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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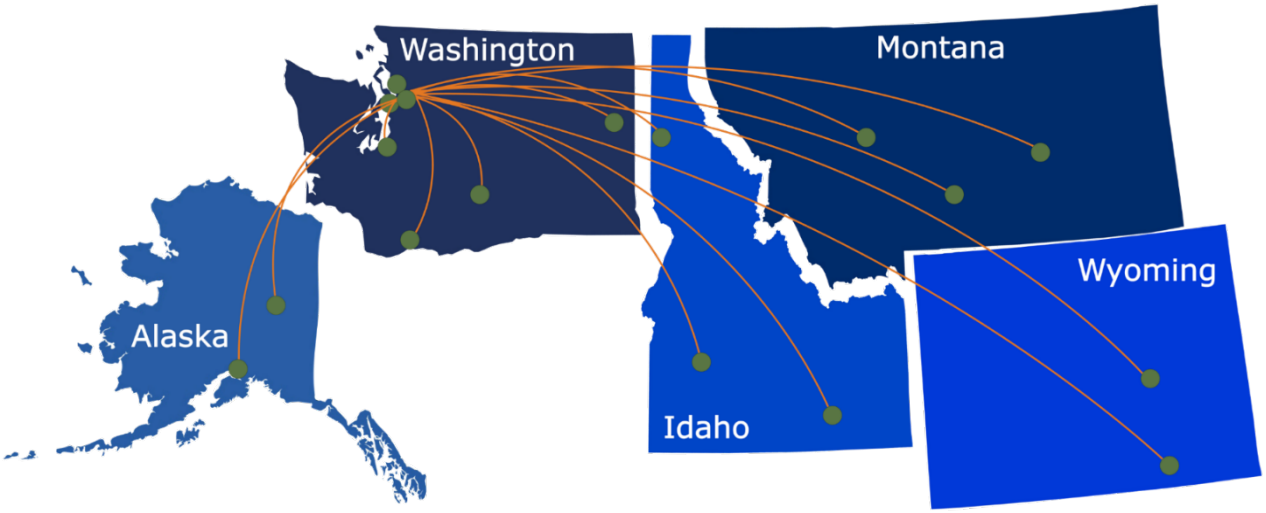

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What We Offer:

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
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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

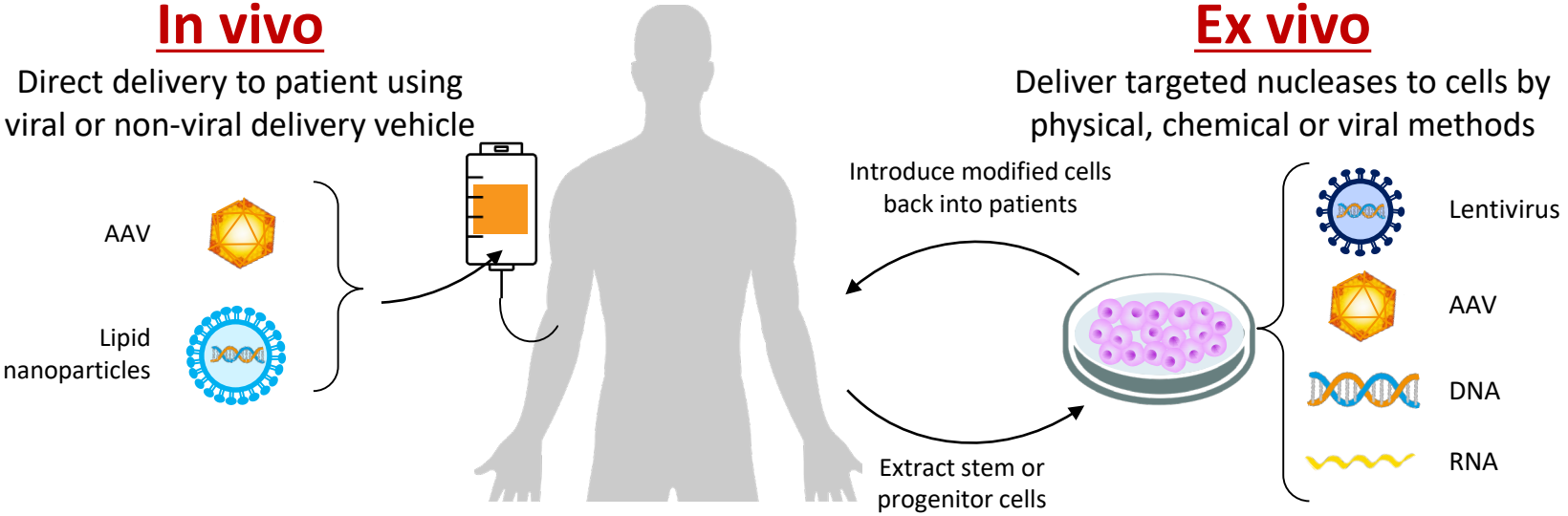
Haoyi Wang, Hui Yang

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.

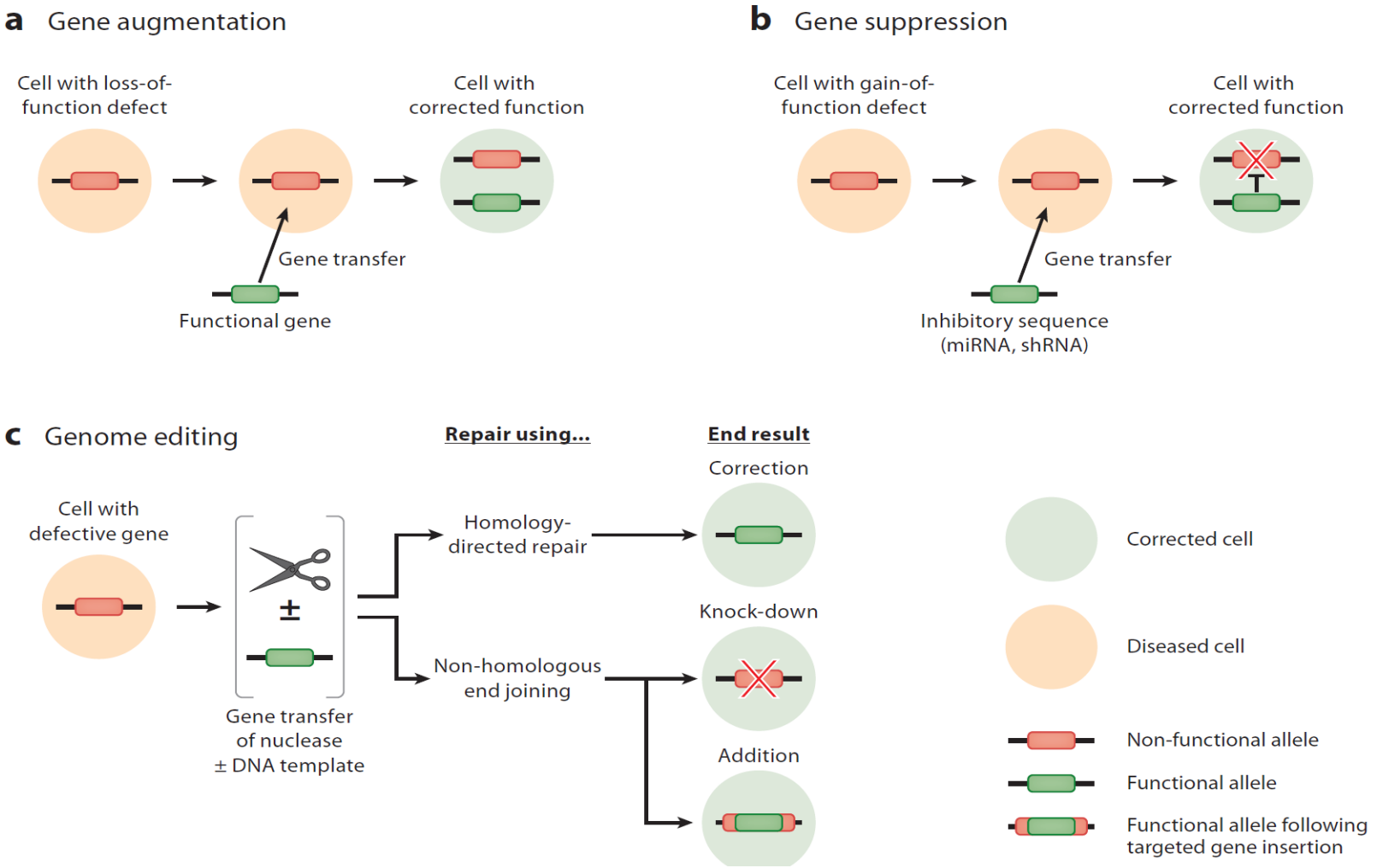
Approaches to Gene Therapy



- 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

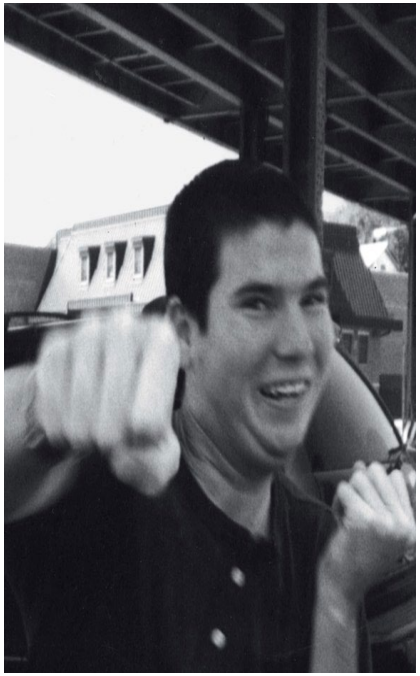
- Early studies with advances, but also setbacks
- First therapeutic ex-vivo gene therapy in 1990s
  - X-linked severe combined immune deficiency (SCID)
    - First generation γ-retroviral vectors with gene expressed under the control of viral regulatory elements
    - Positive response, however 5/20 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

