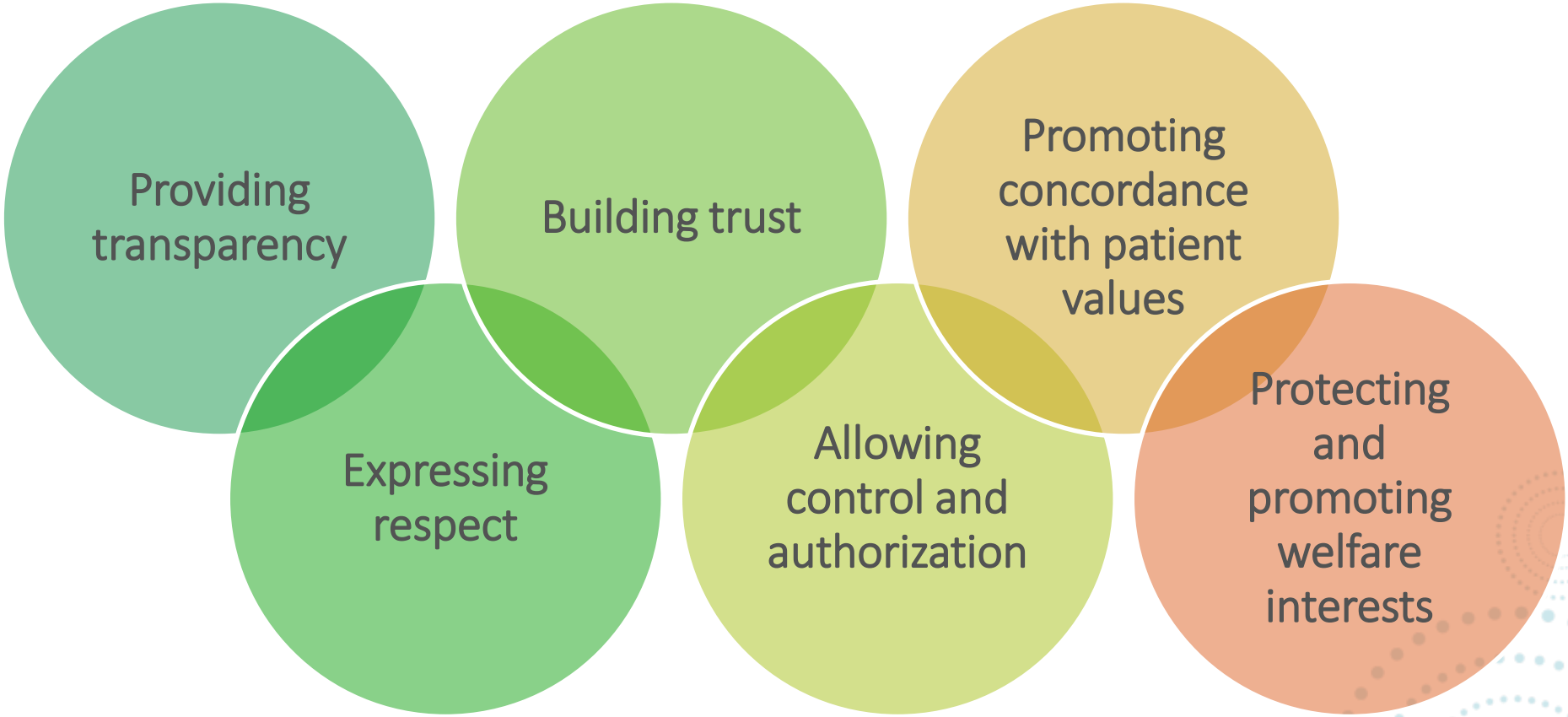
7. Informed Consent

Informed Consent

- A process (not a form or an episode) by which participants decide whether to take part in a study

- Some research can be ethical without consent, or without one or more elements of consent
  - E.g., research on de-identified biospecimens
  - E.g., waiver of documentation

Informed Consent Serves a Variety of Functions



8. Respect for Participants and Communities

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Respect for Participants and Communities

Ethical requirements of research do not start or end with signed consent document, and may include:

- Protecting confidentiality
- Respecting right to withdraw
- Developing monitoring plan, stopping rules
- Compensation for research injury
- Post-trial obligations

Conclusions

- There are historical and ethical reasons for caring about ethics of clinical research
- Eight benchmarks can help identify issues that need attention
  - Systematic approach
  - Balancing is often necessary
- Informed consent is ethically important, but imperfectly realized
  - And not the only benchmark we should care about

Learning Objectives

- Describe the eight ethics benchmarks for ethical clinical research
- Discuss how empirical data illustrates challenges with informed consent
- Identify the role of researcher-participant interactions in the ethical conduct of research

Questions

Case Study

- Background:
  - Up to 75% of African-born individuals have evidence of past or current HBV infection; at least 25% are at risk for infection
  - In a large US city with a large African-born population, only 10% of at-risk adults completed vaccination when offered free of charge
  - Community focus groups revealed no particular objection to vaccination
- Proposed study: Compare effects of education vs. financial incentives ($10 or $20) on vaccination uptake
- Main question: Is it ethically appropriate to offer financial incentives for hepatitis B vaccination in a randomized trial?

Discussion Questions

1. How should the research team **partner with the community**? About what? When in the research process?
2. How would you describe the **value** of this research? Are the results likely to be generalizable?
3. What other study designs might be feasible and **scientifically valid**?
4. Does the selection of this **study population** seem fair?
5. What is the **risk/benefit ratio** in this study? Is it appropriate?
6. Should all participants be **informed** that some people in the study are getting a larger financial incentive? How and when might this disclosure be done?

1. Collaborative partnership
2. Social value
3. Scientific validity
4. Fair subject selection
5. Favorable risk/benefit ratio
6. Independent review
7. Informed consent
8. Respect for participants and communities

Emanuel et al. What makes clinical research ethical? *JAMA* 2000;283:2701-11; *JID* 2004;189:930-37.

ITHS Research Bioethics Consultation Service

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Research Bioethics Consultations

The ITHS Research Bioethics program provides a forum for discussion and analysis of ethical issues in clinical and translational research.

The Consultation Process

ITHS offers research bioethics consultations to researchers, trainees, research staff, and personnel involved in the protection of human subjects. Discussions with consultants can take place by telephone or in person. There is generally no charge.

Bioethics consults are advisory and provide a forum for in-depth conversation and analysis of ethical issues in clinical and translational research. Recommendations are supplemental to the authority and oversight of review groups such as an Institutional Review Board or Data Monitoring Committee.

To ensure a balanced understanding of the facts or to facilitate resolution of a conflict, the consultant is available to talk with others involved in the issue if the requestor so desires.

Acknowledgments

- Thanks to the ITHS staff who supported the development of this session
  - NCATS UL1 TR002319

- Thanks to Christine Grady, Chief of the Department of Bioethics at NIH, for sharing her slides

- Thanks to the members of the Clinical Research Ethics Consultation Collaborative who shared this case study and offered their expertise

Questions?

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www.iths.org/bioethics

Noncompliance, Unanticipated Problems & Complaints

Presented by Jason Malone, MPH

3:25pm-4:25pm

UW Husky Union Building

Noncompliance, Unanticipated Problems & Complaints:

Learn to Prevent, Correct and Report

Presented by: Jason Malone, MPA, CIP
Assistant Director, Regulatory Affairs
University of Washington – Human Subjects Division

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Learning Objectives

By the end of this session, you will be able to:

- Discuss the roles and responsibilities related to reporting new information
- Describe the who, what and why for reporting new information
- Describe the framework for developing a corrective and preventive action plan in response to an event
- Identify processes to set studies up for success in order to prevent unanticipated problems and non-compliance

Framework

Initial Application

- Known Risks
- Theoretical Risks
- Everything will be conducted exactly as described in IRB application/study protocol

RNI = Report of New Information

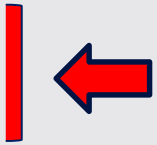
- Known or Theoretical Risks Happen
  - AND are reportable (e.g. occur at greater frequency, severity, nature than anticipated)
- Unknown/Unexpected Risks Happen (related, reportable)
- Things don't go according to plan (e.g. noncompliance with study protocol)
- Other New Information (e.g. revised IB, publication)

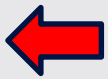
What to Report?

What needs to be reported? The regs say:

- 45 CFR 46.108(a)(3) *Establish and follow written procedures for:… (iii) ensuring prompt reporting to the IRB of proposed changes in a research activity…* [21 CFR 56.108(a)(3)]
- 45 CFR 46.108(a)(4) *Establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections, HHS, or any successor office, or the equivalent office within the appropriate Federal department or agency of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB;* [21 CFR 56.108(b)]
- 45 CFR 46.116(b)(5) Additional Elements of Informed Consent - *A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject* [21 CFR 50.25(b)(5)]

Information or Event	When to report
Qualifying Medical problem covered by UW HSAP	Report within 24 hours
Breach (or risk of breach) or loss of subject confidentiality or privacy	
Inappropriate access or use of protected health information (PHI)	
Incidental incarceration of a research subject in a study that the IRB has not approved for the inclusion of prisoners and where study activities or data collection will continue while the subject is incarcerated.	Report within 3 business days
For DOD funded EFIC studies only: All incidental incarceration of a research subject even if study activities and data collection will not occur during the incarceration	
Unanticipated problem	Report within 10 business days
Unanticipated adverse device effect	
Serious non-compliance	
Continuing non-compliance	
Emergency deviation from IRB-approved procedures made without prior IRB review to eliminate an apparent immediate hazard to a subject or others	
Continuation of research after IRB approval has lapsed, because the procedures are of direct benefit to the individual subjects or withholding the research intervention (if any) may increase risks to subjects	
Complaint from a subject or person about the study, which cannot be resolved by the study team	
Audit, inspection, compliance or safety-related inquiry from a federal agency	
Information that indicates a new or increased risk or safety issue (or a decrease in study benefits) (e.g. revised IB, package insert, or device manual; changes to FDA-approved labeling, restrictions, or warnings)	
Premature suspension or termination of some or all of the research by the sponsor, researcher, or institution	
Data Safety Monitoring Board (DSMB) or other study monitoring reports	
Change in credentialing, licensing, resources, or facilities that affect the research	





What to Report - Unanticipated Problem

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

OHRP Unanticipated Problems Involving Risks & Adverse Events Guidance (2007)

What to Report - Unanticipated Adverse Device Effect

- Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

21 CFR 812.3(s) Unanticipated adverse device effect

What to Report - Noncompliance

An action or omission on the part of the researcher that is inconsistent with any of the following:

- The ethical principles of human subjects research as described in the Belmont Report;
- Federal, state, and/or local regulations applicable to human subjects research under the jurisdiction of the UW IRB;
- UW policies and procedures governing human subjects research;
- The research activities as approved by the UW IRB, including any IRB requirements or determinations.

What to Report - Serious Noncompliance

Non-compliance which meets any of the following criteria:

- Significant increase of the risks to, or jeopardizes the safety, welfare, and/or rights of, one or more subjects or others;
- Significant decrease of the potential benefits;
- Compromises the scientific integrity of a study such that important conclusions can no longer be reached.

What to Report - Continuing Noncompliance

A pattern of repeated non-compliance by the same investigator or the IRB that meets any of the following criteria:

- Suggests the likelihood that non-compliance will continue without intervention;
- Represents a failure to respond to a request to resolve an episode of non-compliance or a pattern of minor non-compliance;
- Increases the potential for serious non-compliance

I have been repeating the same mistakes in life for so long now, I may as well call them traditions.

What to Report - Research Complaint

- Complaints or concerns about UW research from a potential, past or current research subject (or the subject's representative), or

- Concerns about the conduct of UW research from a research staff member or any other concerned person or organization.

Why Do You Need to Report?

We ask for and review RNI so that we can:

- Meet regulatory obligations
  - Researchers must report Changes in research activity, Unanticipated problems, Serious NC, Continuing NC, provide new findings to subjects
  - IRB must assess and make determinations of UAP, SNC, CNC
- Facilitate Federal and Institutional Reporting (i.e. breach notifications and loss of confidentiality to UW Medicine Compliance, UW Privacy Office)
- Ensure the immediate problem has been addressed
- Ensure any proposed corrective action plan (CAP) will prevent future problems
- Ensure the risk level of the study is still appropriate
- Ensure the study continues to meet the criteria for approval

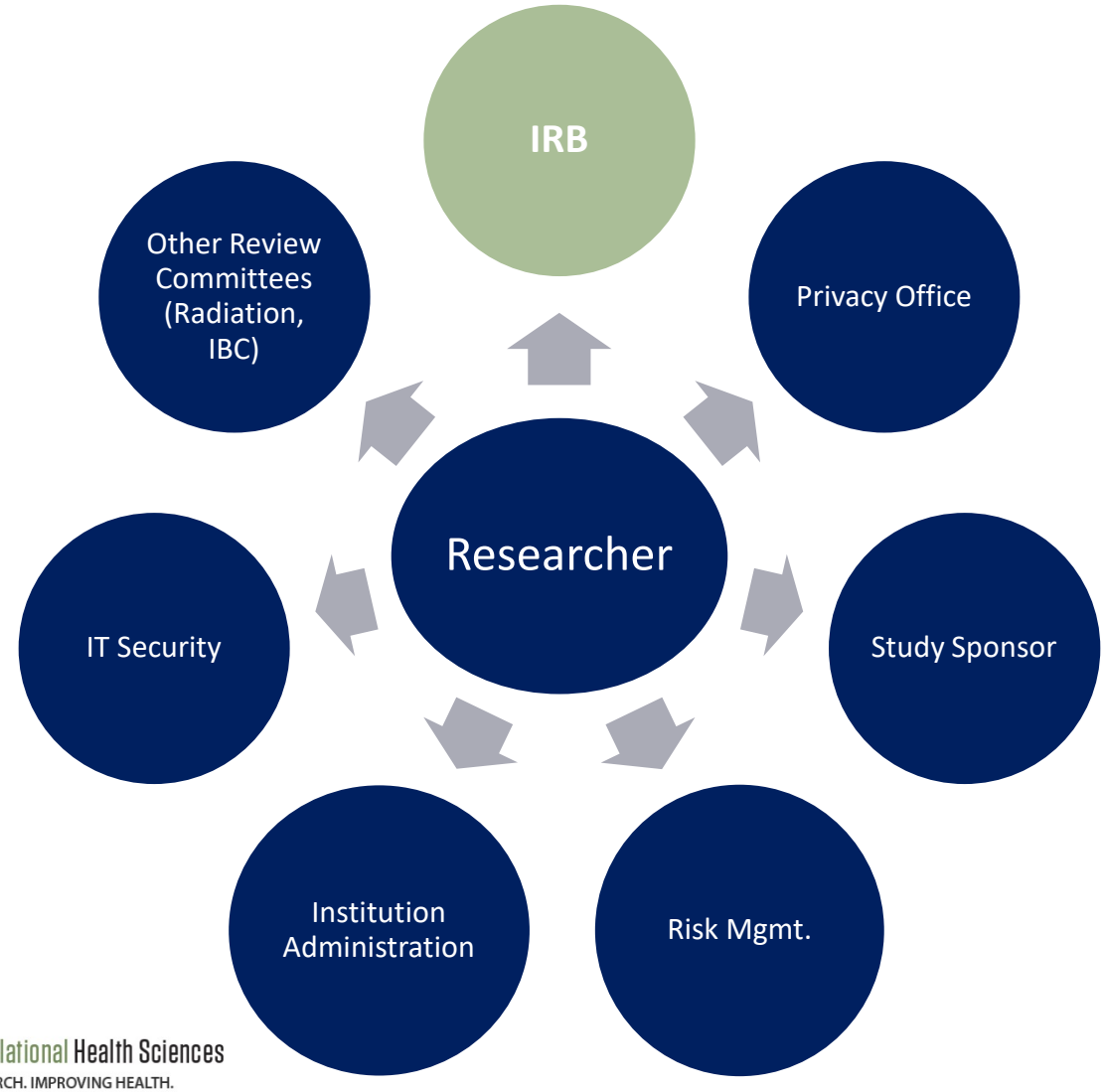
How to Report

- Follow your institution's procedures and use their required forms
- Ensure you've done a root cause analysis of the problem
- Propose appropriate solutions
- Consider using the S.M.A.R.T. approach
  - **S**pecific
  - **M**easureable
  - **A**chievable
  - **R**ealistic
  - **T**ime-bound

Corrective Action Plan (CAP) - SMART

- **S**pecific: Compliant with regulations, addresses the full observation or root cause, accountable to named individual or role
- **M**easurable: Action can be measured to demonstrate whether it is adequate to address the root cause
- **A**chievable: Addresses all implicated processes and levels
- **R**ealistic: Plan can be carried out given available resources, knowledge and expertise
- **T**ime-bound: Assigned to a person or role who can accomplish the action in a given time period, addresses urgency and criticality

Other Reporting



When to Report

- Reporting timelines vary from institution to institution and in some instances depend on the nature of the event
  - Example – UW
    - 24 hours: Breach, loss of confidentiality, inappropriate access/use of PHI
    - 3 business days – incarceration of a study subject
    - 10 business days – everything else
  - Example – Seattle Children's
    - 5 business days for everything
- It is your responsibility to know when to report and to do so in a timely fashion

Available Resources

- UW Reporting New Information - https://www.washington.edu/research/hsd/study-activities/report-events-and-new-information/
- Seattle Children's Reporting New Information - https://www.seattlechildrens.org/globalassets/documents/research/irb/click/reporting-new-information-2018.pdf
- Fred Hutch - https://extranet.fredhutch.org/en/u/irb/policies-and-procedures/_jcr_content/leftParsys/download_29/file.res/IRB-Reporting-Obligations-PIs-Policy.pdf
- WIRB Promptly Reportable Information - https://www.wirb.com/Documents/PRI.pdf

How to Avoid Reportable Events

"A clever person solves a problem.
A wise person avoids it."
-Albert Einstein

How to Avoid Reportable Events

Unanticipated Problems/Adverse Device Effects

- Adequately assess all known and possible risks
  - Literature review
  - Expert clinical assessment
- Outline risks in the consent form
- Incorporate adequate safeguards in study design to mitigate risk
- Have an effective data and safety monitoring plan
  - Routine collection and review of AEs
  - Independent monitoring where appropriate (medical monitor, Data & Safety Monitoring Board)

How to Avoid Reportable Events

Noncompliance

- Study design
  - Realistic (e.g. both subjects and study staff can follow)
  - Flexible where appropriate
- Case Report Forms
  - Match current protocol (i.e. capture only data outlined in protocol and IRB application)
    - Updated as modifications occur
  - Avoid unnecessary subject identifiers
  - Avoid duplicative data capture (e.g. paper forms and REDCap)

How to Avoid Reportable Events

Noncompliance continued…

- Training
  - Study Staff
  - Collaborators
- Communication
  - Frequency & methodology
  - Inclusive of entire research team and non-research collaborators
  - Address multi-site collaborations (if applicable)
- Quality Assurance
  - Appropriate ‘check steps’

How to Avoid Reportable Events

Subject Complaints

- Set Reasonable Expectations
- Be Clear in Your Communications
  - Recruitment
  - Consent Form
  - Study Materials
- Be Responsive
  - Subjects know who and how to contact research team
  - Inquiries returned in a timely fashion
- Honor your commitments
  - Compensation
  - Return of results

Available Resources

Don’t reinvent the wheel!

- Many institutions have templates (e.g. study protocol, case report forms) you can use
  - ITHS Study Document Templates - https://www.iths.org/investigators/forms-templates/study-document-templates/
- Consultations
  - Mentor/Experienced colleague
  - IRB Office

Case Studies - Questions

1. Is this a reportable event to the IRB?
2. Are there other offices this should be reported to?
3. What's the root cause of the event?
4. How would you solve the immediate problem?
5. What would you do to prevent the problem from occurring in the future (SMART)?
6. What could have been done to prevent the problem in the first place?

Introduction to Clinical Research Boot Camp 2019

Faculty Track -Wednesday, July 31

UW Husky Union Building

Room 250

8:30am-3:00pm

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Increase Study Success Through Integration of Team Science

Presented by Jennifer Sprecher & Nicole Summerside

8:30am-9:30am

UW Husky Union Building

ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

Increase Study Success through Engaged and Effective Research Teams

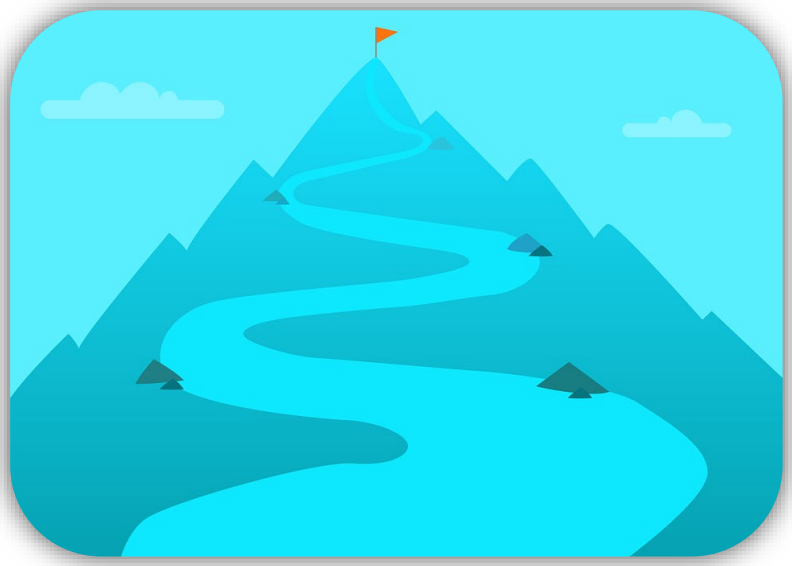
Jennifer Sprecher &

Nicole Summerside

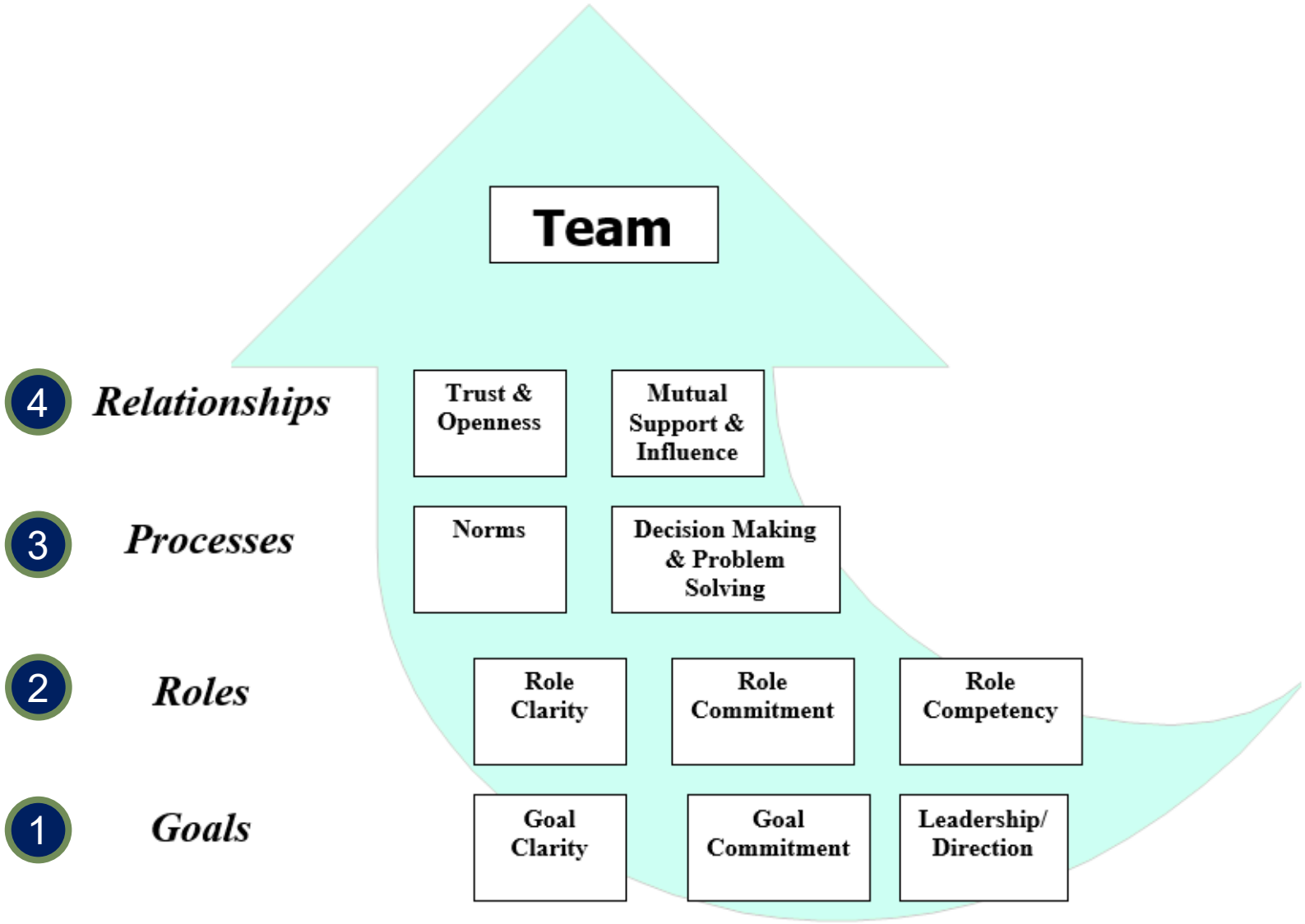
ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

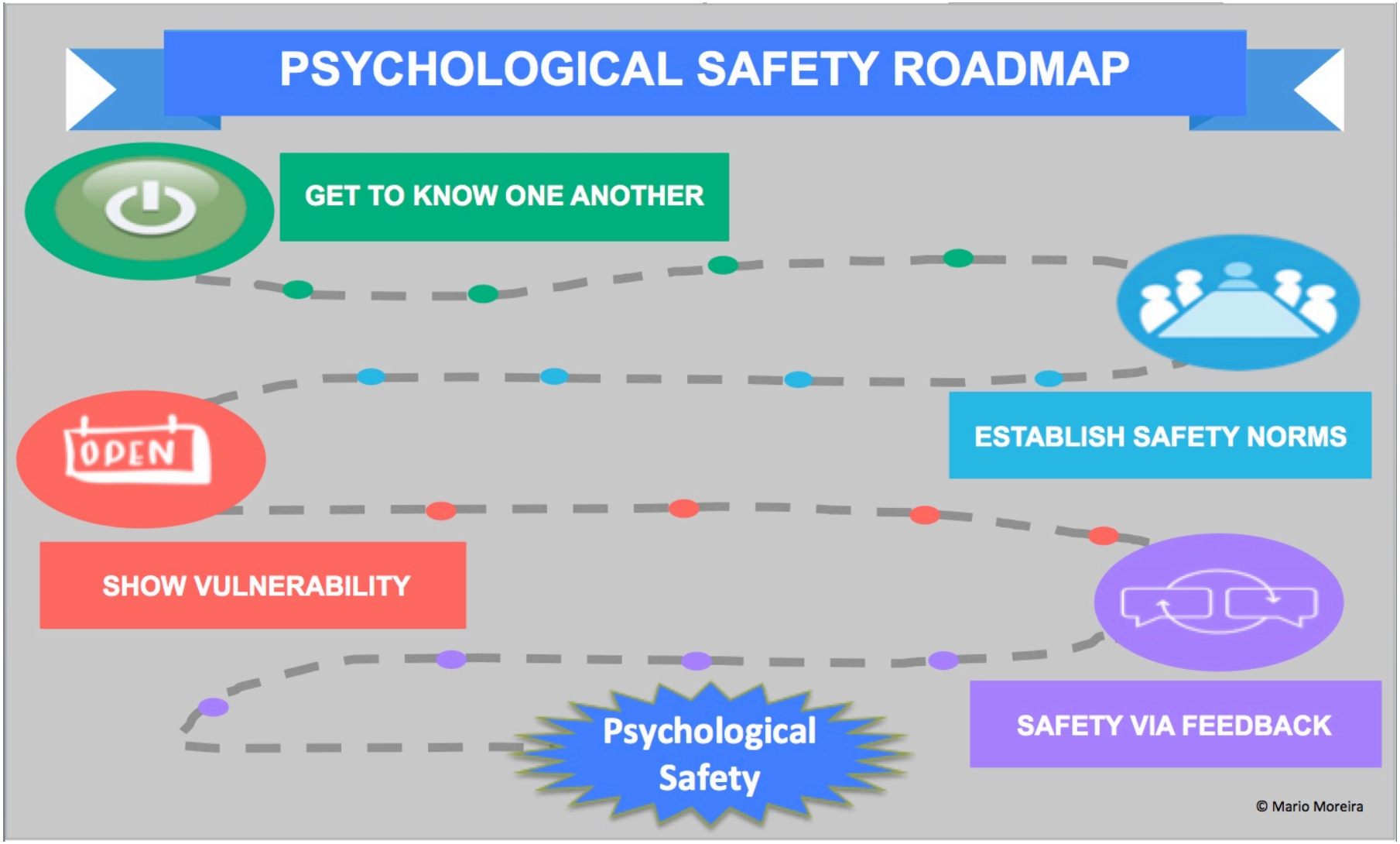
Learning Objectives

- Understand what drives effective and efficient teams
- Learn/practice strategies to improve team processes, roles, and goals

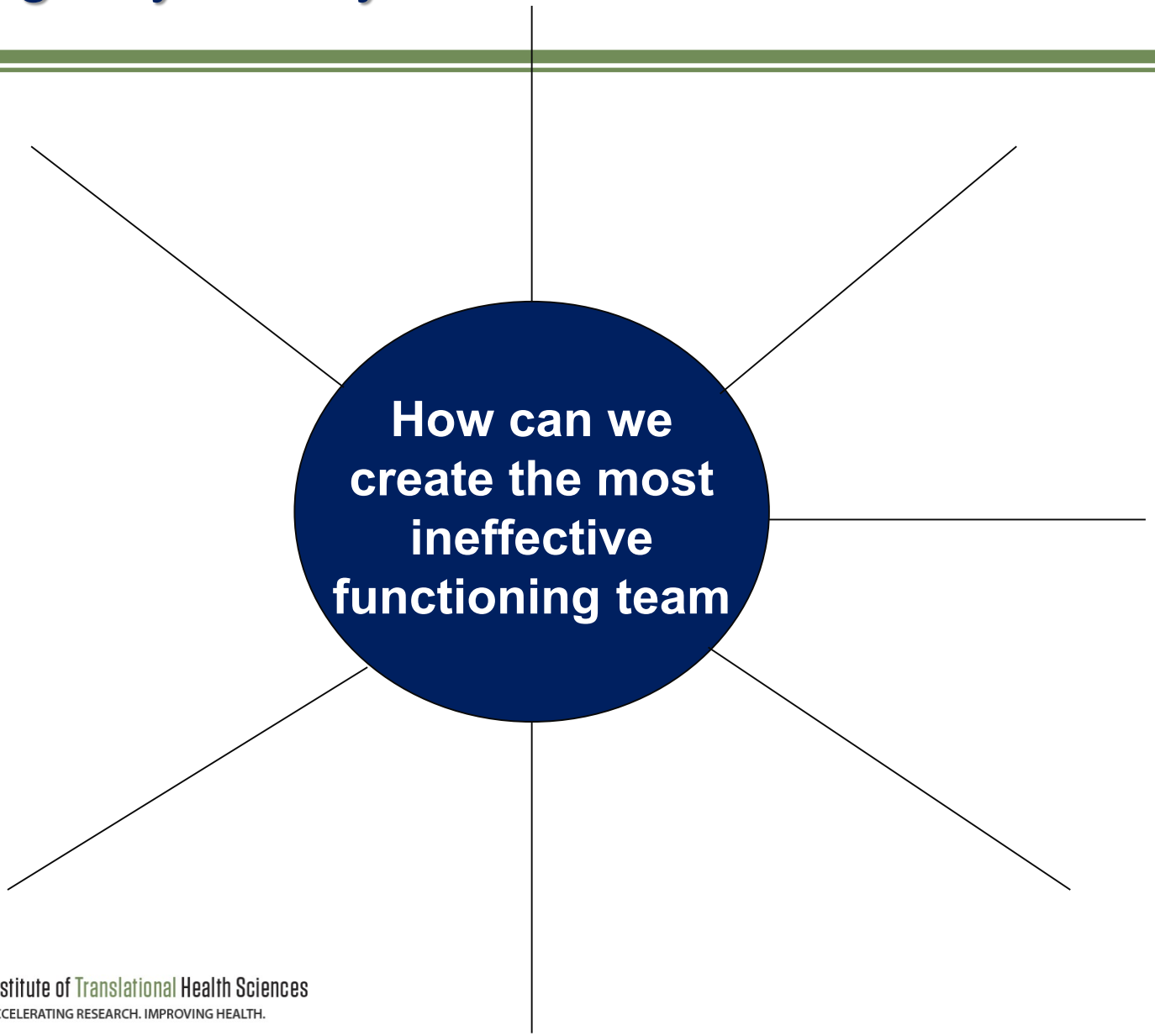


Managing Teamwork




PSYCHOLOGICAL SAFETY ROADMAP
GET TO KNOW ONE ANOTHER
ESTABLISH SAFETY NORMS
OPEN
SHOW VULNERABILITY
SAFETY VIA FEEDBACK
Psychological Safety
© Mario Moreira

Contingency Activity



Team Agreements

Team Agreement

In order to work effectively and efficiently we have outlined some basic tenants we have all agreed to follow. Throughout this project we will adhere to the following:

1. Attend meetings at agreed times
2. Meet all deadlines
3. Have a positive attitude
4. Do not ignore group communication
5. Be honest and willing to ask for help
6. Do not assume someone else is doing the work, communicate, take initiative!

CCU Team Agreements

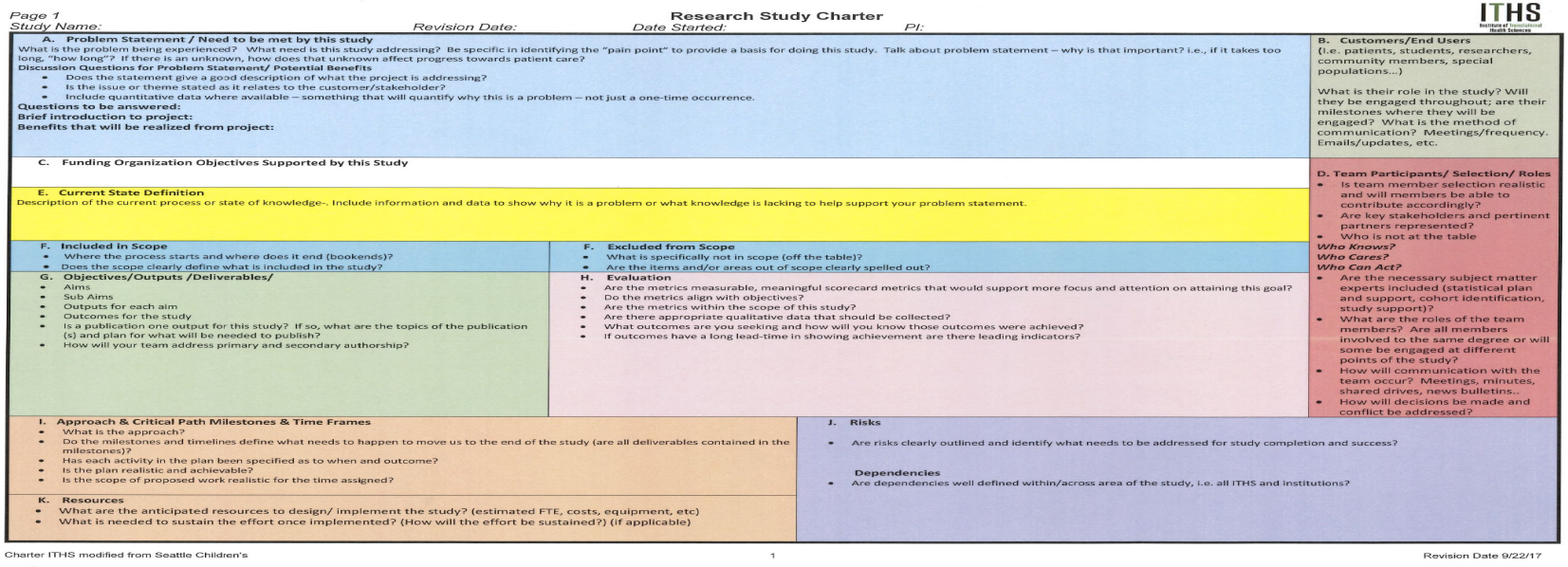
1. Suspend Assumptions
2. Listen, Don't Re-load
3. Balance Advocacy with Inquiry
4. Attribute Positive Intent
5. Minimize Interruptions
6. Strive to Participate

Written by members of the CCU on August 13, 2015

Lean Project Charters

BASED ON CONCEPTS WITHIN:

- Project management institute
- Agile
- Continuous improvement (PDSA)
- Theories of change management



Page 1

Research Study Charter

Study Name: Revision Date: Date Started: PI:

ITHS Institute of Translational Health Sciences

A. Problem Statement / Need to be met by this study

What is the problem being experienced? What need is this study addressing? Be specific in identifying the "pain point" to provide a basis for doing this study. Talk about problem statement – why is that important? i.e., if it takes too long, "how long"? If there is an unknown, how does that unknown affect progress towards patient care?