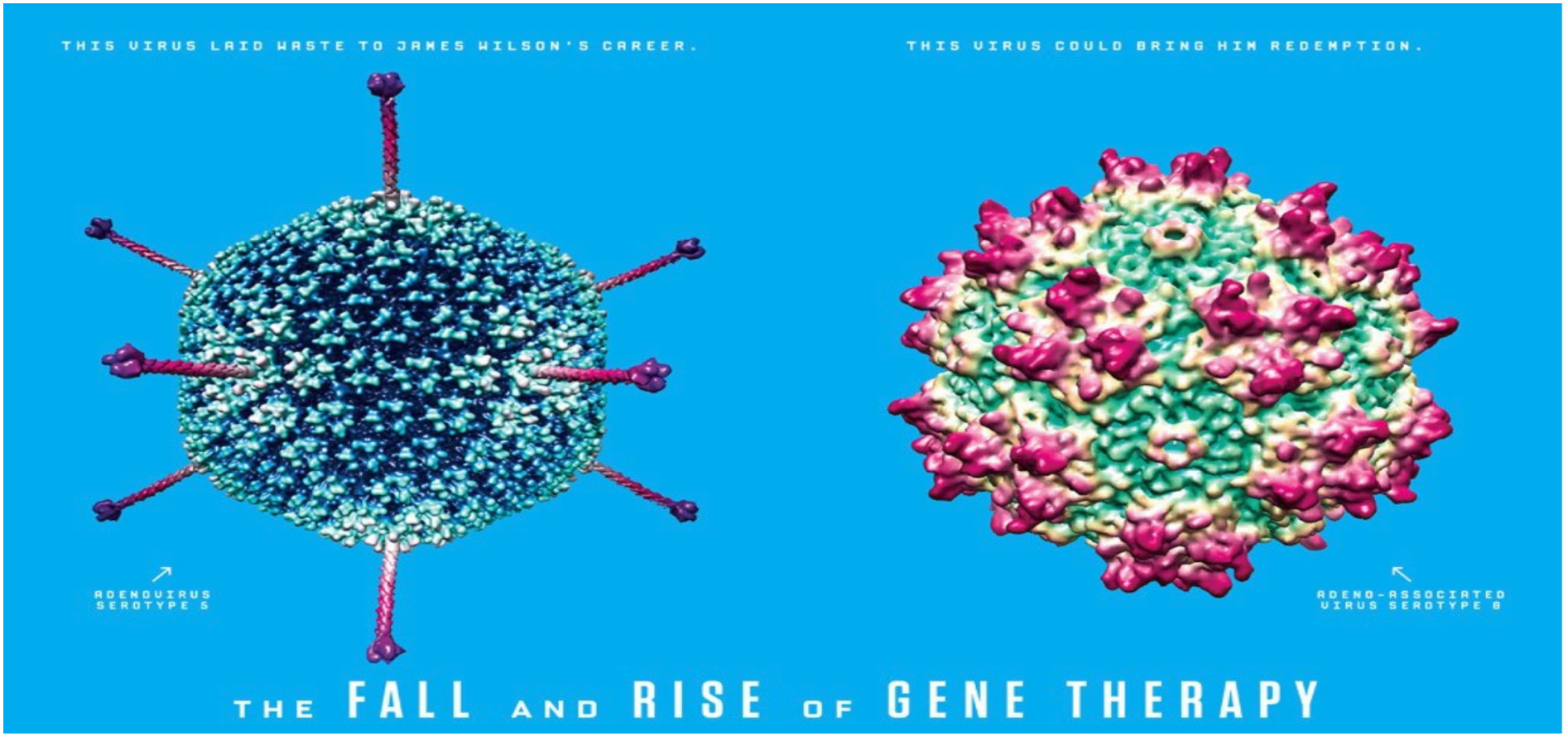
This gene therapy for vision loss will initially cost $850,000

- 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

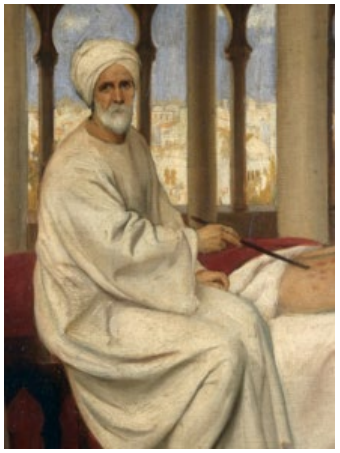
- Recognised early as good target
  - Single gene disorder[1]
  - Wide range of levels can produce therapeutic effect without safety concerns for factor activity[1]

- 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

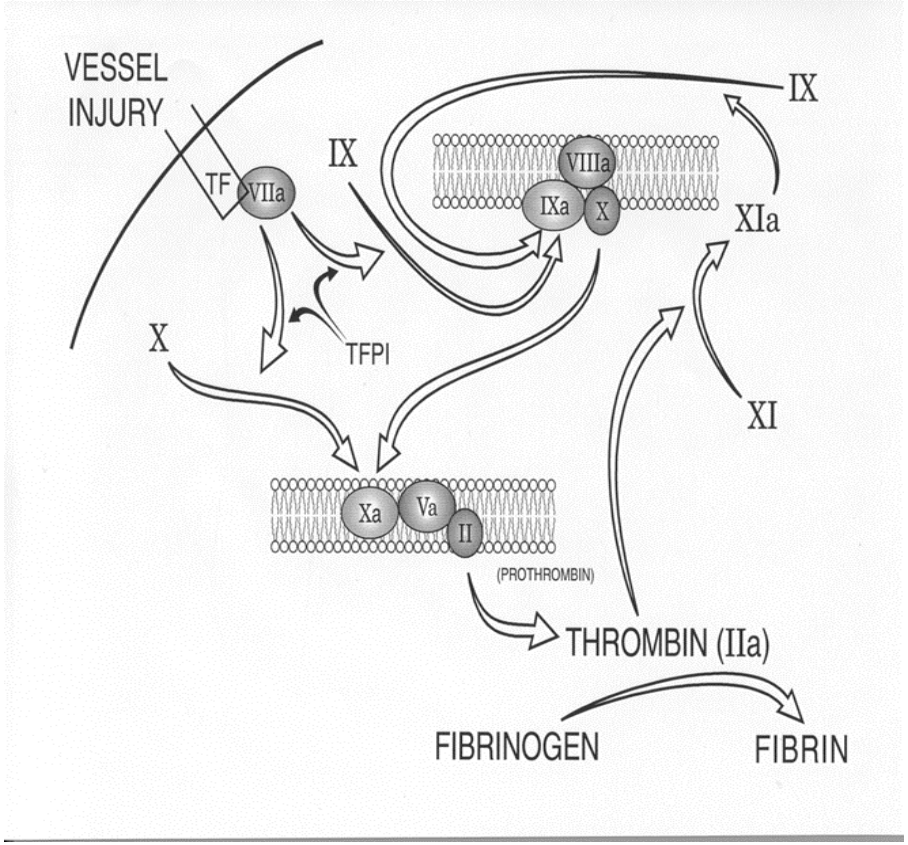


Hemophilia: Recognition

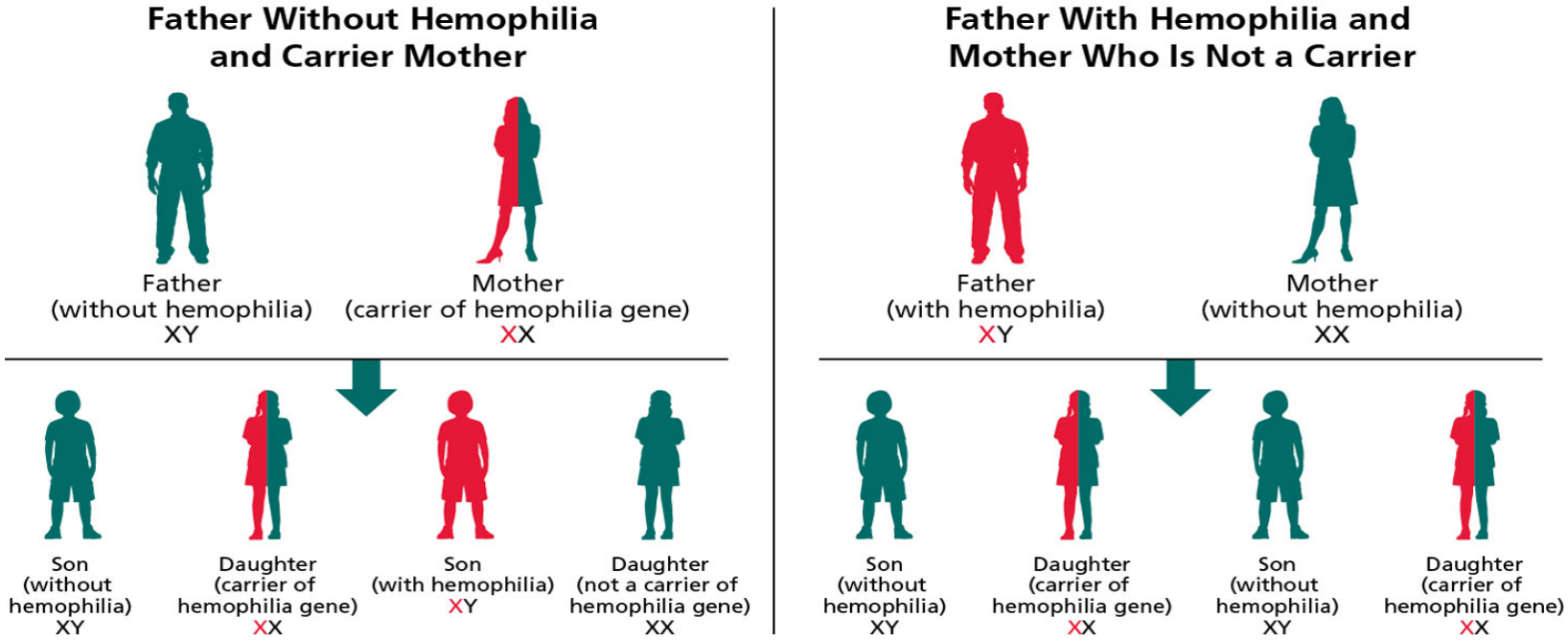
- Worldwide: At least 1/5000 male births
- New mutation rate ~ 30%
  - Thus hemophilia seen in all racial groups
  - First presentation may be bleeding symptoms in a female genetic carrier
- Hemophilia A - ~ 80% of cases
- Hemophilia B - ~ 20% of cases
- Presentation and diagnostic approach the same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

Hemophilia: Pathophysiology

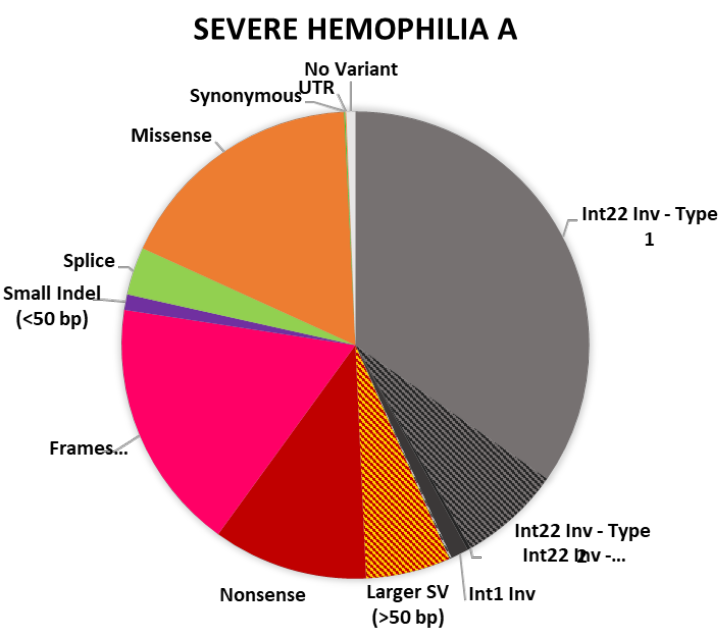
- FVIII accelerates the rate of FX activation by FIXa, eventually leading to the generation of thrombin (FIIa) and subsequent formation of the fibrin clot
- Deficiency of either FVIII or FIX predisposes to spontaneous and trauma-induced hemorrhage

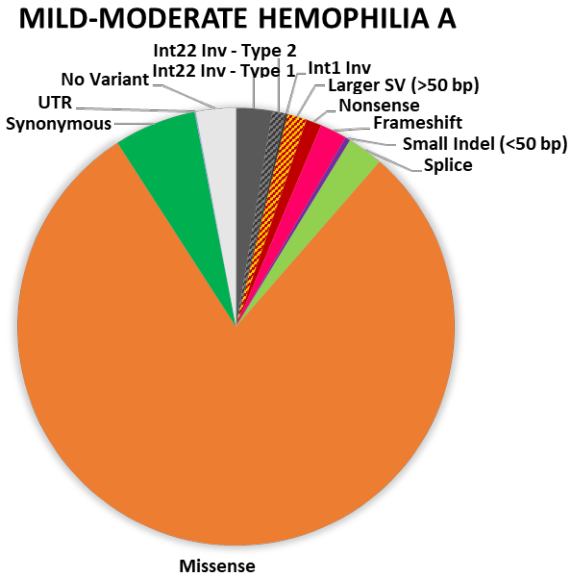


Inheritance of Hemophilia



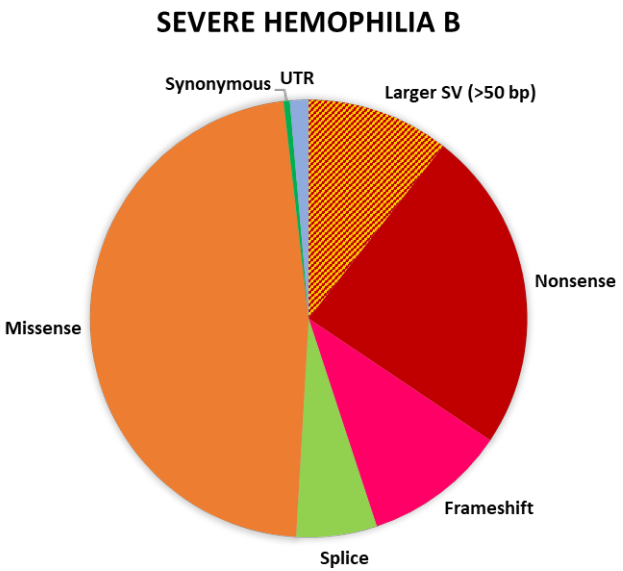
Genetics of Hemophilia A

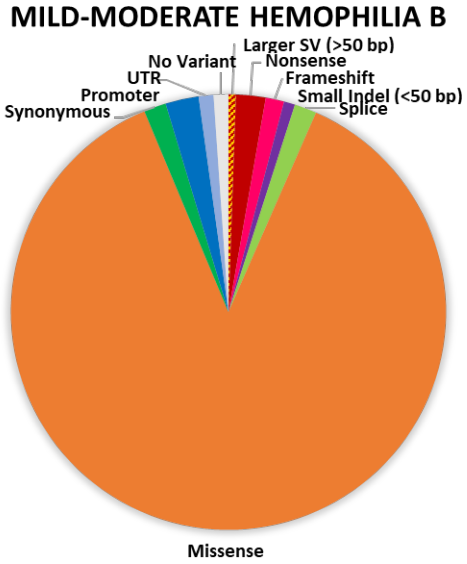




Johnsen JM, et al. *Blood Advances* 2017;1:824-834

Genetics of Hemophilia B





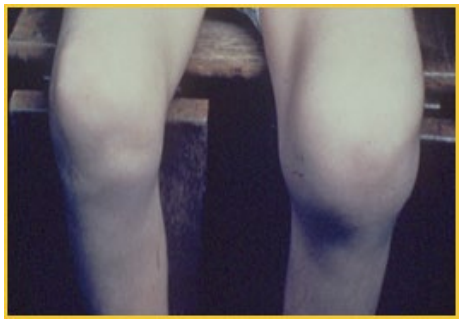
Johnsen JM, et al. *Blood Advances* 2017;1:8

Presentation of Hemophilia

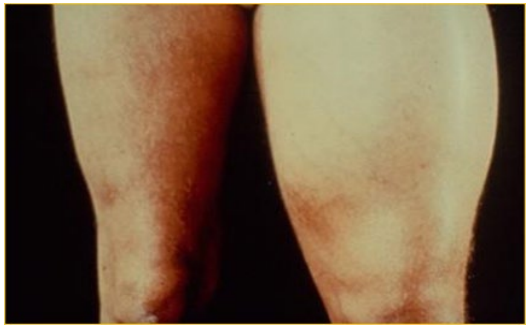
- Average onset of clinical symptoms
  - Severe: 1.5 years (many will present at birth)
  - Moderate: 3 years
  - Mild: 5 years
- Initial presentation:
  - Early postnatal procedures
  - With intramuscular injections
  - With dental eruptions/loss/tongue biting
  - Spontaneous hemarthroses after onset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

Sites of Bleeding

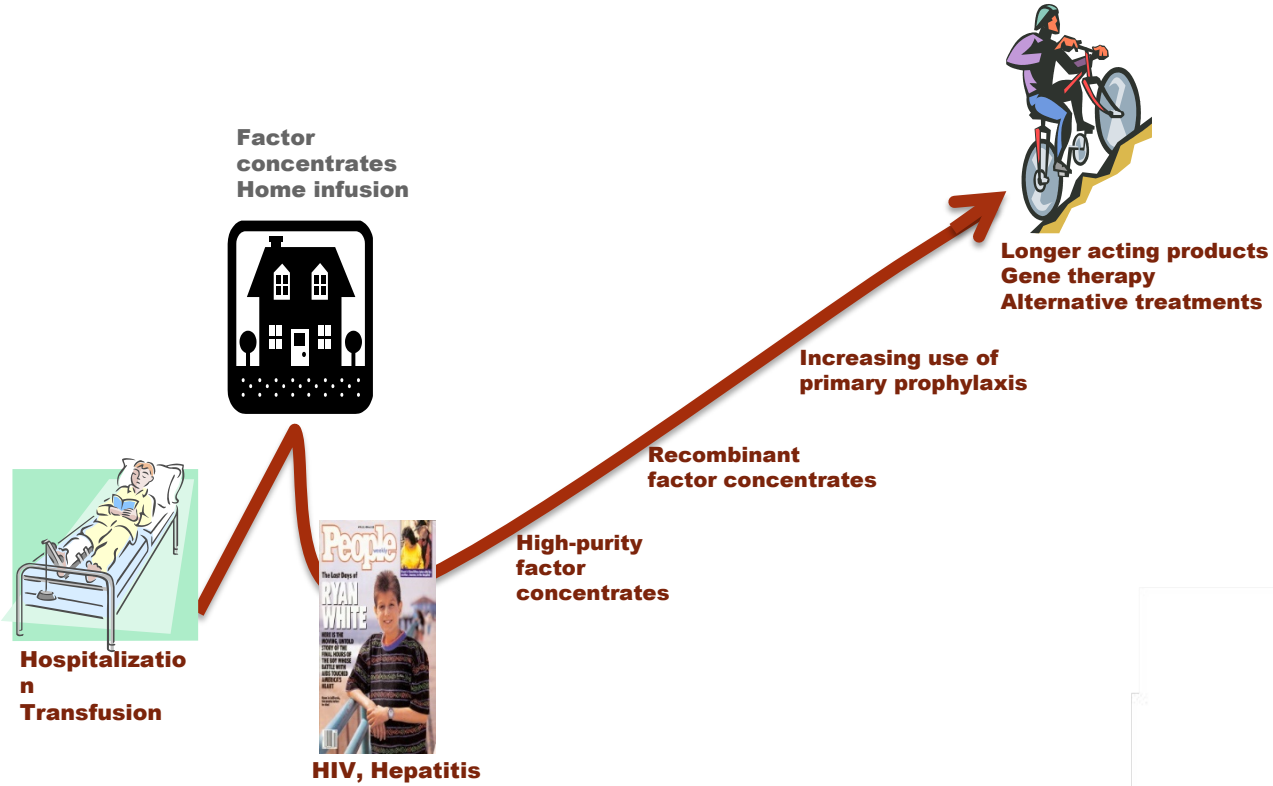
- Common
  - Mucous membrane
  - Soft tissue
  - Muscle
  - Joints (hemarthroses)