Discussion Questions for Problem Statement/ Potential Benefits

- Does the statement give a good description of what the project is addressing?
- Is the issue or theme stated as it relates to the customer/stakeholder?
- Include quantitative data where available – something that will quantify why this is a problem – not just a one-time occurrence.

Questions to be answered:

Brief introduction to project:

Benefits that will be realized from project:

B. Customers/End Users

(i.e. patients, students, researchers, community members, special populations…)

What is their role in the study? Will they be engaged throughout; are their milestones where they will be engaged? What is the method of communication? Meetings/frequency. Emails/updates, etc.

C. Funding Organization Objectives Supported by this Study

D. Team Participants/ Selection/ Roles

- Is team member selection realistic and will members be able to contribute accordingly?
- Are key stakeholders and pertinent partners represented?
- Who is not at the table

Who Knows?

Who Cares?

Who Can Act?

- Are the necessary subject matter experts included (statistical plan and support, cohort identification, study support)?
- What are the roles of the team members? Are all members involved to the same degree or will some be engaged at different points of the study?
- How will communication with the team occur? Meetings, minutes, shared drives, news bulletins..
- How will decisions be made and conflict be addressed?

E. Current State Definition

Description of the current process or state of knowledge-. Include information and data to show why it is a problem or what knowledge is lacking to help support your problem statement.

F. Included in Scope

- Where the process starts and where does it end (bookends)?
- Does the scope clearly define what is included in the study?

F. Excluded from Scope

- What is specifically not in scope (off the table)?
- Are the items and/or areas out of scope clearly spelled out?

G. Objectives/Outputs /Deliverables/

- Aims
- Sub Aims
- Outputs for each aim
- Outcomes for the study
- Is a publication one output for this study? If so, what are the topics of the publication (s) and plan for what will be needed to publish?
- How will your team address primary and secondary authorship?

H. Evaluation

- Are the metrics measurable, meaningful scorecard metrics that would support more focus and attention on attaining this goal?
- Do the metrics align with objectives?
- Are the metrics within the scope of this study?
- Are there appropriate qualitative data that should be collected?
- What outcomes are you seeking and how will you know those outcomes were achieved?
- If outcomes have a long lead-time in showing achievement are there leading indicators?

I. Approach & Critical Path Milestones & Time Frames

- What is the approach?
- Do the milestones and timelines define what needs to happen to move us to the end of the study (are all deliverables contained in the milestones)?
- Has each activity in the plan been specified as to when and outcome?
- Is the plan realistic and achievable?
- Is the scope of proposed work realistic for the time assigned?

J. Risks

- Are risks clearly outlined and identify what needs to be addressed for study completion and success?

Dependencies

- Are dependencies well defined within/across area of the study, i.e. all ITHS and institutions?

K. Resources

- What are the anticipated resources to design/ implement the study? (estimated FTE, costs, equipment, etc)
- What is needed to sustain the effort once implemented? (How will the effort be sustained?) (if applicable)

Charter ITHS modified from Seattle Children's 1 Revision Date 9/22/17

Clarifying the Objective (Section A)

PROBLEM STATEMENT

- What problem or issues is your project addressing?
- What are the benefits of addressing this issues?
- What are the objectives of your project?

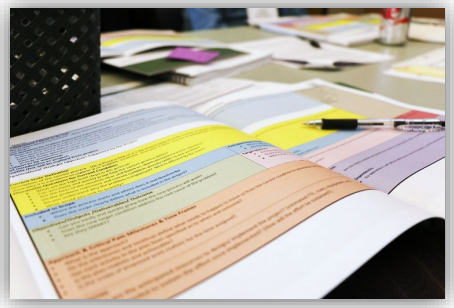
The Team (Section D)

Members

- E.g. sponsor, team lead, facilitator, member, subject matter expert
- Who knows? Who cares? Who can act?

Purpose

- Who are you representing? (e.g. researchers, community, underserved populations, disciplines/departments)



Communication

- Involvement (i.e. attend all meetings or as requested)
- Action items
- Modes of communication

RESOURCES

- Annual Team Science Boot Camp
- Leadership and Team Coaching
- Facilitation Work/Services

CONTACT US

- Jennifer Sprecher: sprechj@uw.edu
- Nicole Summerside: nicoles1@uw.edu

CONNECT WITH ITHS

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Visit ITHS.org to Become an ITHS Member

Join a unique catalyst that accelerates discoveries to practice.

Access

Members gain access the different research services, resources, and tools offered by ITHS, including the ITHS Research Navigator.

Education and Training

Members can access a variety of workforce development and mentoring programs and apply for formal training programs.

Funding

Members can apply for local and national pilot grants and other funding opportunities. ITHS also offers letters of support for grant submissions.

Collaboration

Members can connect with collaborators across the CTSA consortium.

Protocol Design: Balancing Scientific Validity

Presented by Andrei Shustov, MD

9:40am-10:40am

UW Husky Union Building

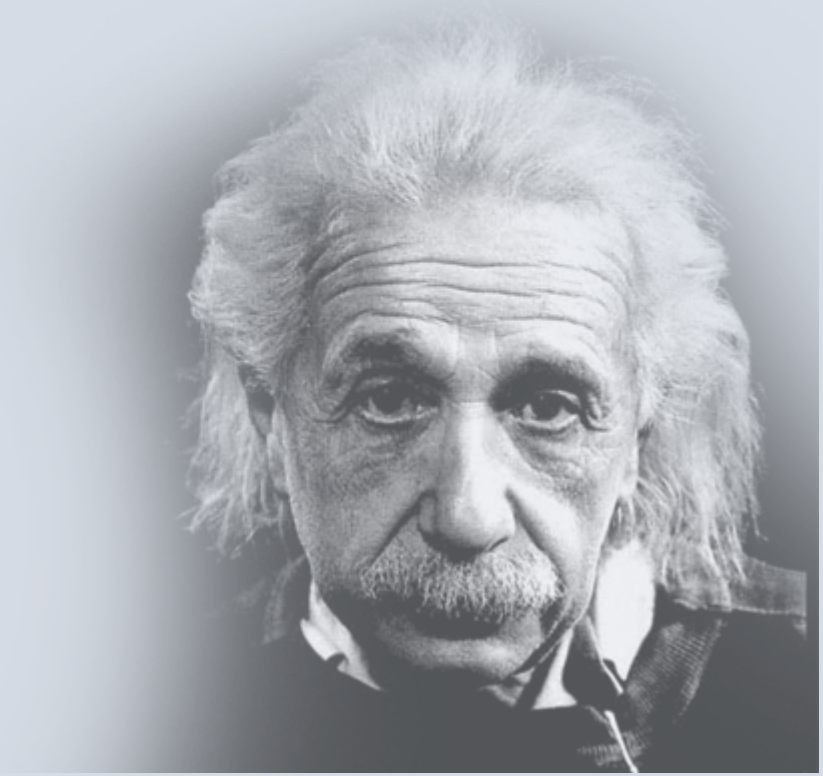
ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

Protocol Design: Balancing Scientific Validity with Ethical Approaches and Pragmatic Operations

Andrei Shustov, MD
Professor of Medicine
University of Washington
Fred Hutchinson Cancer Research Center

"If we knew what it is we were doing, it wouldn't be called research, would it?"

Albert Einstein



The goals of clinical trials

- Researcher perspective
  - Discover new treatments
  - Evaluate measurable endpoints (i.e. ORR, CR, DOR..)
  - Create new knowledge about Dz
  - Advance career
- Patient perspective
  - Cure, prolong life, improve symptoms
  - Minimize side effects
  - Improve quality of life

Ethical pitfalls of clinical trials

- Phase I
  - Majority of patients are treated at ineffective dose
  - Not powered to assess early efficacy
  - Majority of patients are heavily pretreated and are most susceptible to side effects and lack of efficacy
  - Potential risk over benefit is underemphasized
  - The goal of the study is not sufficiently conveyed to patient population
  - Vulnerable populations are at increased risk
  - End-of-life burden for unlikely benefit

Ethical pitfalls of clinical trials

- Phase II
  - Very exclusive patient population resulting in limited generalization potential
  - Not powered to fully assess toxicity burden
  - Primary objectives are not aligned with patient's goal
  - Very demanding schedules
  - The goal of the study is not sufficiently conveyed to patients
  - Vulnerable populations have limited access
  - Treatment-related QOL burden is under-evaluated

Ethical pitfalls of clinical trials

- Phase III
  - Randomization process
    - Study patients lack access to new therapy
    - Introduced investigator bias
    - Often powered for drug approval and not patient benefit
    - Phase II efficacy looks much better then historical SOC
  - Study powered for efficacy and not toxicity
  - Futility boundary identified “too late”
  - Burdensome enrolment process excludes high risk patients
    - Overestimates efficacy of experimental arm
    - Underestimates efficacy of experimental arm

Ethical pitfalls: special topics

- Informed consent:
  - Should all patients undergoing interventional trials be consented?
  - Does informed consent compromise scientific soundness of the clinical trial?
  - What are special situations?
  - Way around informed consent?

  - Should all of the cancer patients be considered a “vulnerable population”?
  - Should terminal cancer patients considered a “vulnerable population”?

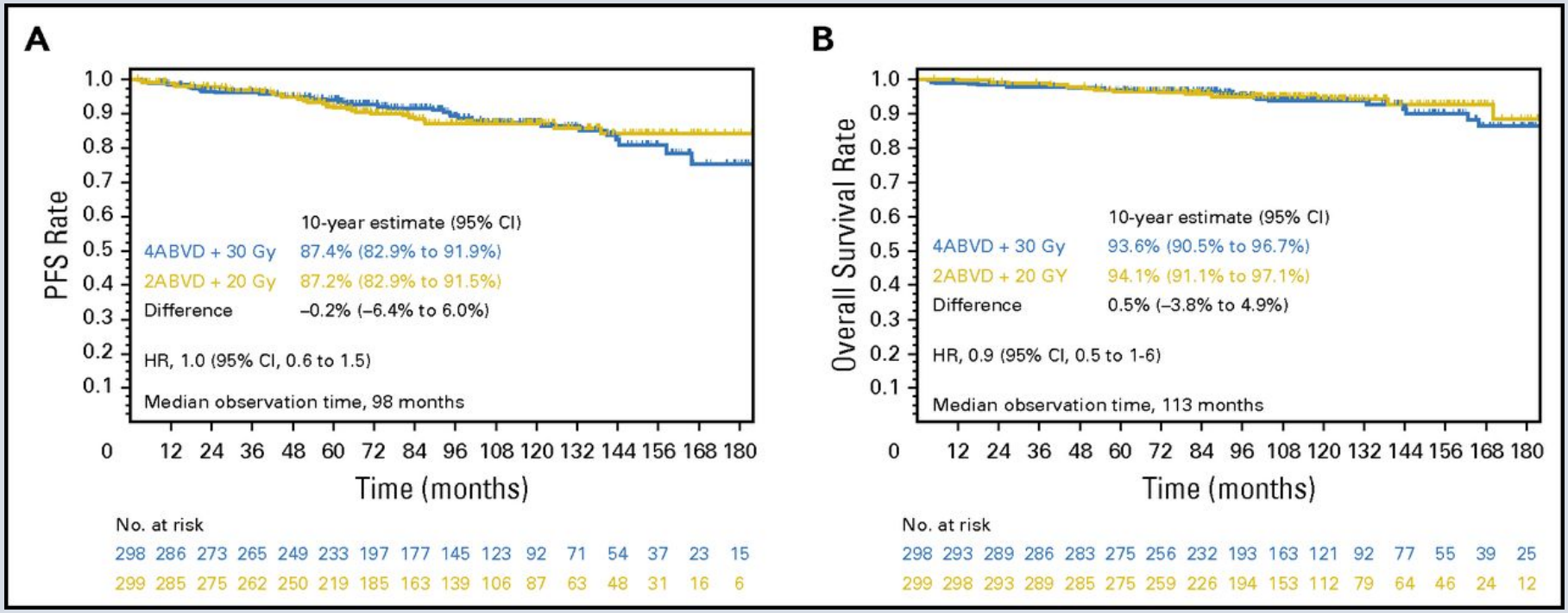
Scientific pitfalls of clinical trials

- All Phases
  - Informed consent compromises scientific soundness
  - Patient non-compliance
  - Rigidness of study designs and protocols
  - Diversity of disease biology and genomics
  - Diversity of pharmacogenomics and immunogenetics of the host (patient)
  - Ethical and regulatory barriers to correlative studies
  - Financial limitations to conduct a comprehensive trial

Operational pitfalls of clinical trials

- All Phases
  - Cost of personnel and materials
  - Facility limitations
  - Patient's preferences
  - Multi-center challenges
  - Central review panel challenges
  - Real time communication challenges across time zones
  - Financial limitations to conduct a comprehensive trial

Early stage Hodgkin Lymphoma

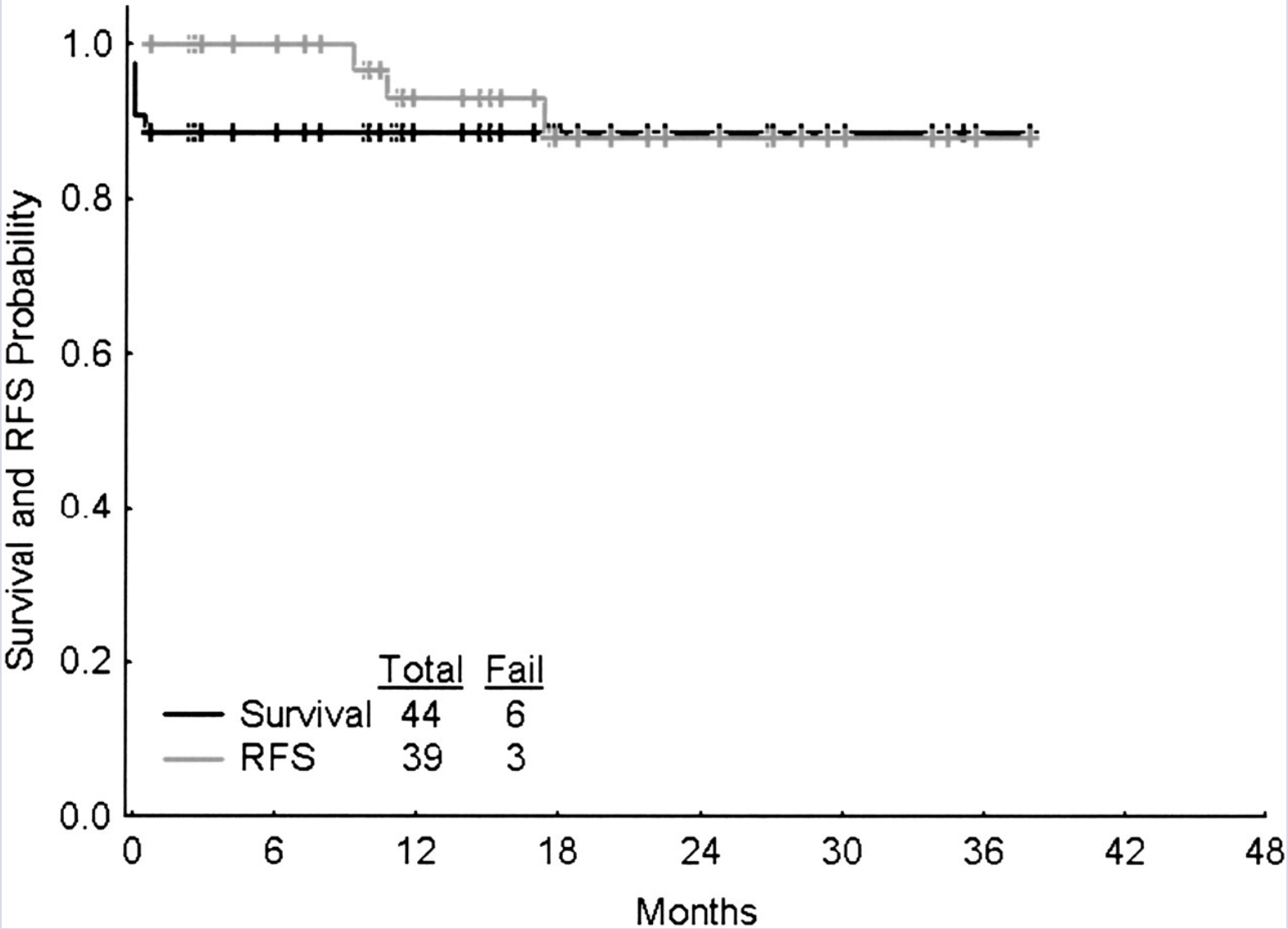


Paul J. Bröckelmann et al. Blood 2018;131:1666-1678

- Should this population be subject to clinical trials?