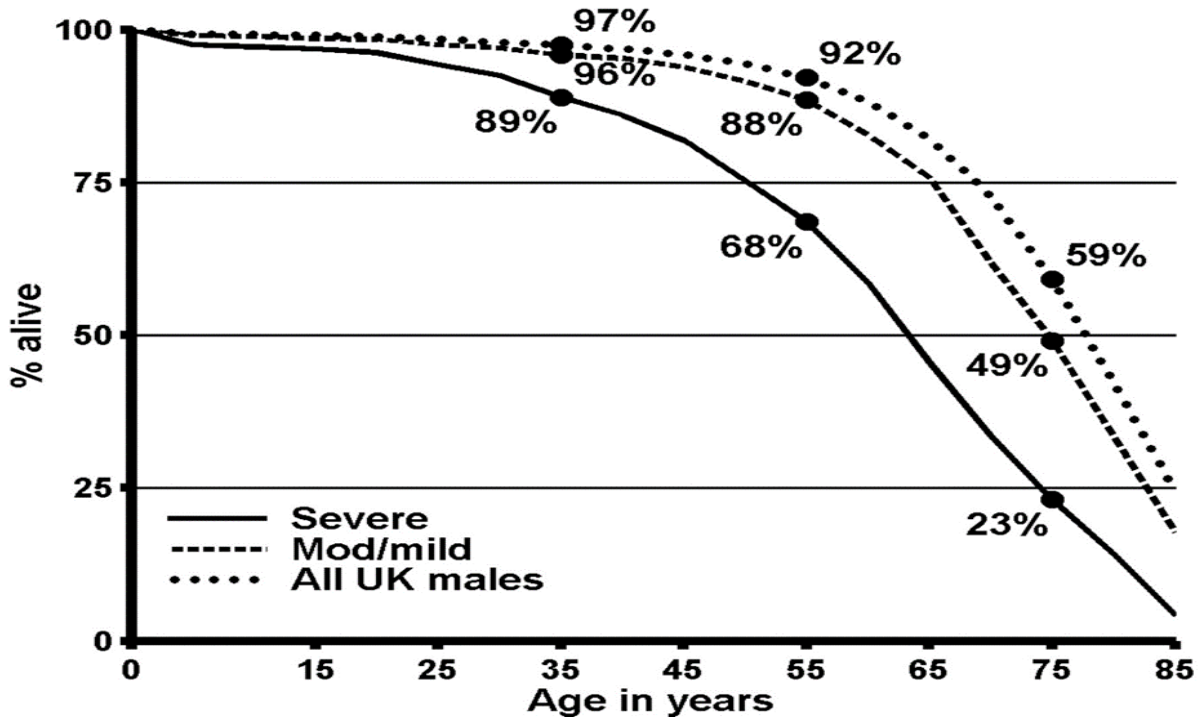
- Life-threatening
  - Central nervous system
  - Head
  - Neck and throat
  - Gastrointestinal
  - Retroperitoneal



Advances in Hemophilia Care: The Past Six Decades



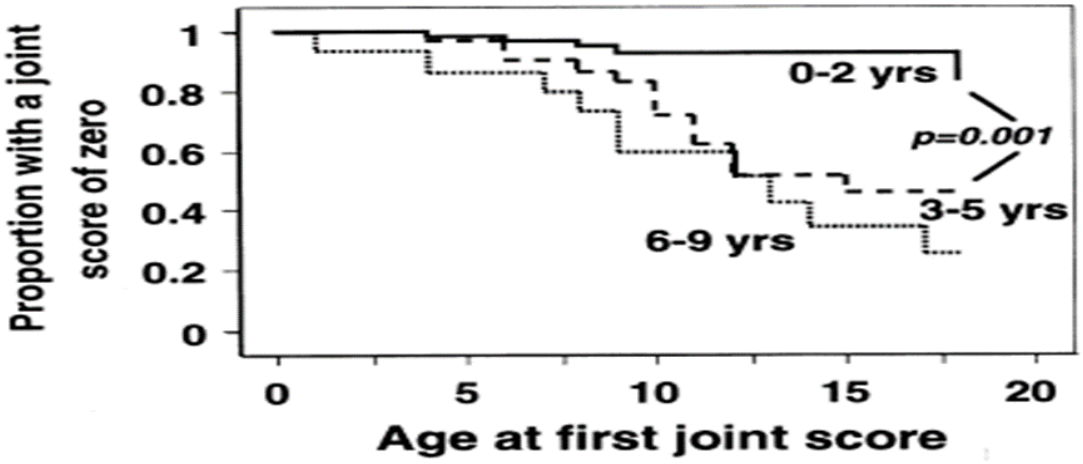
Effective therapy normalizes life expectancy



Darby et al, 2007

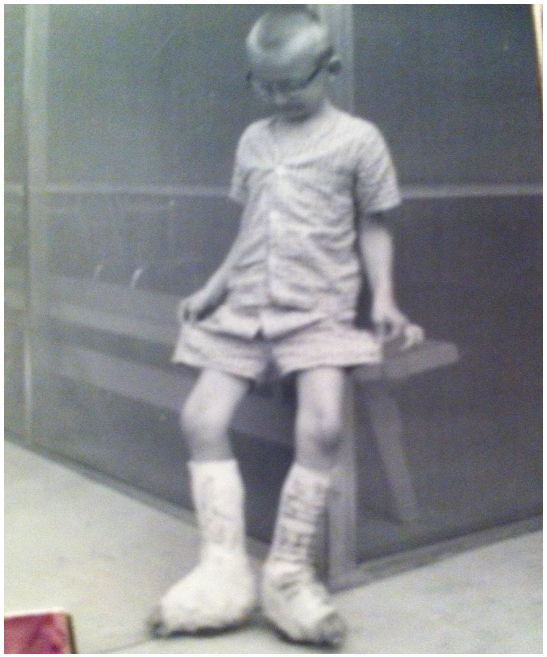
Joint Disease: Prevent by Primary Prophylaxis

- 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

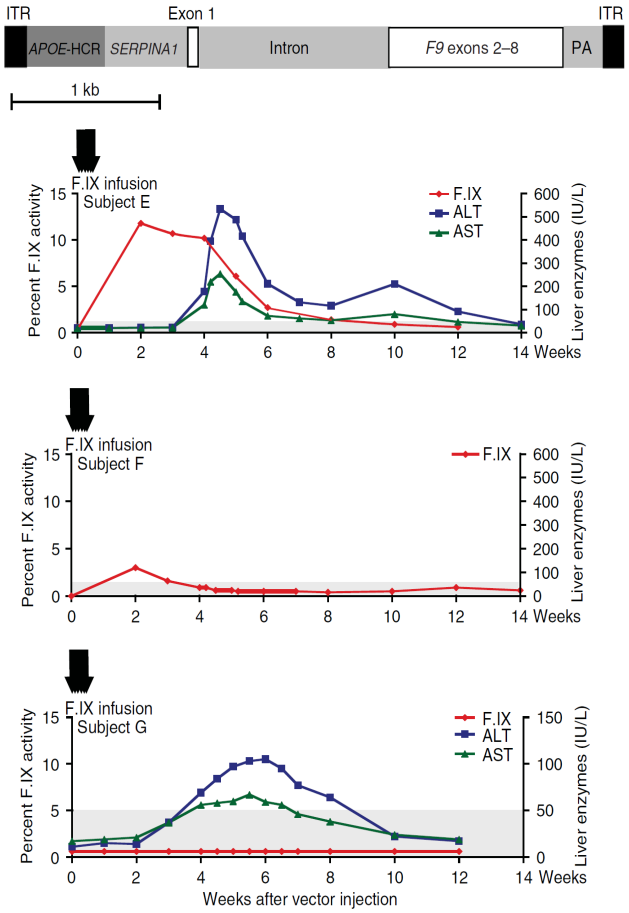
Gene Therapy Approaches in Hemophilia

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

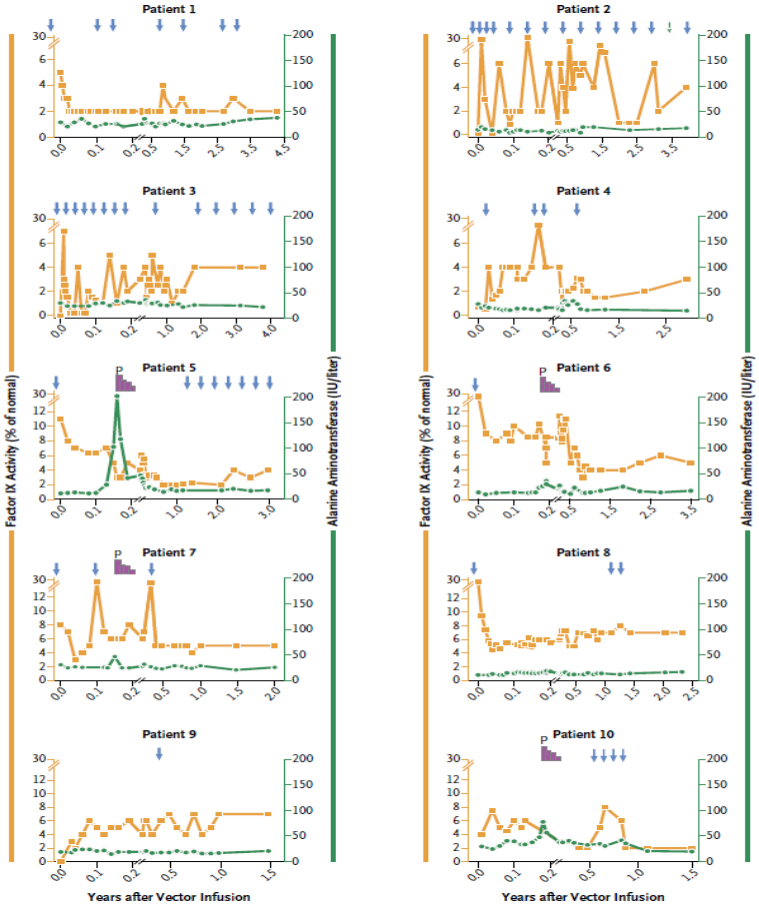


This slide contains information about a product that has not been approved by the Therapeutic Goods Administration.
Image from Manno *et al*.[3]
AAV: Adeno-associated virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.
1. Kay MA, et al. *Nat Genet* 2000;24:257. 2. Buchlis G, et al.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

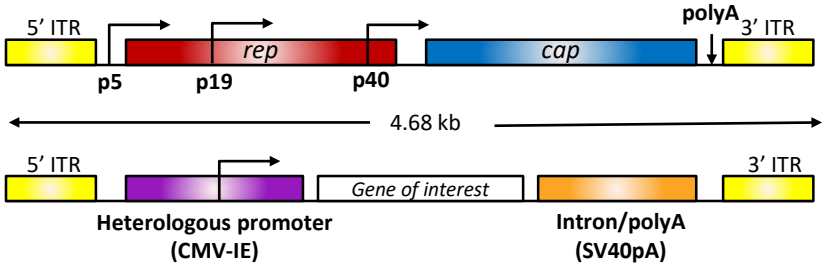
- Persistent FIX activity reported to date
  - Marked decrease in factor consumption
- Loss of transgene associated with transaminitis responsive to steroid therapy
- Study in long-term follow up



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.