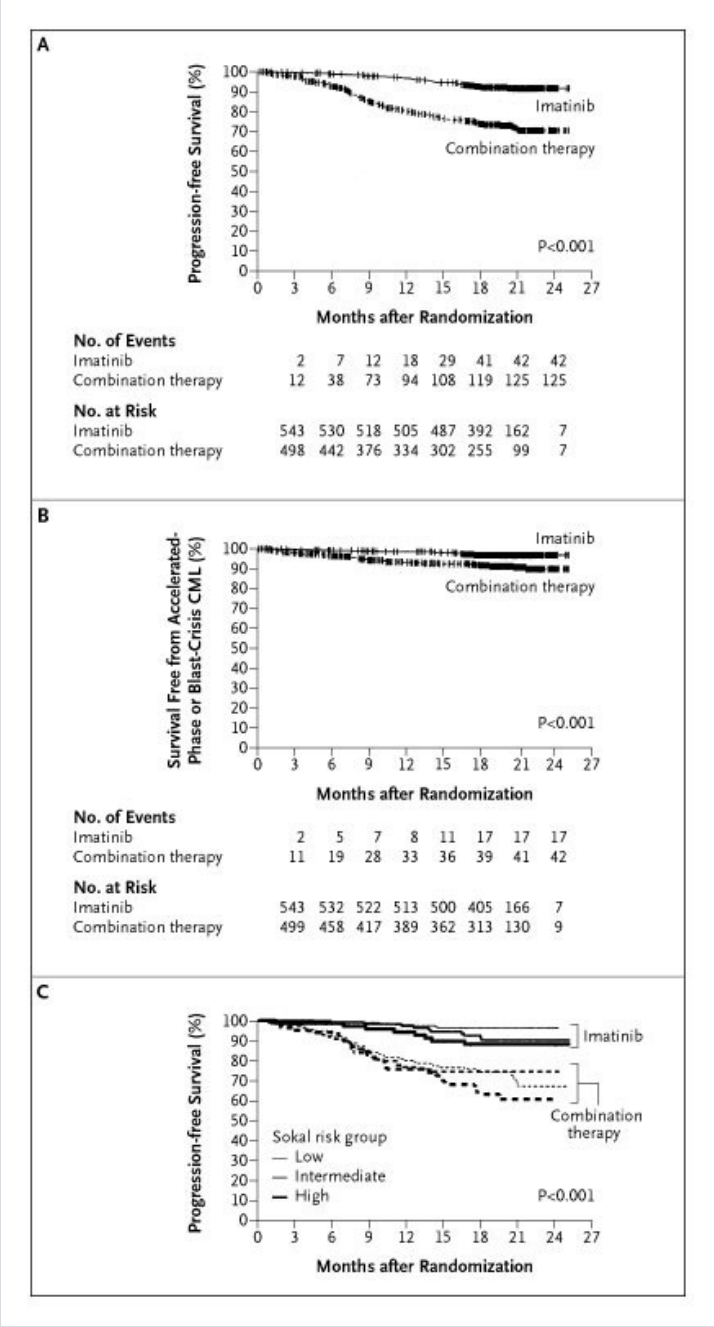
- What are the goals of such studies?

Acute Promyelocytic Leukemia



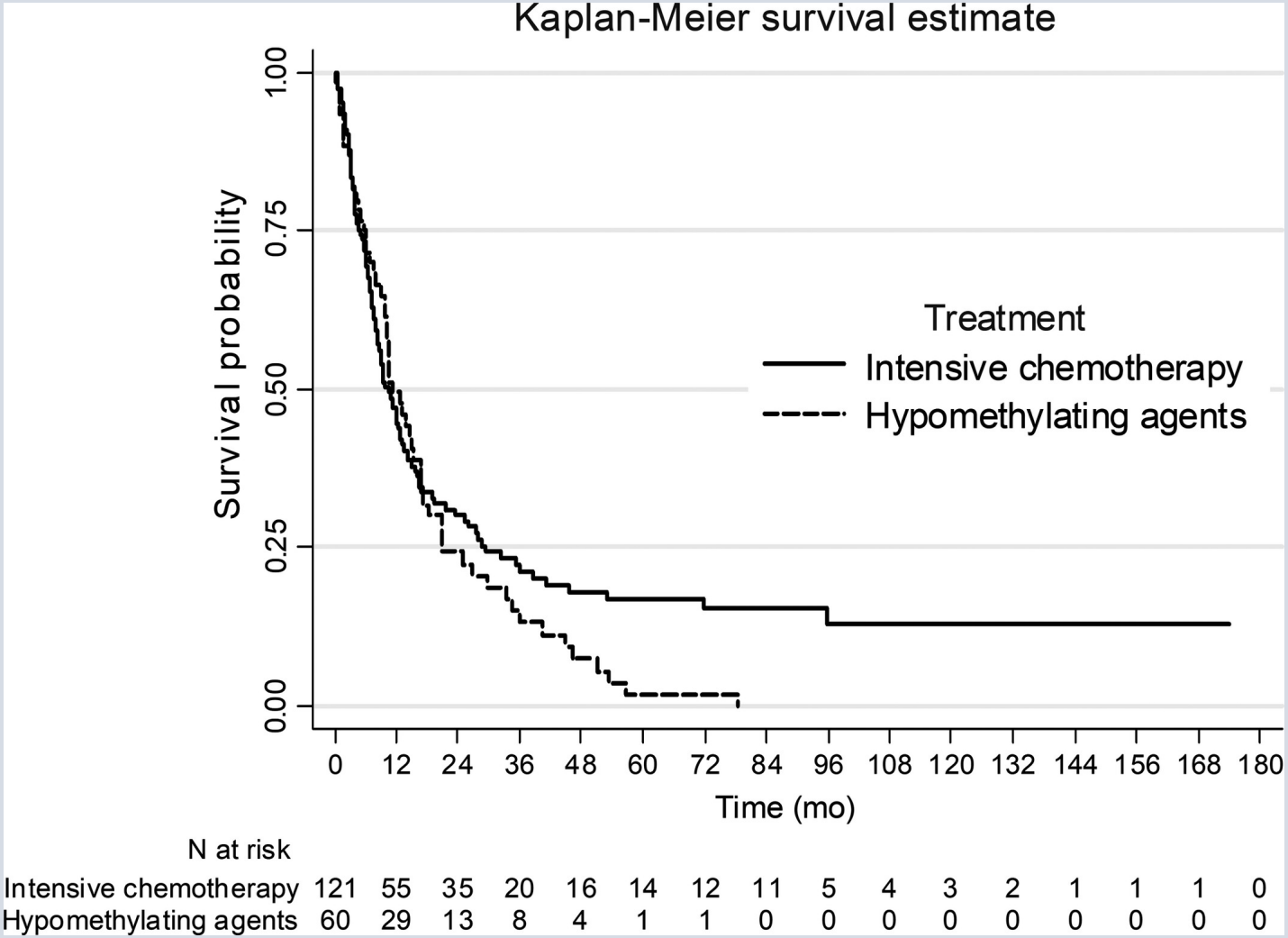
Elihu Estey et al. Blood 2006;107:3469-3473

Chronic Myeloid Leukemia



S. O'Brien et al. N Engl J Med 2003;348:994-1004

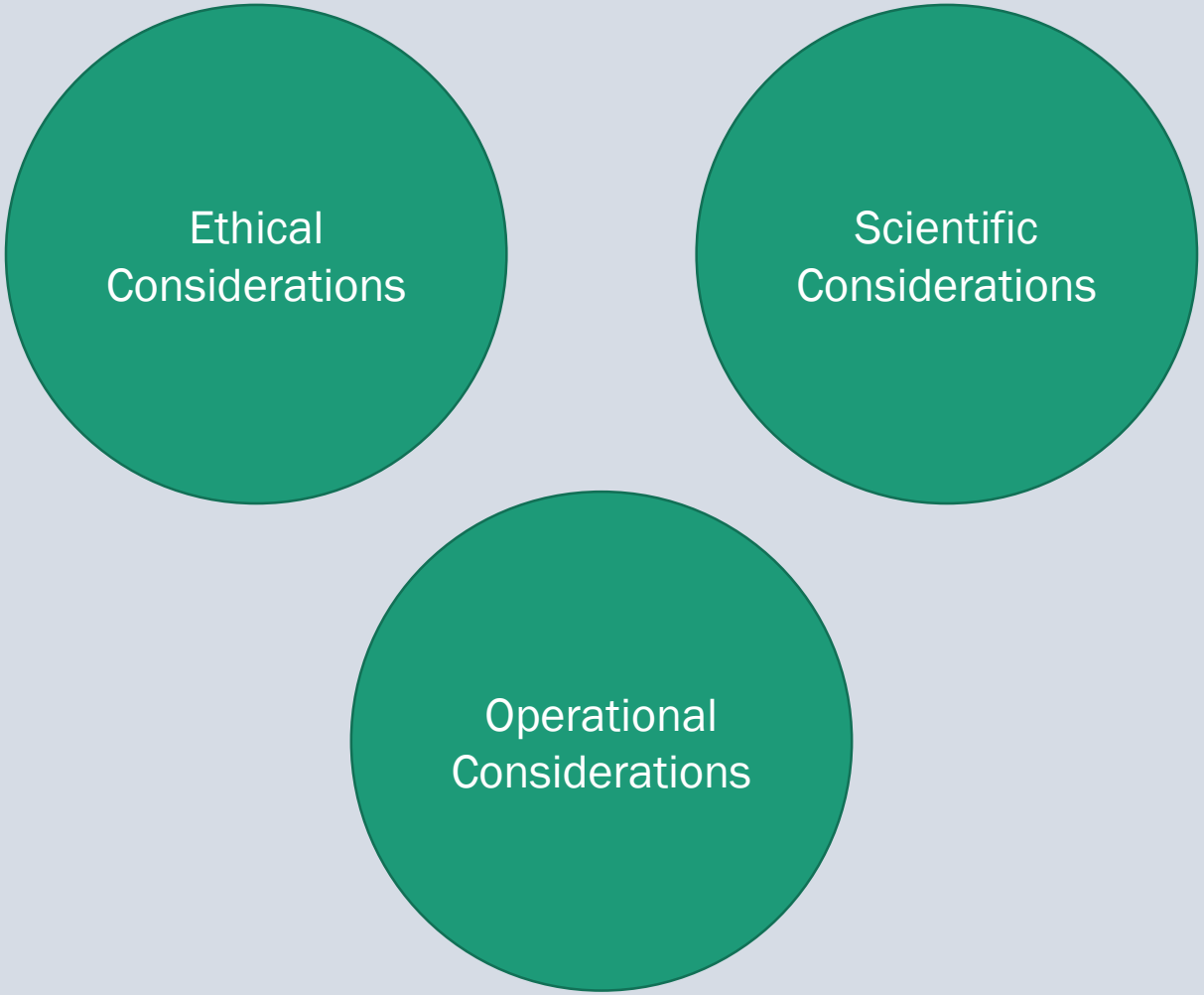
Secondary Acute Myeloid Leukemia in Elderly

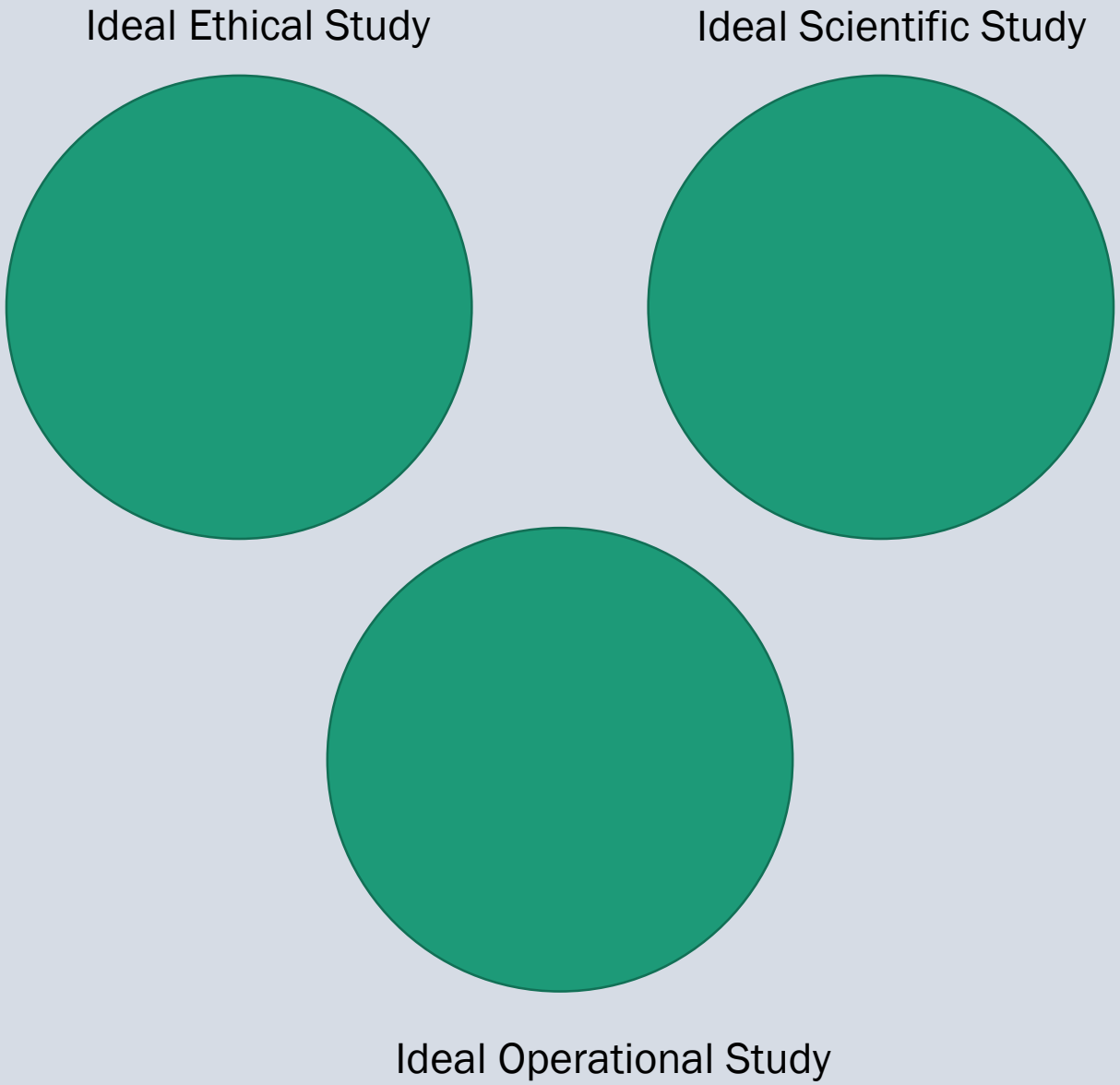


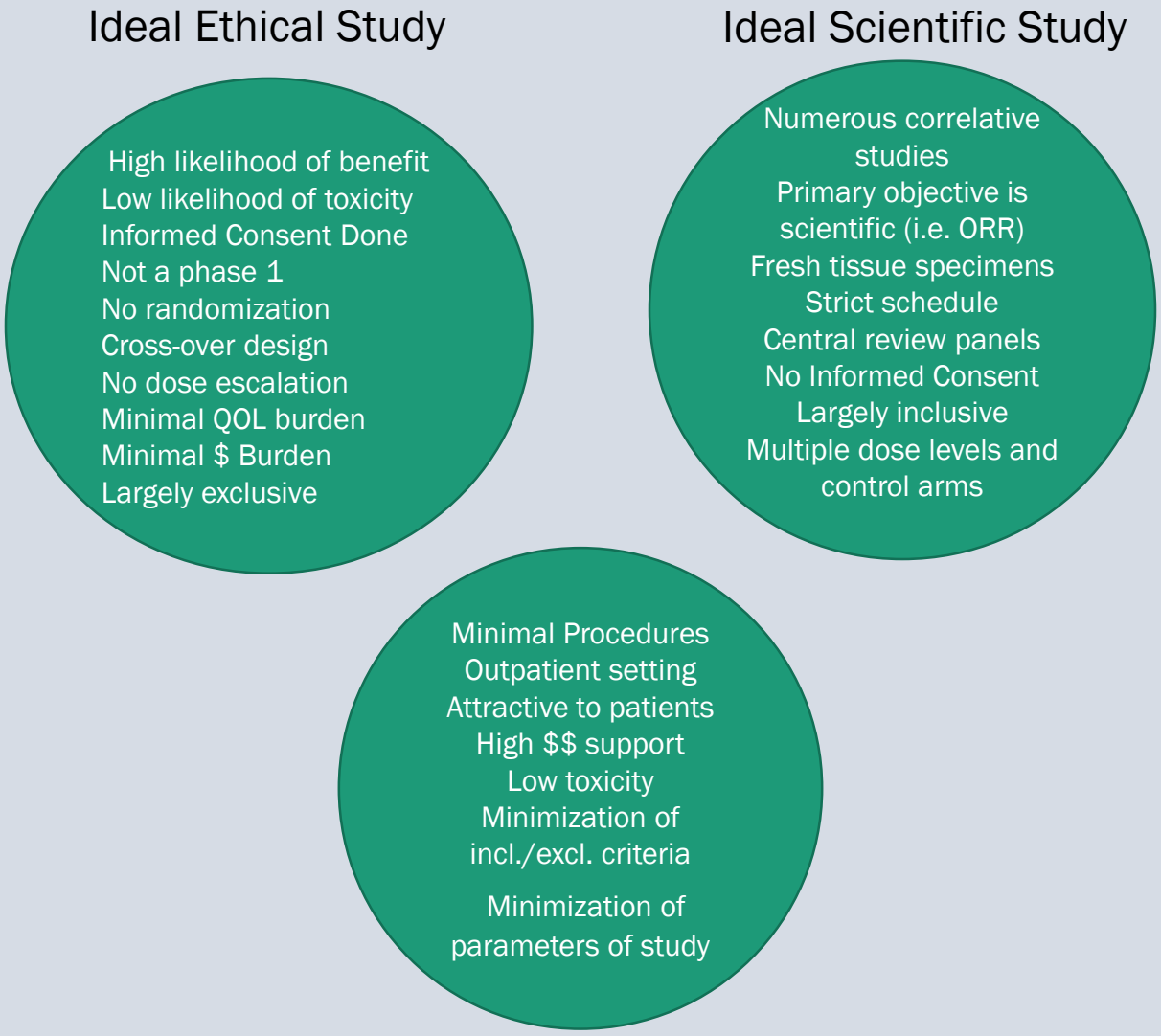
S. Bertoli et al. Cancer Medicine 2019; 8:

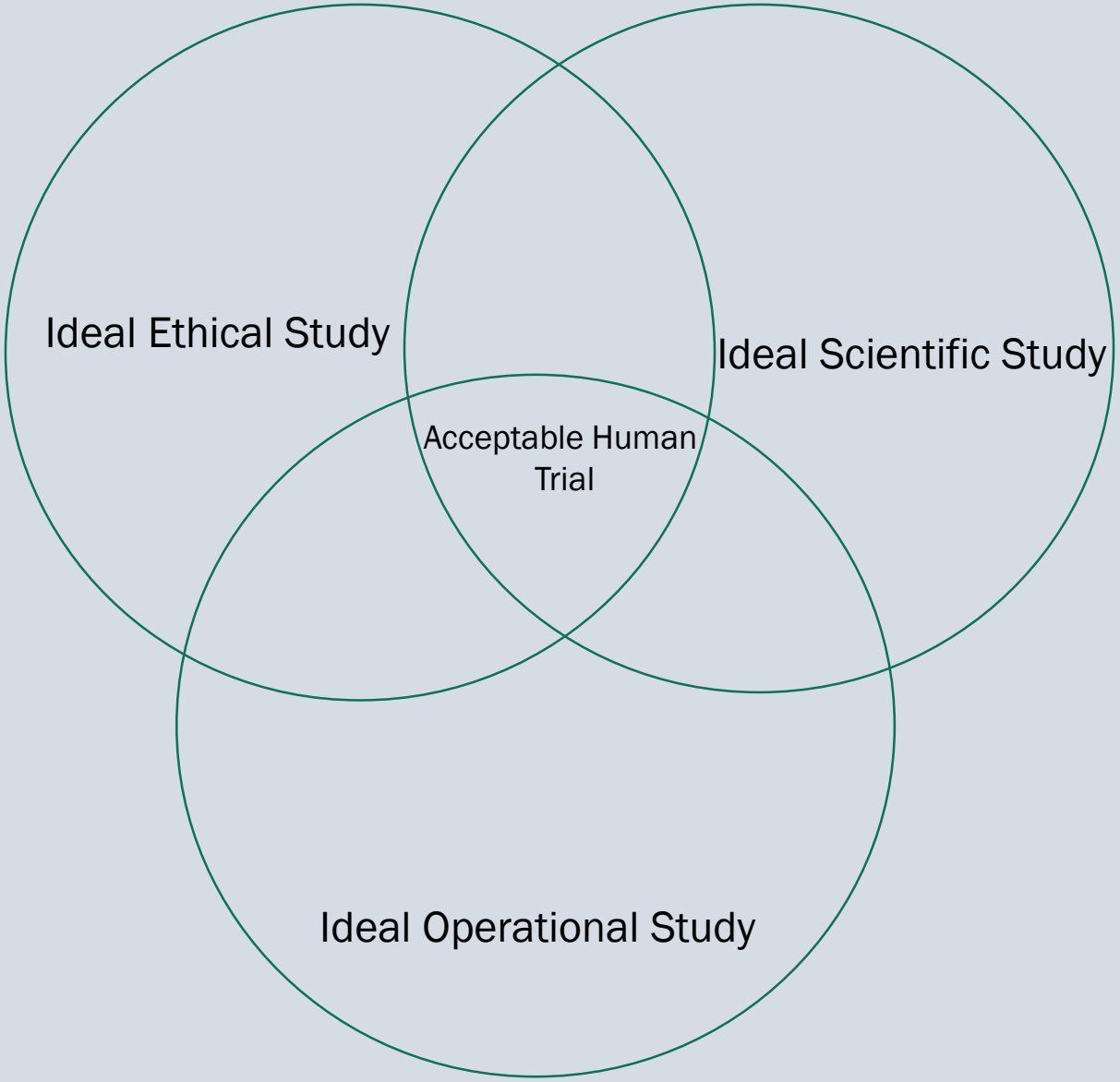
- Should this population be subject to clinical trials?

- What are the goals of such studies?


Ethical Considerations
Scientific Considerations
Operational Considerations


Ideal Ethical Study
Ideal Scientific Study
Ideal Operational Study


Ideal Ethical Study
High likelihood of benefit
Low likelihood of toxicity
Informed Consent Done
Not a phase 1
No randomization
Cross-over design
No dose escalation
Minimal QOL burden
Minimal $ Burden
Largely exclusive
Ideal Scientific Study
Numerous correlative studies
Primary objective is scientific (i.e. ORR)
Fresh tissue specimens
Strict schedule
Central review panels
No Informed Consent
Largely inclusive
Multiple dose levels and control arms
Minimal Procedures
Outpatient setting
Attractive to patients
High $$ support
Low toxicity
Minimization of incl./excl. criteria
Minimization of parameters of study
Ideal Operational Study

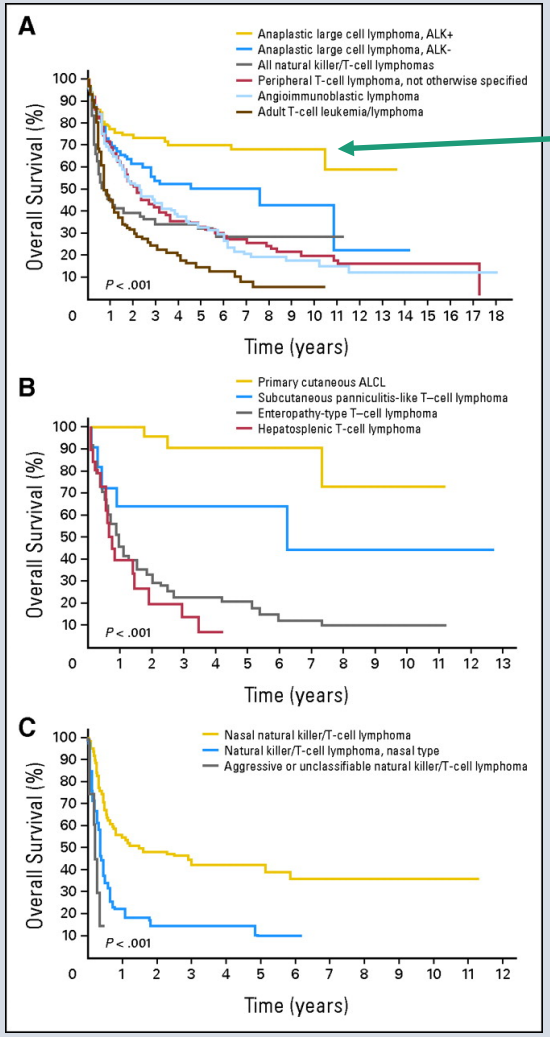

Ideal Ethical Study
Ideal Scientific Study
Acceptable Human Trial
Ideal Operational Study

A Phase IA/IB Open-Label Dose-Finding Study of Ceritinib Combined with Brentuximab Vedotin for Front-Line Treatment of ALK-positive Anaplastic Large Cell Lymphoma

Principal Investigator:

Dr. Andrei Shustov

09/21/2017


A
Anaplastic large cell lymphoma, ALK+
Anaplastic large cell lymphoma, ALK-
All natural killer/T-cell lymphomas
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic lymphoma
Adult T-cell leukemia/lymphoma
Overall Survival (%)
P < .001
Time (years)
B
Primary cutaneous ALCL
Subcutaneous panniculitis-like T–cell lymphoma
Enteropathy-type T–cell lymphoma
Hepatosplenic T-cell lymphoma
Overall Survival (%)
P < .001
Time (years)
C
Nasal natural killer/T-cell lymphoma
Natural killer/T-cell lymphoma, nasal type
Aggressive or unclassifiable natural killer/T-cell lymphoma
Overall Survival (%)
P < .001
Time (years)

ALK+ ALCL

Selected Study Design Basics

- Brentuximab Vedotin: ORR 79%, CR 59%
  - 5-year CR-PFS > 80%
- Ceritinib: Lung Ca ORR 58%; ALCL CR ~ 80%
- bCRM design
- Early stopping rules
- Rigid futility boundary
- Patient #4 risk failure < 2%

CALGB/Alliance 50303: R-CHOP vs DA-EPOCH-R in Newly Diagnosed Diffuse Large B-Cell Lymphoma

Bartlett N et al. *J Clin Onc* 2019; 37

Andrei Shustov, MD
University of Washington
Fred Hutchinson CRC

CALGB/Alliance 50303: Background

- DLBCL: disease with clinically and molecularly different subtypes[1]
  - GCB subtype
  - ABC subtype
- R-CHOP: standard of care for DLBCL[2]
  - Multicenter phase III trial found 5-yr PFS of approximately 65%[3]
- DA-EPOCH-R: dose-intensive treatment alternative
  - Multicenter phase II trial found 5-yr TTP of 81% and 5-yr OS of 84% with DA-EPOCH-R[4]
- Current CALGB/Alliance 50303 compared R-CHOP vs DA-EPOCH-R in pts with untreated stage II-IV DLBCL (subtypes GCB and ABC)[5]

1. Lenz G, et al. N Engl J Med. 2008;359:2313-2323. 2. Sehn LH, et al. Blood. 2015;125:22-32.
3. Cunningham D, et al. Lancet Oncol. 2013;14:1306-1315. 4. Wilson WH, et al. Haematologica. 2012;97:758-765. 5. Wilson WH, et al. ASH 2016. Abstract 469.

Define a Perfect Study

- Does it exist?
- If it does:
  - Prospective
  - Randomized
  - Double-blind
  - Stratified
- Power factors:
  - Multi-center
  - High number of patients
- Hidden pitfalls
  - Selection bias
  - Treatment complexity
  - Excessive burden/delay of Tx
  - Genomic diversity of Dz under study

Define a Perfect Study

- Does it exist?
- If it does:
  - Prospective √
  - Randomized √
  - ~~Double-blind~~
  - Stratified √
- Power factors:
  - Multi-center √
  - High number of patients √
- Hidden pitfalls
  - Selection bias √
  - Treatment complexity √
  - Excessive burden/delay of Tx √
  - Genomic diversity of Dz under study √

CALGB/Alliance 50303: Study Design

- Randomized phase III study

Untreated, newly diagnosed stage II-IV DLBCL (stage I PMBCL), ECOG PS 0-2, LVEF > 45%, tumor biopsies available, no CNS disease
(N = 465)

6 cycles

DA-EPOCH-R*
Rituximab 375 mg/m^2 IV
Cyclophosphamide† 750 mg/m^2 IV
Doxorubicin† 10 mg/m^2 IV on Days 1-4
Etoposide† 50 mg/m^2 IV on Days 1-4
Vincristine 0.4 mg/m^2 IV on Days 1-4
Prednisone 60 mg/m^2 BID on Days 1-5
G-CSF as needed SC on Days 6-12
(n = 262)

R-CHOP*
Rituximab 375 mg/m^2 IV
Cyclophosphamide 750 mg/m^2 IV
Doxorubicin 50 mg/m^2 IV
Vincristine 1.4 mg/m^2 IV (max 2 mg)
Prednisone 40 mg/m^2 PO on Days 1-5
G-CSF as needed SC
(n = 262)

- Primary endpoint: EFS
- Secondary endpoints:
  - RR
  - OS
  - Safety

*Included CNS prophylaxis if BM/testicular involvement or elevated LDH plus ≥ 2 extranodal sites. Prophylaxis: MTX IT x 4 doses on Day 1 of Cycles 3-6.
†Increased 20% if ANC nadir > 0.5. De-escalated if ANC < 0.5 for > 3 days.

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: Baseline Characteristics

Characteristic	R-CHOP	DA-EPOCH-R	*P* Value
Median age, yrs (range)	58 (18-86)	58 (19-84)	.85
ECOG PS, %			.20
▪ 0/1	88	87	
▪ 2	12	13	
Stage, %			.66
▪ 1 (PMBCL)	3	3	
▪ 2	22	20	
▪ 3	29	25	
▪ 4	46	52	
IPI criteria, %			.60
▪ 0/1	27	25	
▪ 2	39	36	
▪ 3	25	26	
▪ 4/5	10	13	

- No significant differences in characteristics between treatment arms

Bartlett N et al. *J Clin Onc* 2019; 37

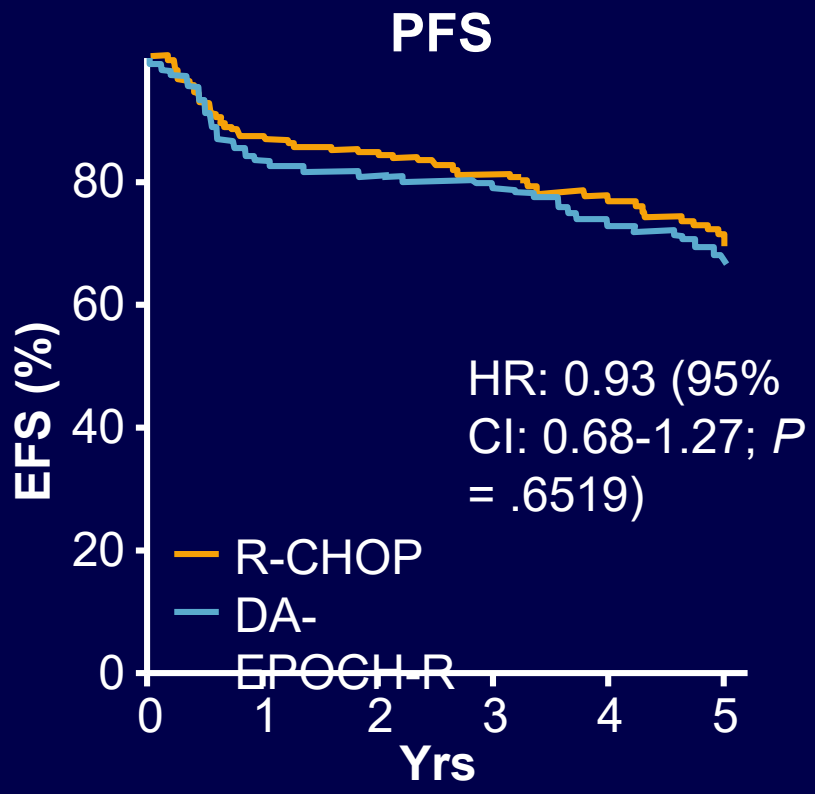
CALGB/Alliance 50303: Response Outcomes

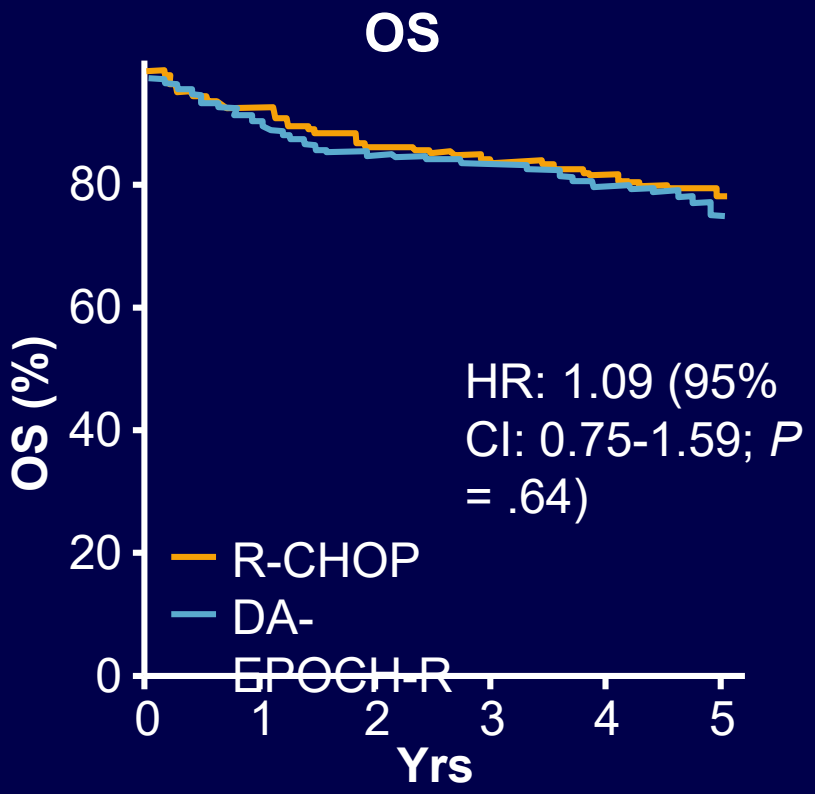
Response, %	R-CHOP	DA-EPOCH-R	*P* Value
ORR	88.0	86.7	.67
▪ CR/CRu	59.6	61.1	
▪ PR	28.4	25.6	
▪ SD	9.2	12	
▪ PD	2.8	1.3	

- No significant difference in response rates between treatment arms

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: Event-Free Survival and OS





Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	250	83	0.72 (0.67-0.78)	0.66 (0.60-0.72)
DA-EPOCH-R	241	76	0.76 (0.70-0.81)	0.68 (0.62-0.74)

Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	250	53	0.85 (0.80-0.89)	0.78 (0.73-0.84)
DA-EPOCH-R	241	56	0.85 (0.79-0.89)	0.77 (0.72-0.83)

Bartlett N et al. *J Clin Onc* 2018;37

CALGB/Alliance 50303: PFS by Age and IPI Score

5-Yr PFS by Subgroup, %	Pts	ALL	R-CHOP	DA-EPOCH-R	*P* Value
Age					
▪ ≤ 60 yrs	59	71	73	70	.073
▪ > 60 yrs	41	63	65	61	
IPI criteria					
▪ 0/1	27	82	90	72	
▪ 2	38	70	72	68	< .001
▪ 3	25	55	50	61	
▪ 4/5	10	53	40	60	

- Posttreatment substudy (n = 171) using PET found no significant difference in 3-yr PFS between PET-positive and PET-negative subsets (80% vs 72%; *P* = .057)

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: AEs

AEs Grade 3-4, %	R-CHOP	DA-EPOCH-R	*P* Value
Treatment-related deaths*	5	5	.975
All grade 3-4 AEs	76.3	96.5	< .001
▪ Hematologic	73.7	97.5	< .001
▪ Nonhematologic	43.2	72.2	< .001
ANC	68	96	< .001
Platelets	11	65	< .001
Febrile neutropenia	18	35	< .001
Infection	11	17	.049
Mucositis	2.1	8.4	.0017
Neuropathy			
▪ Sensory	3.3	18.6	< .001

*5 deaths per arm. R-CHOP: congestive heart failure, 1; CNS bleed, 1; infection, 1; febrile neutropenia, 1; unknown, 1. DA-EPOCH-R: infection, 2; myocardial infarction, 1; unknown, 2.

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: Conclusions

- No differences between R-CHOP vs DA-EPOCH-R for EFS and OS with 5-yr follow-up
- No benefit with DA-EPOCH-R identified among clinical subgroups defined by age and IPI criteria
- Moderately increased rates of grade 3-5 AEs in the DA-EPOCH-R arm vs R-CHOP arm (cytopenias, febrile neutropenia, neuropathy)
- Investigators plan to perform future correlative analyses to potentially identify prognostic subsets, novel treatment targets, and new response or toxicity biomarkers

Bartlett N et al. *J Clin Onc* 2019; 37

Remaining Role For DA-EPOCH-R in DLBCL

- Myc+ DLBCL (?)
- DE DLBCL (?)
- DH DLBCL (?)
- High-Ki67 DLBCL (?)
- High-IPI DLBCL (?)

The Study Start-Up Process

Presented by Emily Cox, PhD

10:50pm-11:50pm

UW Husky Union Building

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ACCELERATING RESEARCH. IMPROVING HEALTH.

The study start-up process

Navigating the sequence and timing of reviews, approvals, and resources before your study starts

Emily Cox, PhD, ACSM CEP
Project Manager/Scientific Publication Writer
Providence Medical Research Center

Today's topics

- How to navigate extramural research
  - Federally funded trials
  - Industry-funded trials
- How to analyze failures and initiate process improvements

- Objective
  - Understand infrastructure maturity requirements for clinical research
  - Understand the general pathway for study start-up
  - Know how to conduct an after-action review

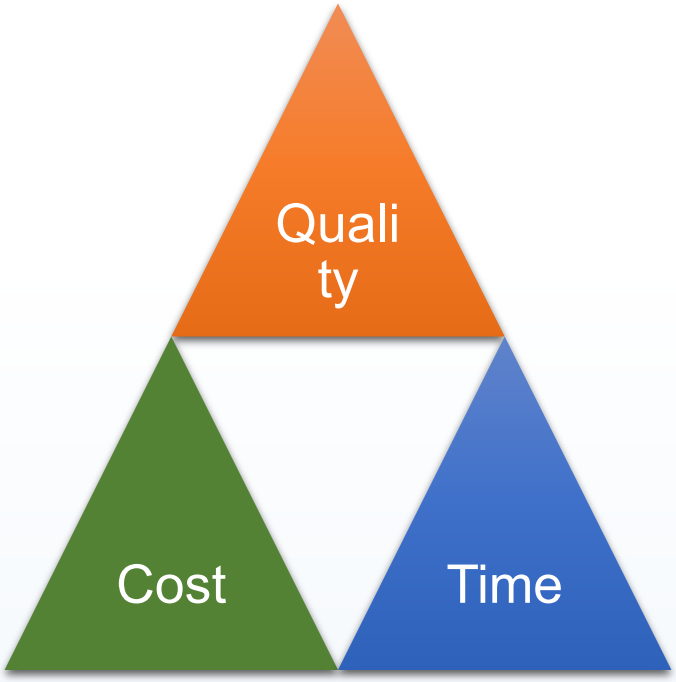

Writing
Grant submission
Funding
Start-up

“Why does start-up take so long?”

PROVIDENCE Health & Services

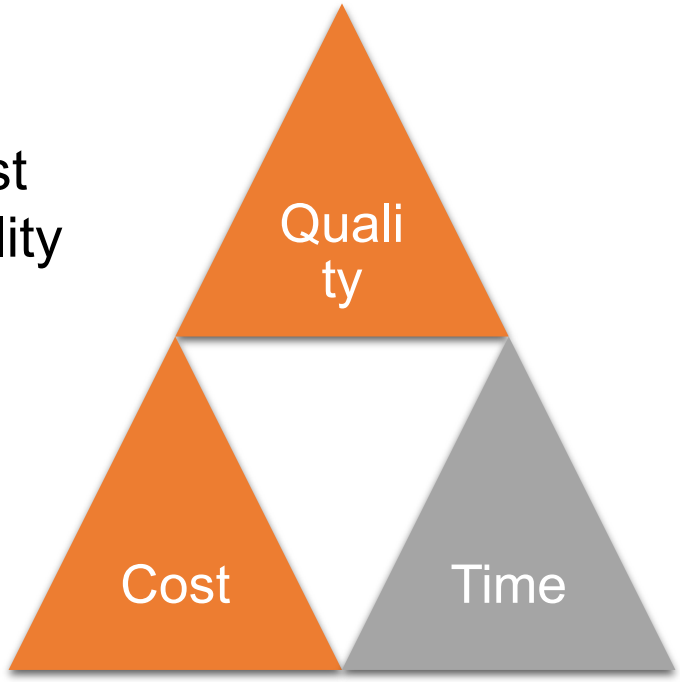
- Slow CRO responses
- Legal or compliance questions
- Sponsor acquisition
- Inexperienced sponsor team
- New hardware
- New software
- Contracting with 3rd party suppliers
- Staff PTO
- Insufficient feasibility assessment
- Regulatory disagreements
- Medical device purchasing
- Lack of subject injury protection
- Investigator loss of interest
- IRB turnaround times
- Staff turnover
- Changes in workload
- Protocol amendments
- Unexpected study closure
- Budget stalemate
- Change of clinic location
- Pharmacy issues

Project management constraints

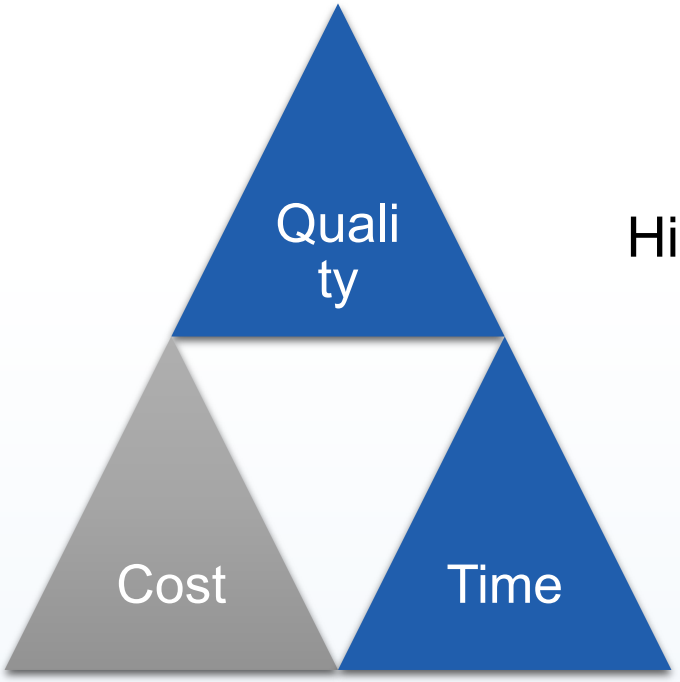


Project management constraints

Low cost
High quality
Slow

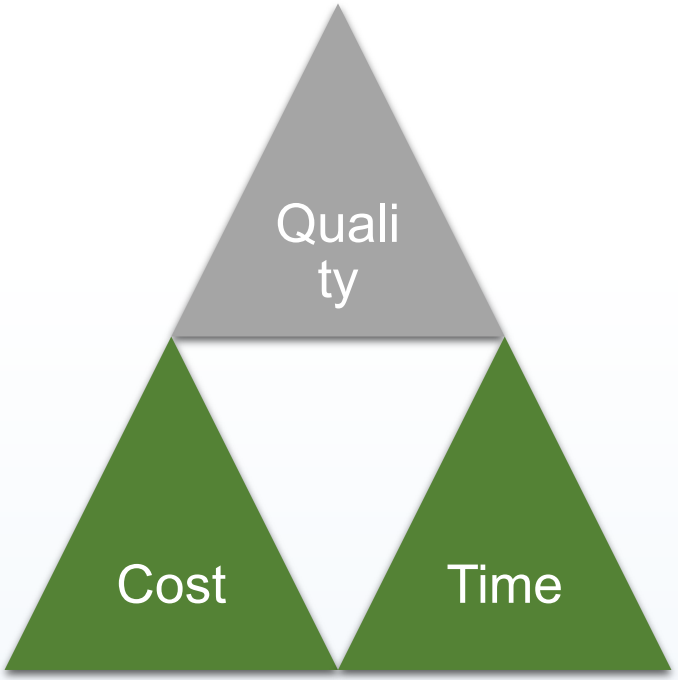


Project management constraints



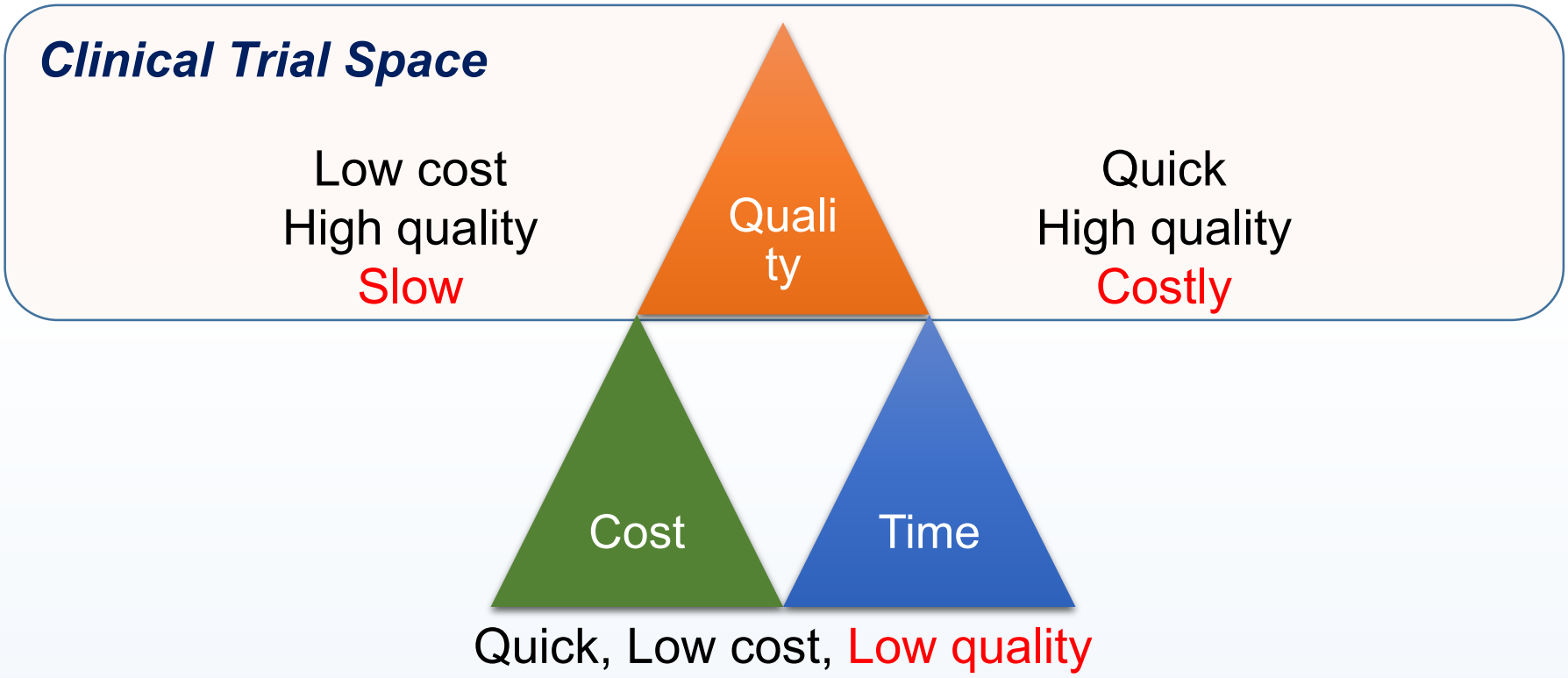
Quick
High quality
Costly

Project management constraints



Quick, Low cost, Low quality

Project management constraints



Quality is federally mandated and highly regulated

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NIH clinical trials

- Yes to all:
  - Does the study involve human participants?
  - Are the participants prospectively assigned to an intervention?
    - An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.
  - Is the study designed to evaluate the effect of the intervention on the participants?
  - Is the effect being evaluated a health-related biomedical or behavioral outcome?

FDA investigations

- 21 CFR 312
  - Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.
- Do you need an IND?
  - Exemptions given in 21 CFR 312.2
- 21 CFR 812
  - A clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device

Infrastructure maturity in clinical research

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	Grant prime award	Grant sub-award	FDA-regulated trials	Unfunded intramural study
Standard start-up process	✓	✓	✓	✓
Multi-site coordination	✓			
Federal grants management	✓	✓		
Contract negotiation	?	?	✓	
Clinical trial budgeting	?	?	✓	
FDA inspection management	?	?	✓	
Patient recruitment	✓	✓	✓	✓
Clinical processing/labs	?	?	✓	
Storing and handling data	✓	✓	✓	✓
IRB review	✓	✓	✓	✓
Essential document management	✓	✓	✓	✓

Funding types and research pathways

Funding types and research pathways

Responsibilities of sponsors and investi

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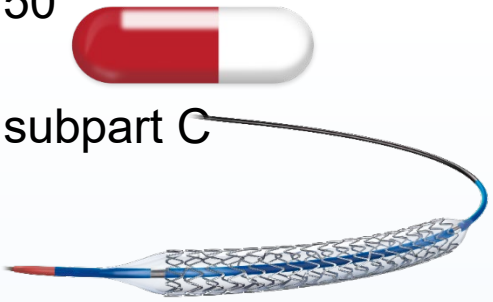
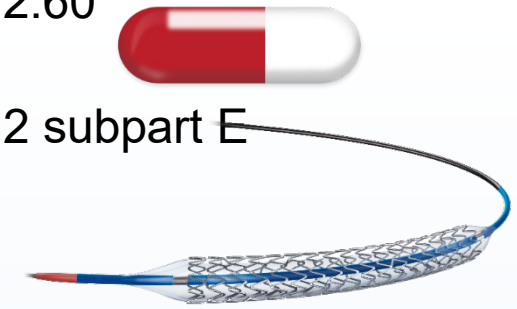
Sponsor