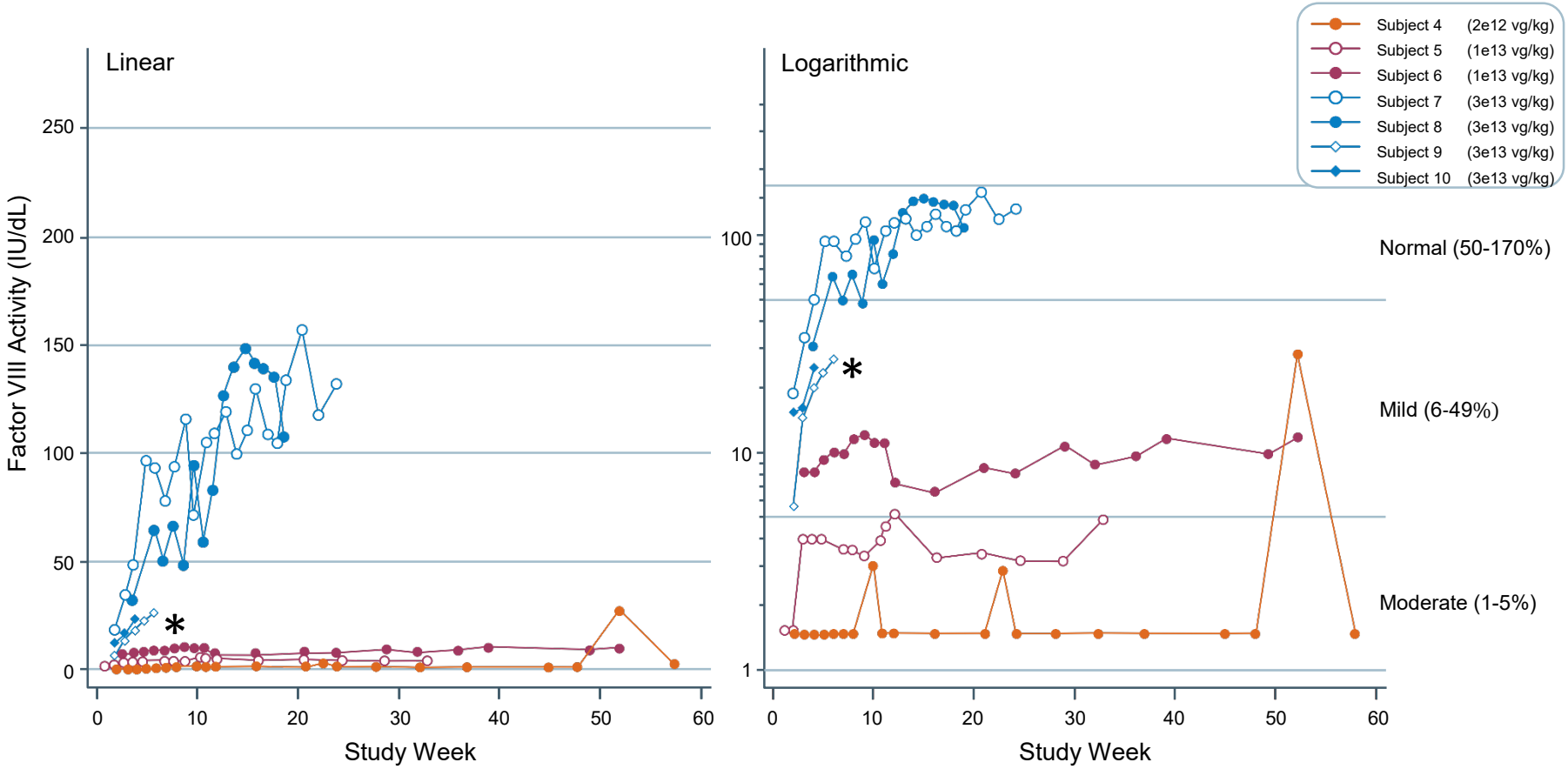
Successes in Haemophilia Gene Therapy

- 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

Staff Track -Tuesday, July 30

UW Husky Union Building

Room 145

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

The Human Research Protection Program

Presented by Adrienne Meyer, MPA, CIP

9:30am-10:30am

UW Husky Union Building

Room 145

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

The Human Research Protection Program

Cultivating a Partnership with Your IRB

Adrienne Meyer, MPA, CIP
Assistant Director, Reliances
Human Subjects Division

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

Learning Objectives

- Discuss the dynamic relationship of the IRB and research staff in the regulatory compliance environment
- Describe, and possibly begin to create a strategy for how to plan a response to the IRB
- Identify the location of resources for partnering with the IRB

There is nothing insignificant in the world. It all depends on the point of view.

-- Johann Wolfgang von Goethe

If you wish to please people, you must begin by understanding them.

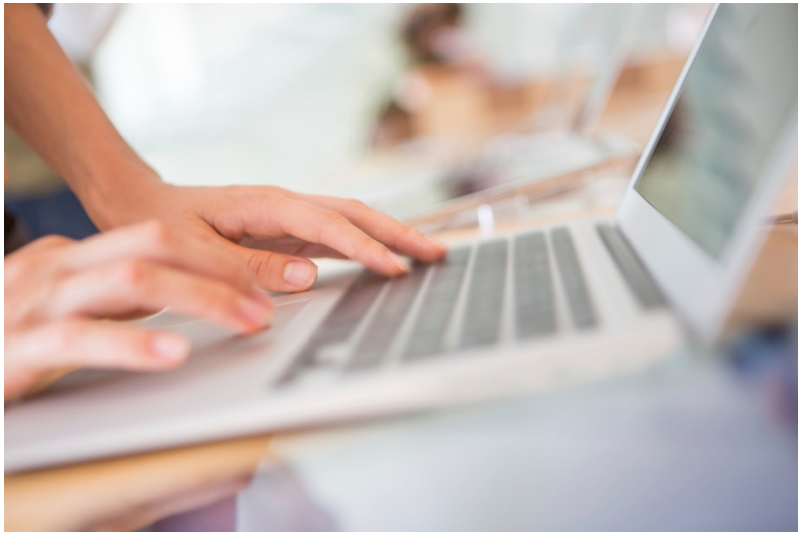
– Charles Reade

What role does the IRB play?

The primary purpose of the IRB is to protect the rights and welfare of human subjects involved in research activities being conducted under its authority.

The IRB primarily does this by reviewing research protocols before they are implemented and assessing them against:

- Federal Regulations
- State Laws
- Institutional Requirements



Federal Regulations

- Common Rule (45 CFR 46)
- FDA Regulations (21 CFR 50 and 21 CFR 56)
- HIPAA Privacy Rule
- Family Educational Rights and Privacy Act (FERPA)*
- Protection of Pupil Rights Amendment (PPRA)*

Example: Federal Criteria for IRB Approval

- Risks to subjects are minimized using
  - procedures consistent with sound scientific design and which do not unnecessarily expose subjects to risk
  - whenever appropriate by using procedures already being performed on subjects for diagnostic or treatment purposes
- Risks are reasonable in relation to anticipated benefits
- Selection of subjects is equitable (no groups are being exploited)
- Informed consent will be obtained or meets criteria for being waived
- Informed consent will be documented or meets criteria for being waived
- Privacy and confidentiality will be protected as appropriate to the study
- Data and safety monitoring provisions are appropriate to the study
- Additional protections for vulnerable populations such as children and prisoners

State and Other Laws

APPLICABILITY OF THESE LAWS DEPENDS ON LOCATION OF RESEARCH AND OTHER FACTORS SPECIFIC TO THE RESEARCH

- WA State Law → additional considerations for use of medical records
- CA State Law → additional requirements for consent information presented
- Various → age of majority, mandatory reporting

Institutional Requirements

- Training and qualifications of research team
- Coordination with other review offices
  - Office of Sponsored Programs (OSP)
  - Radiation Safety
  - Institutional Biosafety Committee
  - Financial Conflict of Interest Review
- Policies about how recruitment or other aspects of the study must be carried out
- Metrics and reporting requirements for the institution

The IRB Needs Information

- Initial Application
- Requests for additional information
  - Pre-Review
  - Deferral
  - Conditional Approval
- Status Reports
- Modifications
- Reports of New Information

Empowered Responses to IRB Requests Consider Four Things

- What information does the IRB want?
- Why does it want that information? (What is it trying to determine or decide?)
- What is the best source for that information?
- How should we respond?

Exercise: What does the IRB want and why?

The committee is not clear as to whether children will be enrolled because guidelines for children are described as part of the exclusion criteria for population 1 in section 2.2 of the IRB Protocol.

- Please clarify whether children will be enrolled either as part of population 1 or 2?