- Complies with
  - 21 CFR 312.50
  - 21 CFR 812 subpart C



Investigator

- Complies with
  - 21 CFR 312.60
  - 21 CFR 812 subpart E



FDA-regulated clinical trial start-up

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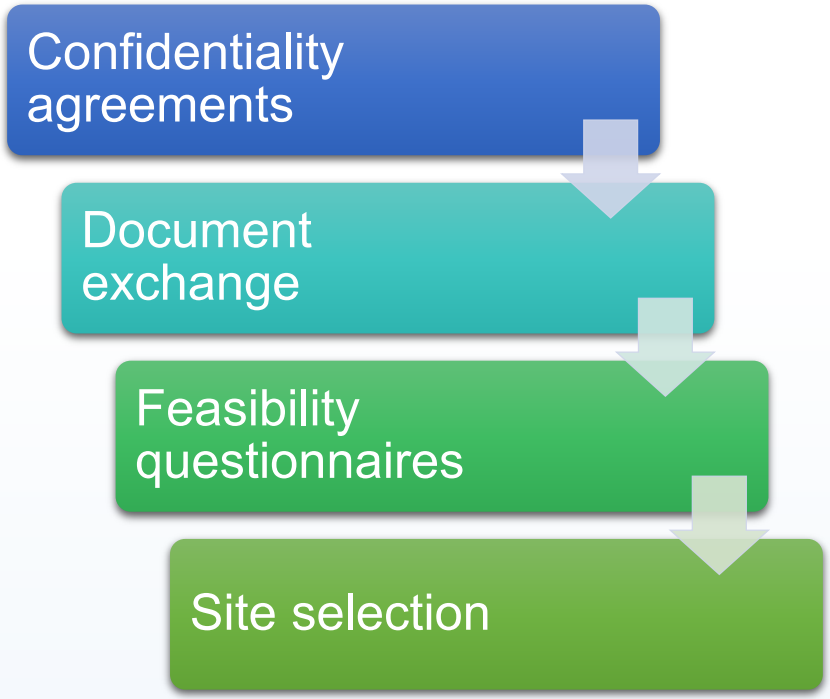
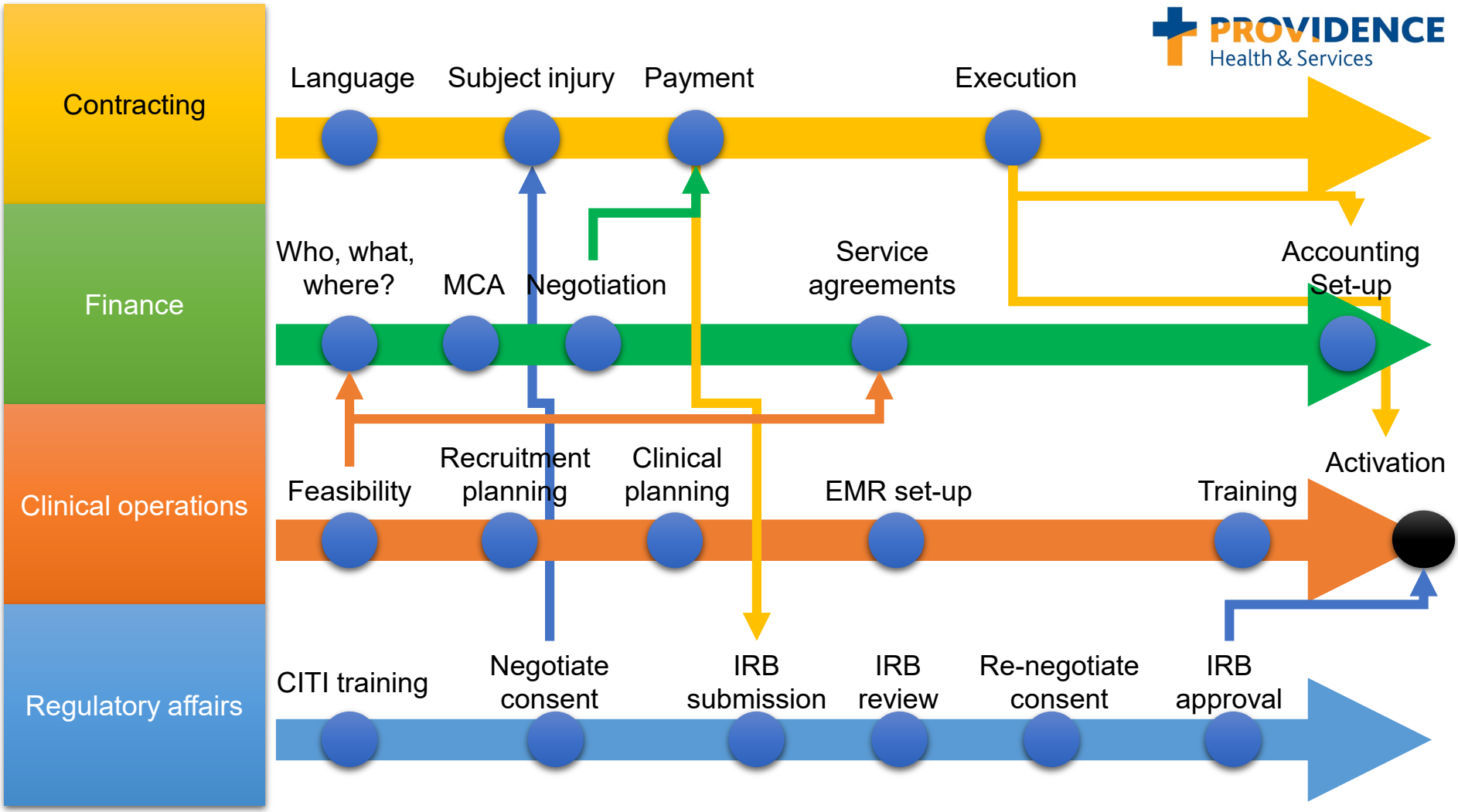
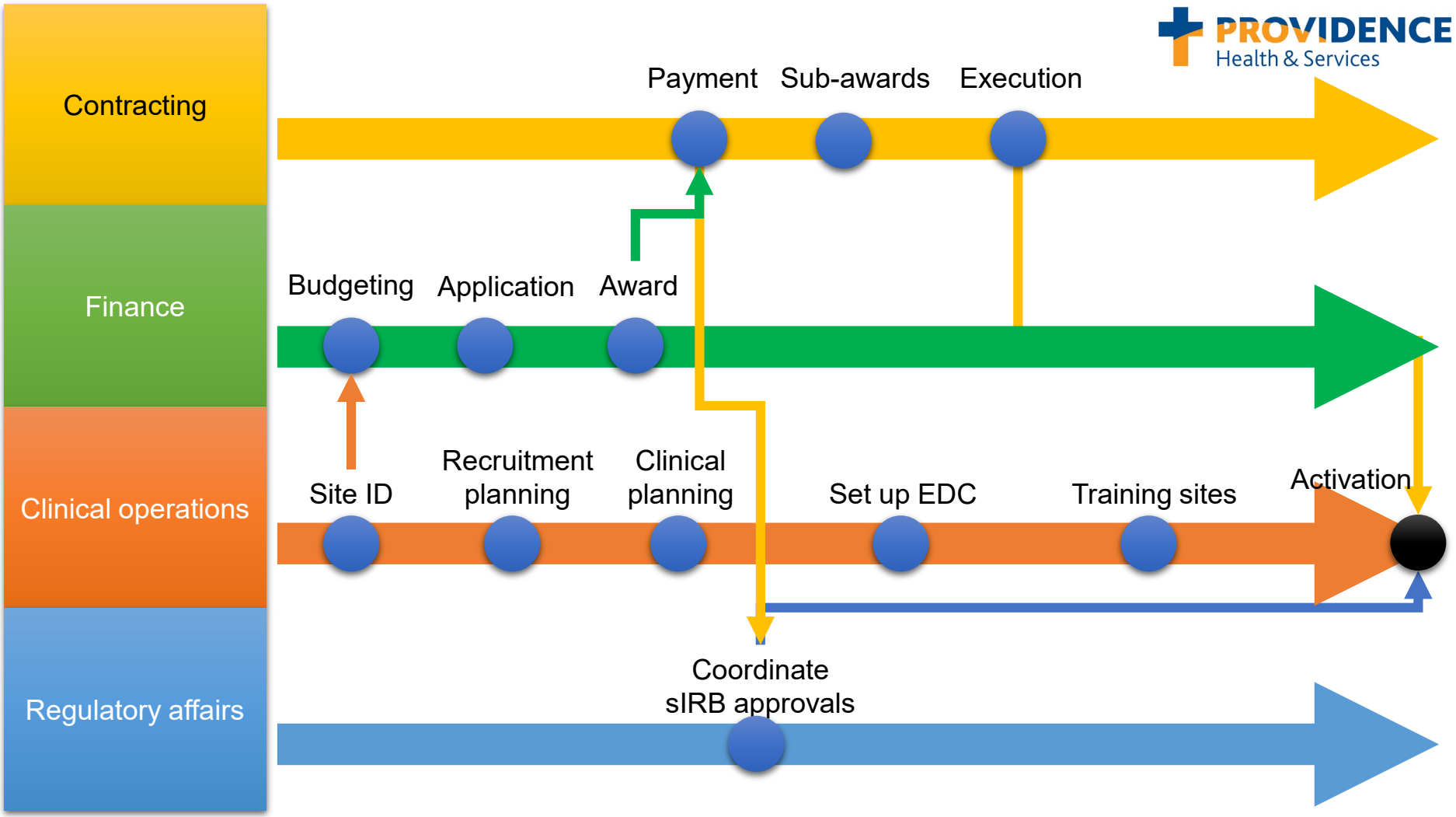
- Study start-up is a mutual evaluation between the sponsor and the site
- Feasibility is crucial




Contracting
Finance
Clinical operations
Regulatory affairs
PROVIDENCE
Health & Services
Language
Subject injury
Payment
Execution
Who, what, where?
MCA
Negotiation
Service agreements
Accounting Set-up
Feasibility
Recruitment planning
Clinical planning
EMR set-up
Training
Activation
CITI training
Negotiate consent
IRB submission
IRB review
Re-negotiate consent
IRB approval

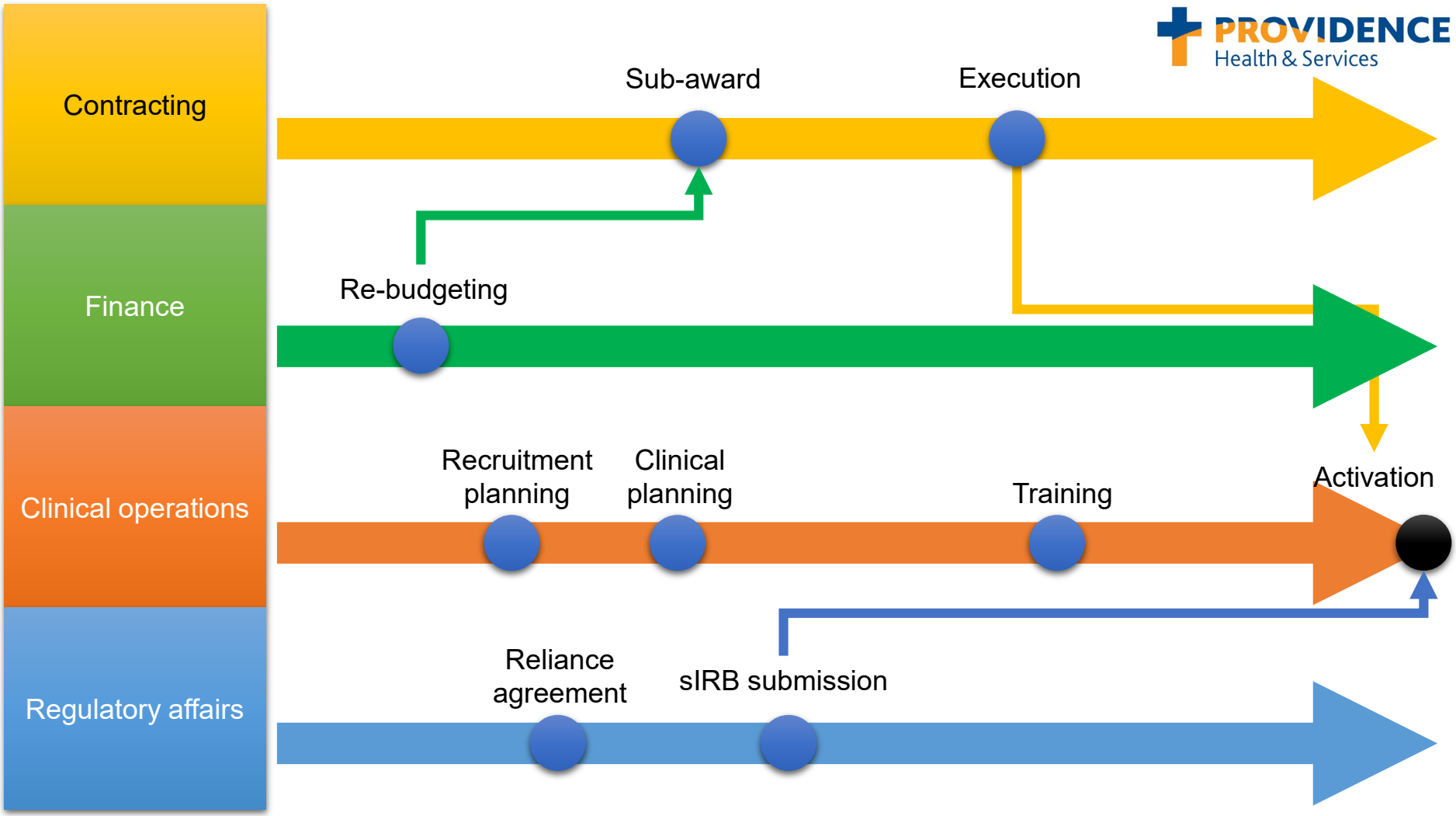
Funding types and research pathways


Contracting
Finance
Clinical operations
Regulatory affairs
PROVIDENCE
Health & Services
Payment
Sub-awards
Execution
Budgeting
Application
Award
Site ID
Recruitment planning
Clinical planning
Set up EDC
Training sites
Activation
Coordinate sIRB approvals

How will I…

- Do I need an IND or IDE?
- Ensure every site can handle federal awards?
- Organize contact information and track staff changes?
- Coordinate IRB reliance agreements and approvals?
  - Now, must include single IRB plan in grant applications
  - Changes who can include IRB fees in indirect costs (NIH NOT-OD-16-109)
- Coordinate budgets?
- Plan recruitment?
- Negotiate subaward terms?
- Communicate amendments?
- Collect data?
- Manage protocol deviations?

Funding types and research pathways


Contracting
Finance
Clinical operations
Regulatory affairs
PROVIDENCE
Health & Services
Sub-award
Execution
Re-budgeting
Recruitment planning
Clinical planning
Training
Activation
Reliance agreement
sIRB submission

Common pitfalls for PIs

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- Make sure you can start all four pathways at once
  - Send start-up documents for all four pathways
- Plan for extramural process and policy differences
  - Common cause for delay
  - Know the difference between a protocol and a manual of procedures
- Have a plan for site communication
- Plan your electronic data capture (EDC) system
- Have clear-cut and modern recruitment plans

Changing perspectives on start-up “delays”

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Cost of planning

Cost of mistakes

Continuous process improvement

Scott Adams, Dilbert.com

“Why does start-up take so long?”

PROVIDENCE Health & Services

- Slow CRO responses
- Legal or compliance questions
- Sponsor acquisition
- Inexperienced sponsor team
- New hardware
- New software
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- Unexpected study closure
- Budget stalemate
- Change of clinic location
- Pharmacy issues

The TERRIBLE Trial*

PROVIDENCE Health & Services

WHAT WAS SUPPOSED TO HAPPEN

Open in 90 days
Enroll 3 participants in 180 days

- **The TERRIBLE Trial**
  - Investigational new drug
  - Eligible patients have a rare genotype and are treatment naïve
  - Standard of care is to begin therapy at time of diagnosis
- **Recruitment and Consent**
  - Pre-screening via the electronic health record
  - Study team member to approach patient at the beginning of the visit, before drug prescription
  - Interested patients to be consented and provide a blood sample before departing the clinic

* Fictional trial.

The TERRIBLE Trial*

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WHAT ACTUALLY HAPPENED

- IRB review twice
- Change in PI
- Inaccurate feasibility
- Flu season
- Screen fails
- Lost $3,000/patient due to lack of enrollment and $10,000 in startup costs
- Opened in 130 days
- Enrolled 0 patients

* Fictional trial.

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Questions for after-action review

- What are the main process failures?
- What was the significance or impact of the failure?
- What caused the failure?
- What is a solution to the cause of the failure?
- Who will implement the solution?

Questions for consideration

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- What are your institution's global, recurring process failures?
- Who should be involved in the after-action review?
- Who has the ability and/or resources to implement solutions?
- How would you implement an after-action review process at your institution?

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Health & Services

After Action Review Worksheet

Directions: Develop ideas for a Corrective Action / Preventative Action (CAPA) plan. Describe each of the following:

- Process Failure: what went wrong?
- Significance/Impact: what was the result of the process failure? What did it impact?
- Root Cause: identify the root cause of the process failure
- Solution: identify a new checkpoint, process, or procedure that can be implemented to keep the process failure from recurring
- Personnel to Implement Solution: who will be responsible for implementing the solution?

Process Failure	Significance/Impact	Root Cause	Solution	Personnel to Implement Solution
				☐ Study manager ☐ Principal Investigator ☐ Clinical Research Coordinator ☐ Finance Staff ☐ Regulatory Staff ☐ Institutional Official ☐ Other:

“Why does start-up take so long?”

PROVIDENCE Health & Services

- Slow CRO responses
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Responsibilities & Oversight Obligations

Presented by Ann Melvin, MD, MPH

12:45pm-1:45pm

UW Husky Union Building

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Responsibilities and Oversight Obligations:

The Critical Role of the Principal Investigator

Presented by:

Ann J. Melvin, MD, MPH

Professor of Pediatric Infectious Diseases.

Director of the Pediatric HIV program at Seattle Children's Hospital.

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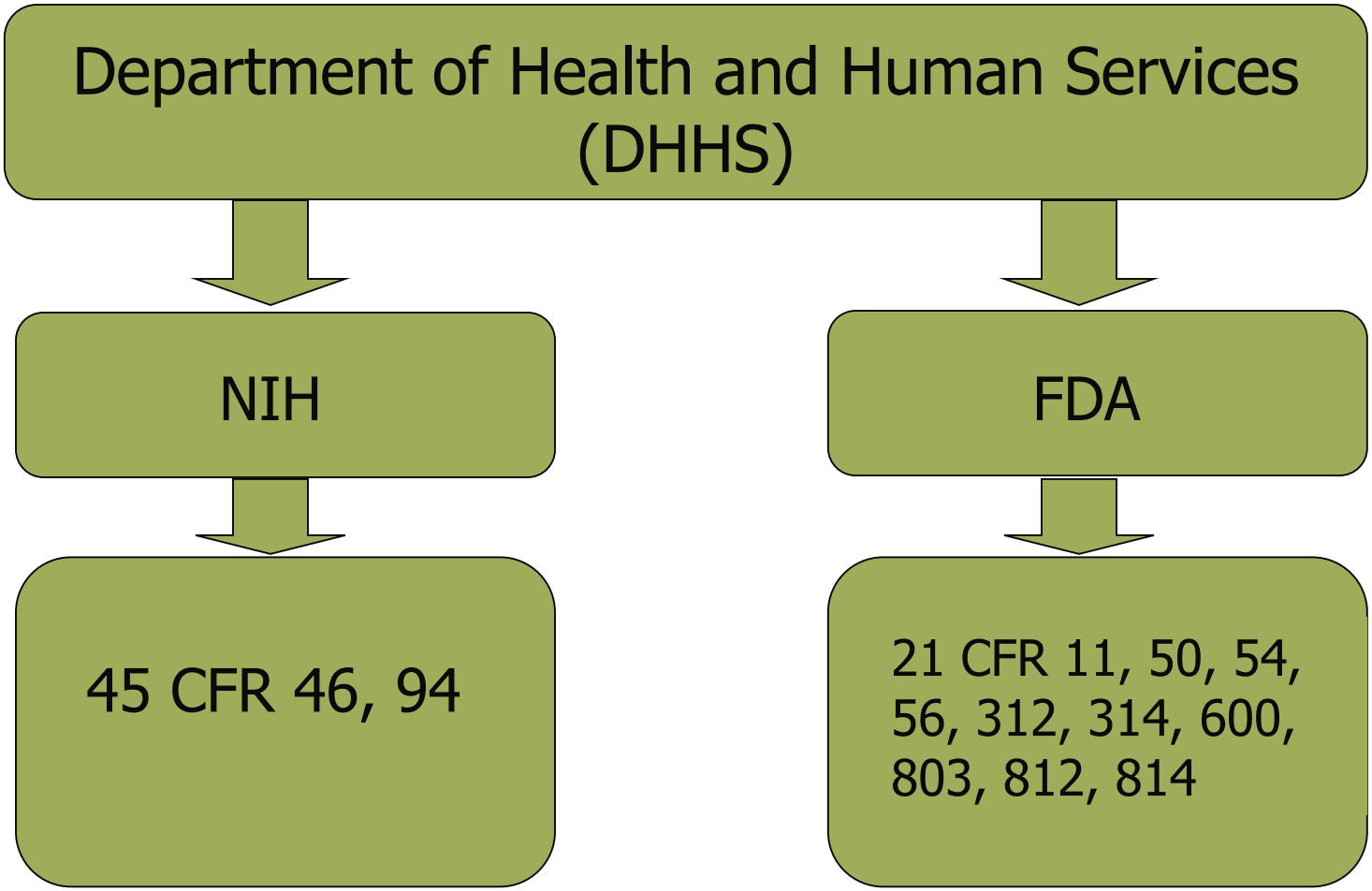
ACCELERATING RESEARCH. IMPROVING HEALTH.

Learning Objectives

By the end of this session, you will be able to:

- Discuss the level of responsibility of the principal investigator to oversee clinical research projects
- Describe how to operationalize tools to meet the training and oversight needed for your study (checklists, logs, templates)
- Discuss best practices for accomplishing adequate supervision despite tight timelines, competing priorities, and limited resources.