- If not, please delete references to children in 2.2 and references to assent in 2.2 and 5.1.

- The committee suggests that you consider that the inclusion of children in population 2 may increase the scientific validity of your data. If you would like to do so, you can either revise the application now to include children or submit a subsequent modification.

Activity: What information does the IRB want and what is the best source for the information?

- **Refer to handouts**

But why, why, why can't people just say what they mean?

– Graeme Simsion

In terms of asking questions, I plead guilty. I ask a hell of a lot of questions. That's my job.

-- Dick Cheney

The Study Team Needs Information Too

The Research Coordinator should play a key role in obtaining information for the study team:

- What information about the study is the IRB going to need? Do we have it all?
- What are the most likely concerns that the IRB will have? Can we address them ahead of time?
- Do we clearly understand what the IRB is asking? Do we need to request clarification?
- Are there any special considerations for this study? What do we do about that?

Activity:
What information do you need and how will you get it?

Preparing Effective Responses

- Write in lay language
- Address *every* request in each question
- Address *every* question
- Format for readability
- Be courteous and professional

Learning Objectives

- Discuss the dynamic relationship of the IRB and research staff in the regulatory compliance environment
- Describe, and possibly begin to create a strategy for how to plan a response to the IRB
- Identify the location of resources for partnering with the IRB

UW Clinical Trials Office: Compliant Research Billing

Presented by Will Dean, Eli Reis, Laurel Weigler

10:40am-11:40am

UW Husky Union Building

Room 145

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

UW CLINICAL TRIALS OFFICE: COMPLIANT RESEARCH BILLING

INTRODUCTION TO CLINICAL RESEARCH BOOT CAMP

WILL DEAN
ELI REIS
LAUREL WEIGLER
JULY 30, 2019

UW Medicine

SESSION TOPICS

What is the CTO?

What does this mean to your work?

The UW Medicine policies that support the compliant research billing

CTO CRBB – WHO WE ARE AND WHAT WE DO

CTO CRBB is a department within the UW School of Medicine created to support clinical research billing compliance through:

- ✓ Billing plans
- ✓ Sound budgeting
- ✓ Operational assistance
- ✓ Policy compliance

Why do we need a support offices like the CTO CRBB?

Is it really that complicated?

RESEARCH COMPLEXITY

- Clinical research itself is complex
- Federal regulatory requirements
- Medicare billing rules
- Multiple sponsors and funding scenarios sometimes have different rules for billing
- The university's decentralized institutional structure and multiple sites of practice
  - Diverse set of medical specialties & faculty investigators
  - Department-specific processes & procedures

SERVICES AND SUPPORT

Services we provide:

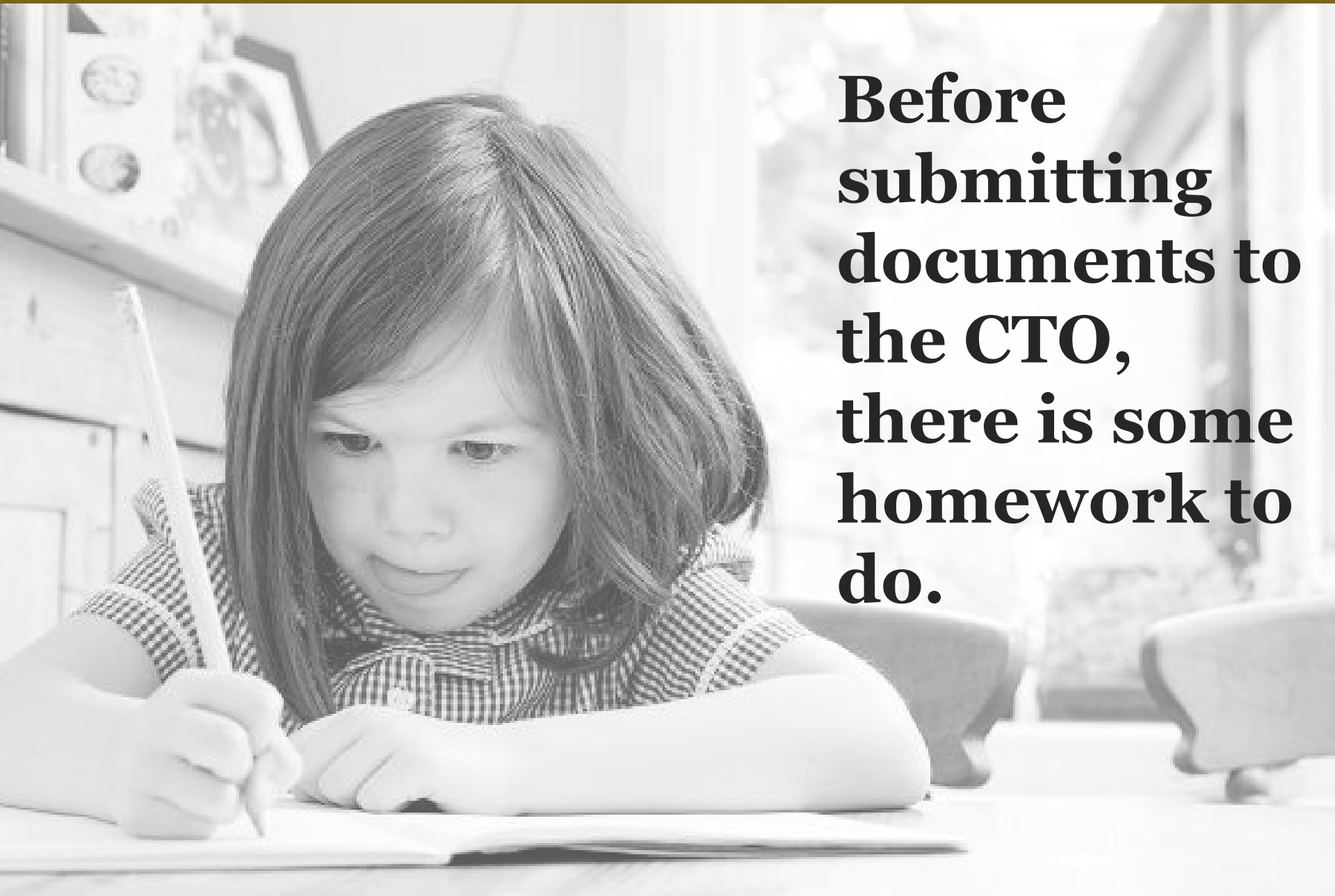
- Pricing for study-billable services, items, and tests
- Coverage analysis
- Billing grid production
- Budget development and negotiation
- Verify alignment among study documents
- UW clinical facility billing for research

SERVICES AND SUPPORT

Typical clinical research studies interact with the CTO throughout life of the study protocol.

- Pre-submission
- Submission
- Review
- Study Implementation
- Post Implementation
- Study Close Out

STUDY STAFF RESPONSIBILITIES: PRE-SUBMISSION



Before submitting documents to the CTO, there is some homework to do.

STUDY STAFF RESPONSIBILITIES: PRE-SUBMISSION

- ✓ Evaluate financial feasibility of conducting the study
- ✓ Evaluate the protocol to determine if the study involves any services, items, or tests that will bill to the patient
- ✓ Coordinate with service center managers for availability of services at specific locations
- ✓ Prepare submission documents
- ✓ Determine if you submit via email or through the Study Review and Management Portal (sRAMP)

If you answer 'yes' to any of these questions, you may need to submit via sRAMP.

- Will any study participants have study-related services, items or tests at SCCA Sites of Practice?
- Is this study cancer or cancer-related with study-related services, items or tests? (*Excludes Seattle Children's studies utilizing only CUMG Providers)*
- Is this study conducted by a Principal Investigator who is a Cancer Consortium Member with study-related services, items or tests at UWM Sites of Practice?

Submitting your study to the CTO involves submitting:

- Completed CRBB Intake form or sRAMP Parts 1-3,
- Protocol
- Draft informed consent form
- There may be additional documents, based on study specifics and review requirements

CTO RESPONSIBILITIES: SUBMISSION

Once the CTO receives your submission, we do a cursory evaluation for completion.

If all documents are included and complete, the study undergoes Coverage Analysis.

CTO RESPONSIBILITIES: SUBMISSION

The completed Coverage Analysis is the basis for Billing Grid.

- The CTO Research Coding team verifies codes and adds prices for research related procedures
- Coordinates with UW Radiology, Pathology, Lab Services and IDS, AKA "The Big Four," to determine the pricing for their services
- Returns completed pricing to study team

CTO RESPONSIBILITIES: REVIEW

During Review, CTO Budget Specialists review the study documents:

- For facility and professional services vs effort
- For document alignment

CTO RESPONSIBILITIES: IMPLEMENTATION

Once the CTO completes its review and the contracts have been signed, the CTO is responsible for:

- ✓ Creating the Epic Research Study Account
- ✓ Notifying study teams and relevant departments of the Epic Research Account creation

CTO RESPONSIBILITIES: POST IMPLEMENTATION

After your Epic Research Account is implemented, the CTO:

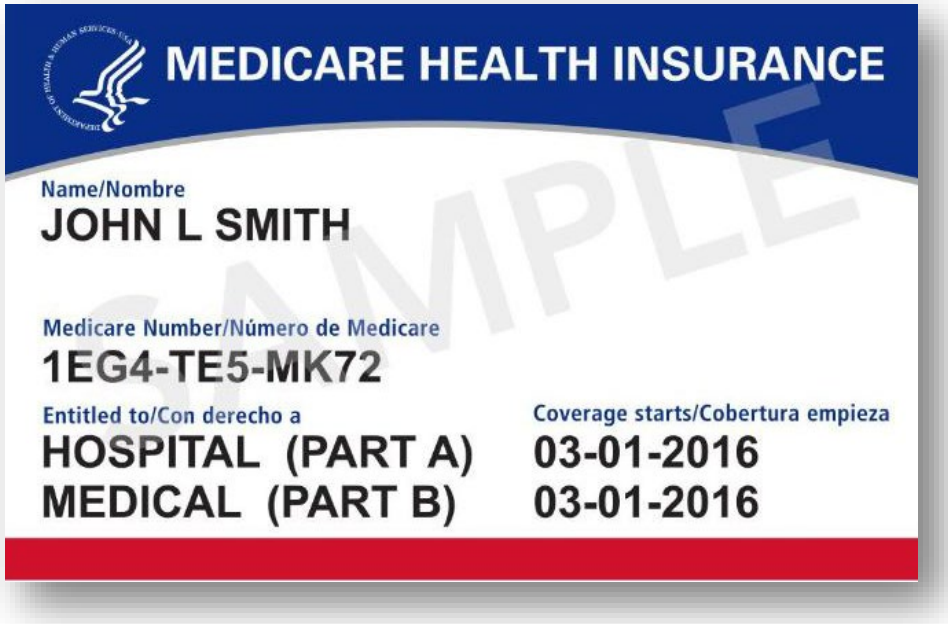
- Monitors subject enrollment status
- Offers support for the hospital charge submission process
- Invoices your study for UW hospital charges
- Assists with billing error resolution

We may not always have the answer to your specific billing questions, but we're a good starting point for finding the correct resource.

MEDICARE MOTIVATION

Many of the patients who participate in clinical research have Medicare as their health insurance.

Because of its complicated nature, and the possibility of expensive fines, Medicare's policies drive much of the University of Washington's methodology regarding billing for clinical research.



MEDICARE CLINICAL TRIAL HISTORY

- Pre-2000, Medicare did not cover care associated with clinical trials
- 2000 (updated 2007), Medicare National Coverage Decision (NCD) allowed coverage of some costs associated with Qualifying Clinical Trials (QCTs)
- 2003 (updated 2015), Medicare Prescription Drug, Improvement, and Modernization Act (MMA) allowed Medicare payment of the routine costs of care furnished to Medicare beneficiaries in certain categories of Investigational Device Exemption (IDE) studies

MEDICARE: HOW DOES A STUDY QUALIFY?

It fulfills 3 basic requirements for Medicare coverage

&

It possesses 7 desirable characteristics, or is assumed to have those characteristics, mostly because of its funding source

MEDICARE: HOW DOES A STUDY QUALIFY?

Must meet all three requirements

Evaluate an item or service that falls within a Medicare benefit category

Have therapeutic intent

Enroll patients with diagnosed disease

Must be at least one of these requirements

Funded by NIH, CDC, AHRQ, CMS, DOD or VA

Supported by center or cooperative group funded by NIH, CDC, AHRQ, CMS, DOD or VA

Conducted under an investigational new drug application (IND) reviewed by the FDA, DOD or VA

IND exempt under 21 CFR 312.2(b)(1)

MEDICARE: HOW DOES A DEVICE STUDY QUALIFY?

Investigational Device Studies have different criteria. A checklist and application instructions are available on the Center for Medicare and Medicaid Services (CMS) website at: https://www.cms.gov/Medicare/Coverage/IDE/Downloads/IDE-Study-Criteria-Crosswalk-Sep-2014.pdf

1. The principal purpose of the study is to test whether the device improves health outcomes of appropriately selected patients.
2. The rationale for the study is well supported by available scientific and medical information, or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
3. The study results are not anticipated to unjustifiably duplicate existing knowledge.
4. The study design is methodologically appropriate and the anticipated number of enrolled subjects is adequate to confidently answer the research question(s) being asked in the study.
5. The study is sponsored by an organization or individual capable of successfully completing the study.
6. The study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 21 CFR parts 50, 56, and 812, and 45 CFR part 46.

MEDICARE: HOW DOES A DEVICE STUDY QUALIFY?

Continued…

7. Where appropriate, the study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Studies of all medical technologies measuring therapeutic outcomes as one of the objectives may be exempt from this criterion only if the disease or condition being studies is life threatening and the patient has no other viable treatment options.
8. The study is registered with the National Institutes of Health National Library of Medicine's ClinicalTrials.gov.
9. The study protocol describes the method and timing of release of results on all pre-specified outcomes, including release of negative outcomes and that the release should be hastened if the study is terminated early.
10. The study protocol must describe how Medicare beneficiaries may be affected by the device under investigation, and how the study results are or are not expected to be generalizable to the Medicare beneficiary population. Generalizability to populations eligible for Medicare due to age, disability, or other eligibility status must be explicitly described.

COVERAGE ANALYSIS

The CTO evaluates protocols to determine how services, items, and tests can be billed according to Medicare National and Local Coverage Determinations.

- Provides the foundation for the billing grid and resulting budget creation
- If your study has NO patient billables, you may elect to skip coverage analysis and create the billing grid on your own. If this describes your study, contact the CTO for more information.

Research billing is a priority for the Department of Justice (DOJ)

Sample of Research-related Settlements:

- 2005 Rush University ($1M)
- 2010 USC/Tenet Healthcare ($1.9M)
- 2013 Emory University ($1.5M)
- 2019 GenomeDX Biosciences Corp ($1.99M)

RESEARCH BILLING RISKS

Double-billing research services by accepting sponsor funding and billing patient (Medicare) for the same services.

Requires that we identify up front the appropriate payer for each service and budget accordingly.

RESEARCH BILLING RISKS

Billing non-covered research services to Medicare, or billing covered services incorrectly.

✓ Requires clear billing plan for each service (Billing Grid)

✓ Requires that charges are directed accurately **at the point of care**

RESEARCH BILLING RISKS

2005 Rush University - $1M
2010 USC/Tenet - $1.9M
2013 Emory - $1.5M
2019 GenomeDx Biosciences Corp - $1.99M

- Accepted funding from grant/contract and also billed Medicare, i.e., **double billing**
- Billed Medicare for services that were stated to be "free of charge" in ICF
- Received reimbursement for services that were not medically necessary
- Received reimbursement for services provided in the context of a non-QCT

UW Medicine

Clinical Research Policies

UW MEDICINE CLINICAL RESEARCH POLICIES

Budgeting and Billing Requirements for Clinical Research Using UW Medicine Faculty, Facilities or Services- COMP.202

- Established in 2015, Current Version Effective October, 2017
- Outlines operational and reporting requirements
    - When clinical research studies require pre-implementation review by the CTO
    - On-study and post-study research-related reporting requirements
    - Medical record documentation requirements

UW MEDICINE CLINICAL RESEARCH POLICIES

Which Studies Are Within Scope?

- All clinical research utilizing the services of a member of UW Physicians (UWP), at any site of practice
- All studies that involve services, items or tests provided by a facility that bills through the CTO or HMC/UWMC/NWH Patient Financial Services (PFS), whether the services are billed to study subjects, study budgets or both

UW MEDICINE CLINICAL RESEARCH POLICIES

Budgeting and Billing Requirements for Clinical Research Applies to Studies That Involve:

Services, items, or tests billed to a study

Services, items, or tests billed to a patient/third party payer as part of a QCT

...or studies that involve a combination of both patient and study billing.

POLICY STATEMENT #1

Each clinical research study must be conducted pursuant to the study's Medicare coverage analysis and an approved billing grid that serves as a guide for appropriately directing and coding charges to the study account, the study subject, or a third party payer…

Site(s) of Service		Clinical Service or Item Description	CPT (or EAP if needed when Billed to Research)	Cost Center (when Billed to Research)	P/E	S	I	Visit Short Title	SCRN D-56	SCRN D-28	SCRN D-14	C1D1	C1D8	C1D15	C2D1	C2D8	C2D15
								Visit Day #									
								Visit Window				+/- 1d	+/- 1d	+/- 1d	+/- 1d	+/- 1d	+/- 1d
								Week/Cycle →									
								Comments ↓									
Billed	UWMC/SCCA	HC FLUORODEOXYGLUCOSE F-18 FDG DX UP TO 45 MCI	A9552	96700				INV if done outside of SOC window ($)									
	UWMC/SCCA	B1&/JT IMG WHBDY	78306	99200	P	S		INV if done outside of SOC window ($)									
	UWMC/SCCA	HC TECHNETIUM TC-99M MEDRONATE DX UP TO 30 MCI	A9503	99200				INV if done outside of SOC window ($)									
	SCCA	HC FOB L4 ESTABLISHED OUTPT VISIT	99211-99215	72900, 73500, 73600, 75300, 75500, 75600, 97600	P			Any levels between II-V; Occur in Lung/Head/Neck, GI, GU, GynOnc, GenOnc, Breast or Melanoma/ Renal clinic; Includes PE, ECOG, Vitals & weight; INV if outside of SOC window at SCRN					1	1		1	1

UW Medicine

POLICY STATEMENT #1

…and be reviewed by the CTO **in advance** of opening the study to subject accrual.

POLICY STATEMENT #2

For industry-funded research contracted through the UW, a study budget which includes a billing grid must be submitted to the CTO and reviewed prior to the execution of the research contract.

POLICY STATEMENT #3

Clinical services, items or tests billed to study sponsors, study subjects, and/or study subjects' Medicare, Medicaid, or other third party payers must be fully documented in the medical record and be consistent with:

- applicable billing rules of the third party payer being billed
- UW Medicine procedures that establish safeguards to prevent billing errors and
- any grant provisions or contractual obligations entered into by UW Medicine or study sites

POLICY STATEMENT #4

Potential costs to the study subject or subject's third party payer associated with participating in the research study must be:

1. clearly disclosed in the Informed Consent Form (ICF) and signed by the study subject; and

2. represented consistently across all study related documents, including the protocol, grant, contract, budget, billing grid and ICF

POLICY STATEMENT #5

All study subjects must:

- Be registered as patients of every UW Medicine hospital and/or site where study services will be delivered, under the procedures applicable at each site;
- Have appropriate information about their research participation documented in their medical record in accordance with the policies of the study site

POLICY STATEMENT #5

All study subjects must:

- Have their initial study enrollment and subsequent enrollment status changes reported within one business day, using the tools and procedures established by the UW School of Medicine/CTO. Specific reporting methods and/or additional requirements may be established by the clinical sites of practice where the study is conducted.