Federal Regulation of Clinical Research



Clinical Trials Oversight: FDA vs. OHRP

- FDA oversight
  - Sponsors, monitors, clinical investigators, contract research organizations involved in IND/IDE studies
  - IRBs reviewing clinical research involving any FDA-regulated product (IND/IDE and non-IND studies)
- OHRP oversight
  - Institutions where clinical research is conducted or supported by HHS or
  - Institutions that agree to assume responsibility for the research in accordance with 45 CFR 46 regardless of the funding source

Investigator Responsibilities

- Conduct the study in accordance with the protocol, except when necessary to protect the safety, rights or welfare of subjects
- Personally conduct or supervise the investigation
- Inform subjects drugs are being used for investigational purposes and ensure informed consent and IRB requirements are met
- Report Adverse Events to the sponsor/IRB
- Read and understand the investigator's brochure

Investigator Responsibilities

- Ensure that all associates, colleagues, and employees assisting in study conduct are informed about their obligations
- Maintain adequate and accurate records
- Obtain initial and continuing review and approval from the IRB. Promptly report to the IRB all changes in the research activity and all unanticipated problems and make no changes in the research without IRB approval
- Comply with all requirements regarding obligations of clinical investigators [21CFR 312]

Lack of Adequate Trial Supervision Results in:

- Poor data
- Frustrated staff
- Study delays
- Risk to subjects
- Risk for audit by IRB/OHRP

Case of the missing ECGs

- L.B. was the PI of a study for a new investigational agent. As the agent could cause prolonged QTc intervals, ECGs were required multiple times during the study.
- An FDA audit revealed that multiple ECGs were missing from several participants.
- FDA determination – the missing ECGs compromised subject safety.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm578987.htm

Case of the missing ECGs

- L.B. response:
  - ECG interpretation was delegated to a subinvestigator and only abnormal ECGs were brought to her attention.
  - ECGs were placed in a separate folder which she didn't review, so could have been misplaced or not done
  - When it was discovered that the ECGs had not been done, the subjects were pulled back to get an ECG and they were all unchanged from baseline

Case of the missing ECGs

- Do you think the FDA was satisfied with L.B.'s response?
- Was it acceptable for L.B. to delegate the reading of the ECGs to a subinvestigator?
- How could L.B. have been aware of the missing ECGs prior to the audit?
- How could L.B. have prevented this situation?

Case of questionable eligibility

- C.N. received a warning letter from the FDA after an inspection found multiple episodes of enrolling participants who did not meet eligibility criteria
  - Several patients did not meet requirements for statin dose at baseline
  - One participant was enrolled with a CK value that was out of range
  - Several patients were enrolled with out of range triglycerides.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm493102.htm

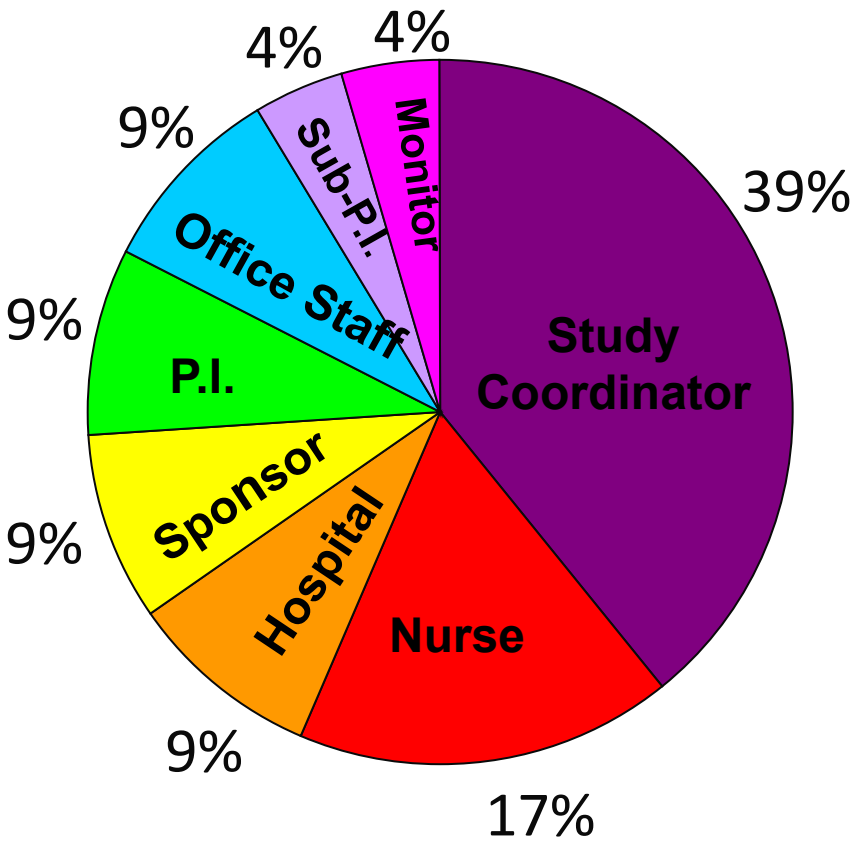
Case of questionable eligibility

- C.N. response:
  - The study coordinator received verbal approval from a study monitor to enroll the participants
- Do you think the FDA was satisfied with C.N.'s response?
- Can a study monitor OK enrollment violations?
- How could C.N. have prevented this situation?

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm493102.htm

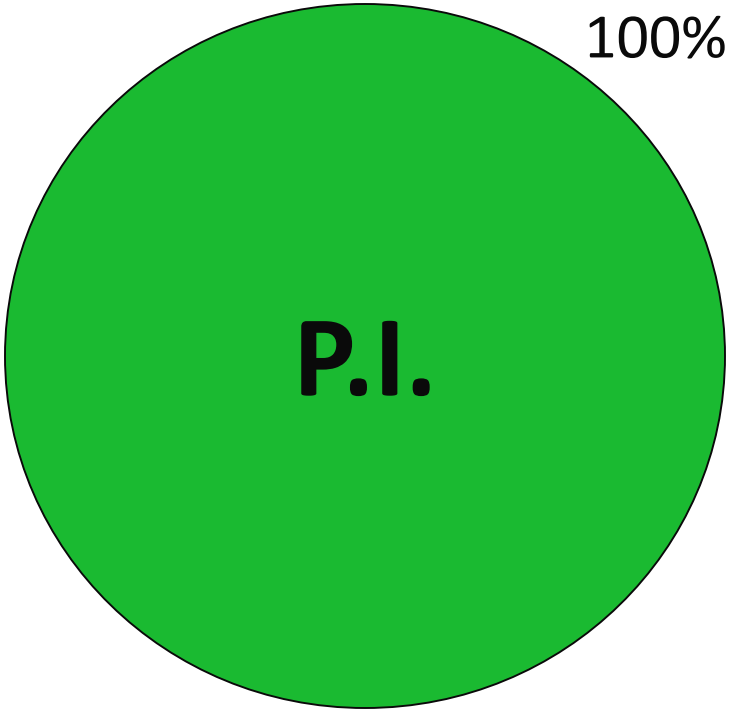
Blame for Poor Trial Conduct

Investigator's Report



n (parties blamed) = 23; n (cases) = 20

FDA/IRB/Institution Position



Woollen, S.W., CDER, FDA, 2000

So what does it mean to "personally conduct or supervise the investigation – I can't do it all!"

How Can This Be Done?

- Appropriate delegation
- Adequate training
- Regular supervision

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

What is Appropriate Delegation of Study-Related Tasks?

- The investigator should ensure that any individual to whom a task is delegated is:
  - qualified by education,
  - training
  - State licensure (where applicable), and
  - experience

  … to perform the delegated task.

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Are they qualified?

- Can a study coordinator process biologic samples?
- Can a non-clinician obtain informed consent?
- Is it acceptable for a study coordinator to code and assess adverse events?

How Can This Be Documented?

- Maintain a list of qualified persons to whom the study-specific task has been delegated
  - Describes the delegated tasks
  - Identifies the qualifying training
  - Identifies the dates of involvement in the study

- Generate an organization chart for yourself.
- Identify the people you need to get the job done.
- Put their specific responsibilities on paper and give it to them.
- Review responsibilities and adherence at set intervals.
- When someone leaves make sure all new credentialing is done.

Sample Study Specific Task Chart

Study task	Specific action	Responsible?
Screen	Telephone screening of interested subjects	RC (name)
	Screening checklist	RC
Eligibility	Initial review w/ potential subject	RC
	Final eligibility assessment	PI
Consent	Obtain Informed Consent	PI/MD
Clinical Procedures	Blood draw	RN
	Interim History/Physical exam	PI/MD
Source Document	Source document for study data	RC & PI
	Data Entry	RC
	Review of source documents	RC
Toxicity Monitoring	Monitoring/review of AEs	PI/PI

ITHS Research Resources

Signature List & Delegation of Responsibility Log

Principal Investigator:	
Study Title:	

Note: *Update this log in a timely manner as new personnel are added and/or study roles change.*

#	Staff Member Name	Staff Member Title ("co-investigator," "research coordinator," "data manager," etc.)	Staff Member Signature	Initials	Delegated Study Tasks (See key below)	Start Date	End Date
1							
2							
3							
4							
5							
6							
7							
8							
9							
	PI Signature:						

Delegated Study Task Key - Add or delete tasks as necessary to fit your study

1. Obtain consent	5. Dispense study drug/device	9. Submit and maintain IRB docs	13. Randomization	17. Staff education
2. Obtain medical history	6. Complete CRFs	10. Data monitoring	14. Blood draw	18. Data analysis
3. Perform physical exam	7. Handle CRF queries	11. Safety monitoring	15. Blood storage	19. Other
4. Assess eligibility criteria	8. Maintain regulatory docs	12. Advertising	16. Questionnaires	20. Other

Create a delegation of duties log

- Think about a study you are involved in – could you complete a delegation of duties log?

What is Adequate Training?

- Have a general familiarity with the study and the protocol
- Have a specific understanding of the details of the protocol and the investigational product (if applicable), relevant to the tasks they will be performing

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

What Is Adequate Training?

- Know the regulatory requirements and standards for the conduct of clinical trials
- Are competent to perform the tasks that they are delegated

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Examples of Required/Recommended Training

- Human subjects protection training
- Good Clinical Practice training
- Protocol-specific training

If Someone Else Wrote the Protocol

- Read the Protocol
- Make sure everyone on the research team reads the protocol

Sample Training Documentation Chart

Study personnel	Specific study tasks performed	Type of training/ certification	Date of training
Research Coordinator (name)	Subject screening Maintenance of source documentation	HSP GCP Protocol specific training by PI	4/12/2016 7/5/2017 2/12/2018
Research nurse (name)	Study drug infusion	HSP GCP RN license Protocol specific training by PI	11/2/2017 3/7/2016 1998 2/12/2018

Tools and Templates

- Standard Operating Procedures
- Study Start-up Checklist
- Study Implementation Checklist
- Study Team Meeting Minutes
- Adverse Event Log
- Protocol Deviation Logs

ITHS Forms - https://www.iths.org/investigators/forms-templates/study-document-templates/

What is Adequate Supervision?

Set Aside The Necessary Time

- PI should have sufficient time to conduct and supervise the trial
  - Level of supervision should be appropriate to the staff, nature of trial and subject population
  - Don't take on more trials than you have time to supervise

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Conduct Regular Meetings With Staff

- Review basic science and clinical issues
- Review trial progress
- Update staff on any changes to the protocol or other procedures
- Review adverse events
- Review deviations/violations

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Pay Attention to Your Planned Informed Consent Process

- Review recruitment and approach procedures
- Assure that anyone who obtains consent* thoroughly understands the protocol
- Use of consent tools to document process

*consent can only be obtained by personnel with the training necessary to adequately explain procedures, risks, benefits, etc.

Study number _____ Version number _____ IRB date stamp _____

Date consent was signed _____ Time _____

_____1. Information about the study, including all available options, was provided in a language that the subject can understand.

_____2. The subject was given ample opportunity to consider all available options.

_____3. Questions were elicited and all answers given prior to signing consent.

_____4. The investigator or sub-investigator is comfortable that by providing adequate information to the subject there is no likelihood of coercion.

_____5. Verification of comprehension was done in one of the following ways (select at least one of the following):

____A) The subject asked relevant questions during the informed consent process.

____B) The clinician asked the subject specific questions about the study.

____C) The clinician asked the subject to repeat information discussed.

6. The following items were covered when discussing the informed consent for a study with the subject:

___a) The study involves research.

___b) Participation is voluntary

___c) Subjects can decide not to participate or withdraw at any time without penalty or loss of benefits.

___d) The purpose, duration of study, and issue of randomization/blinding

___e) The number of screening, pre-entry, entry and on-study visits.

___f) The length of follow up, what happens in case of early withdrawal, and the reasons for which a subject might be involuntarily discontinued from the study.

___g) Risks of study treatments and procedures, including psychosocial ones.

___h) Possible benefits, and if none, this should be stated.

___i) Reimbursement to subjects, if any.

___j) Costs to subject. What happens in case of research-related injury or side effects.

___k) What happens in case of pregnancy, if applicable.

___l) New findings will be communicated to them.

___m) Confidentiality of data.

___n) Phone numbers for questions at a later time, including research questions, questions related to subject's rights, and research-related injuries.

_____7. Copy of consent given to subject.

_____8. HIPAA consent signed, if required.

Comments:

Clinician signature _____ Date _____

What About Outside Parties?

- PI is considered responsible
  - Lab at local site or contracted by PI
  - Pharmacy at local site or contracted by PI
  - Staff not under PI's direct employment if working at local site
- Sponsor is considered responsible
  - Central laboratory retained by sponsor

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Protecting the Rights, Safety, and Welfare of Study Subjects

- During and following the trial, ensure adequate medical care is provided for any adverse events related to the trial.
- Clinical investigators should be available to subjects during the conduct of the trial at their site.

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Protecting the Rights, Safety, and Welfare of Study Subjects

- Failure to adhere to the protocol may be considered a failure to protect the rights, safety, and welfare of subjects.
  - Non-compliance with inclusion/exclusion criteria
  - Failure to perform safety assessments in a timely manner

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Be Proactive

- Select qualified staff and ensure adequate training and supervision
- Write job aids, SOPs and check lists
- Walk through study visits – streamline/standardize activities as much as possible
- Have back-up plans –staff turnover-yikes!

Be Proactive

- Develop a QA plan
  - Real-time cleaning of data
  - Audit trails – should be clear what was changed, who changed it and why it was changed
- Pay attention to queries – do they indicate a system problem that should be addressed

Be Proactive - If You Are Writing the Protocol

- Make it simple, clear and easy to understand
- Write in reasonable flexibility
- Write a good safety and monitoring plan
- Determine which procedures can be done by non-physician staff
- Assure feasibility
  - Staff
  - Resources
  - Budget

Learning the hard way

- Personally review eligibility
- Review study conduct and data in real-time
- Understand the difference between research care and clinical care as it relates to the protocol
- Train, train, train
- Communication and team work

Setting up a mock study

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Impact of a Dietary Supplement on Muscle Function in the Elderly

Study synopsis

Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Impact of a Dietary Supplement on Muscle Function in the Elderly

Purpose: To evaluate the safety, tolerability and efficacy of isoleupro in healthy elderly adults.

Background: Decreased muscle strength with aging has been associated with increased risk for falls, pneumonia and a decreased quality of life. Isoleupro is a dietary supplement that has been shown to increase muscle mass in animal studies and is marketed to body builders. There have been rare reports of acute liver injury associated with the use of isoleupro, but it isn't clear if this is due to isoleupro or a contaminant, as isoleupro is frequently not the only ingredient in marketed products.

Primary objective: To evaluate the 24 week safety and tolerability of isoleupro when given to healthy adults ages ≥ 70 – < 85 years of age.

Secondary objective: To evaluate the effect of 24 weeks of isoleupro on pulmonary function, 6- minute walk test and grip strength in healthy adults ages ≥ 70 – < 85 years of age.

Study population: Adults from 70 years to less than 85 years of age without chronic cardiovascular, pulmonary, hepatic or renal disease.

Sample size: 100 participants

Schedule of evaluations (see page 2)

Make a list of the staff and the training they will need to conduct this study
Make a list of the job aids/SOPs you might need
Fill out a delegations of duties log for the study
Think about your role in the oversight of the study
    Develop an agenda for the study start-up meeting
    Develop an agenda for your regular team meetings
Write a QA plan for the study

Parameters	Screening	Baseline Visit 1[a]	Visit 2 (Day 14)	Visit 3 (Day 28)	Visit 4-7 (ever 4 weeks)	Visit 8 (week 24)
Informed consent	X					
Pulmonary Function Tests	X			X		X
6 minute walk test	X			X		X
Inclusion and exclusion criteria	X					
Medical history	X					
Physical examination	X		X	X	X	X
Height and Weight	X			X		X
Laboratory – CBC, chemistry panel	X			X	X	X
Laboratory – serum biomarkers[b]		X		X		X
Laboratory – liver function tests		X		X	X	X
ECG	X			X		X
Vital Signs[c]	X	X	X	X	X	X
Study Product Dispensed		X	X	X	X	
Peak Flow Meter[d]	X	X		X		X
Review Exercise Diary		X	X	X	X	X
Quality of Life Questionnaires		X		X		X
Concomittent Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X

Learning Objectives

- Discuss the level of responsibility of the principal investigator to oversee clinical research projects
- Describe how to operationalize tools to meet the training and oversight needed for your study (checklists, logs templates)
- Discuss best practices for accomplishing adequate supervision despite tight timelines, competing priorities, and limited resources.

Resources

- International Council on Harmonization (ICH) – 2018 Good Clinical Practice addendum - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1
- FDA Guidance for Industry – Investigator responsibilities - protecting the rights, safety and welfare of study subjects - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Resources

- Institute for Translational Health Sciences (ITHS) www.iths.org
- Additional education http://www.iths.org/education
- ITHS clinical research handbook https://www.iths.org/investigators/handbook/
- Biomedical Sciences Toolkit – UW Healthlinks (select clinical research or search on “translational research toolkit”) http://healthlinks.washington.edu.offcampus.lib.washington.edu/
- PRIMER toolkit - http://researchtoolkit.org/

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