POLICY STATEMENT #5

All study subjects must have every:

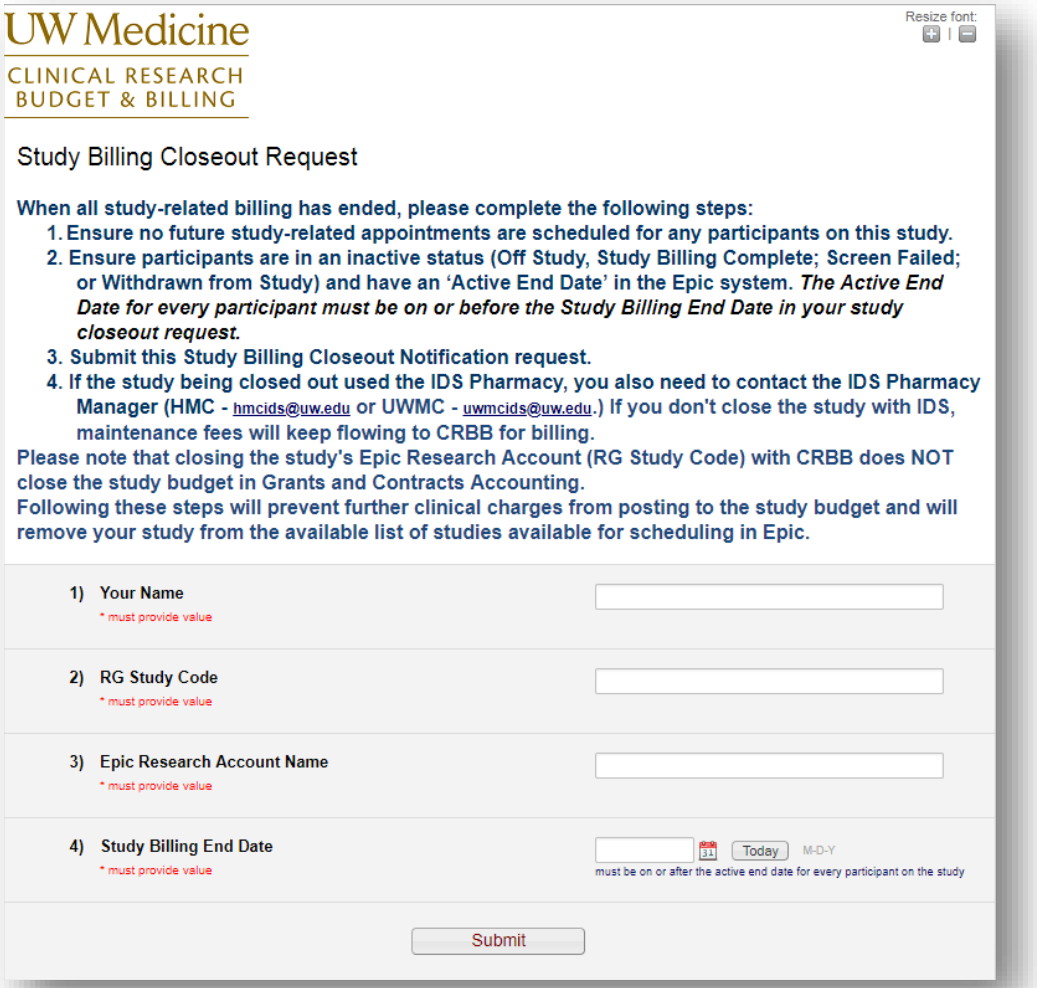
- UW Medical Center,
- Northwest Hospital,
- Harborview Medical Center and
- Seattle Cancer Care Alliance…

Emergency Department (ED) or inpatient admission reported to CTO CRBB when the encounter may include study-related clinical services, items or tests, unless otherwise directed. Study-related hospital inpatient admissions and ED visits must be reported within one business day of the subject's admission.

POLICY STATEMENT #6

The CTO must be informed when all study subjects have received all services in the study billing grid and study billing has ended.

This is accomplished by completing the REDCap Study Billing Closeout Notification located on the CRBB website at:



UW Medicine
CLINICAL RESEARCH BUDGET & BILLING

Resize font:

Study Billing Closeout Request

When all study-related billing has ended, please complete the following steps:

1. Ensure no future study-related appointments are scheduled for any participants on this study.
2. Ensure participants are in an inactive status (Off Study, Study Billing Complete; Screen Failed; or Withdrawn from Study) and have an 'Active End Date' in the Epic system. *The Active End Date for every participant must be on or before the Study Billing End Date in your study closeout request.*
3. Submit this Study Billing Closeout Notification request.
4. If the study being closed out used the IDS Pharmacy, you also need to contact the IDS Pharmacy Manager (HMC - hmcids@uw.edu or UWMC - uwmcids@uw.edu.) If you don't close the study with IDS, maintenance fees will keep flowing to CRBB for billing.

Please note that closing the study's Epic Research Account (RG Study Code) with CRBB does NOT close the study budget in Grants and Contracts Accounting.
Following these steps will prevent further clinical charges from posting to the study budget and will remove your study from the available list of studies available for scheduling in Epic.

1) Your Name
* must provide value

2) RG Study Code
* must provide value

3) Epic Research Account Name
* must provide value

4) Study Billing End Date
* must provide value
Today M-D-Y
must be on or after the active end date for every participant on the study

Submit

https://depts.washington.edu/crbb/Closeout.shtml

REPORTING TIMELINE SUMMARY

1. Clinical research subject enrollment status
   - Within one working day of status change
   - Via Epic or OnCore
2. Study-related inpatient or ED admissions
   - Within one working day of admission
   - Via Epic In Basket message
3. Research study account billing close-out
   - Within 45 days of final billing end
   - Via REDCap survey

UW School of Medicine

Clinical Research Faculty Effort Policy

FACULTY EFFORT POLICY

Established September 2009 to address professional services & faculty effort for clinical research studies

School of Medicine faculty must fully account for all their professional services in clinical research as either:

Effort on a grant or contract (i.e. budgeted salary) if they are the PI or 'key personnel' for the study

OR

Professional fees charged to a patient/third party, Epic Research Study Account, or recharge center

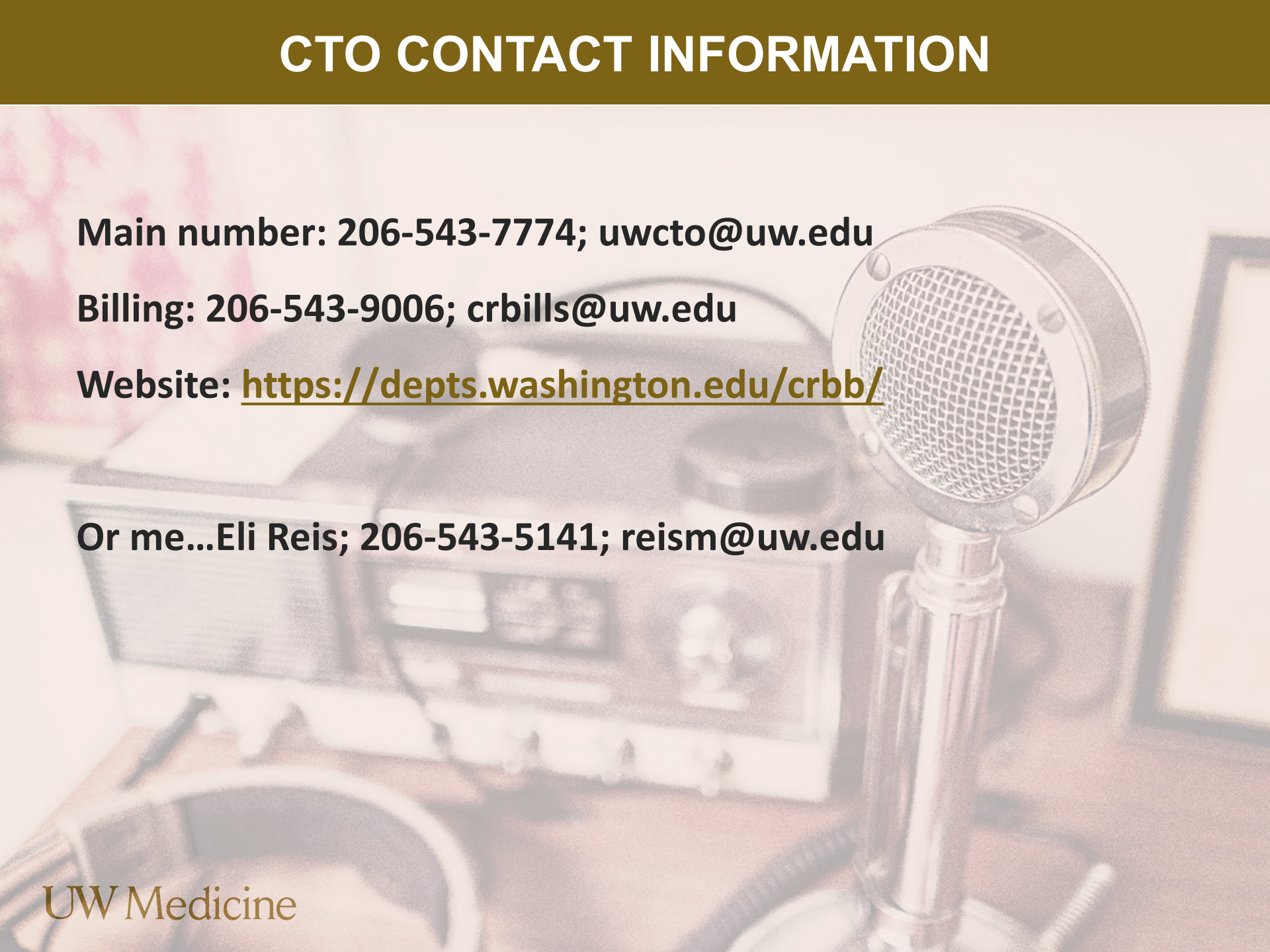
CTO CONTACT INFORMATION

Main number: 206-543-7774; uwcto@uw.edu

Billing: 206-543-9006; crbills@uw.edu

Website: https://depts.washington.edu/crbb/

Or me…Eli Reis; 206-543-5141; reism@uw.edu



UW Medicine

Collaboration via CTMS

Presented by Oscar Cano

Tuesday, July 30

1:00pm-2:00pm

UW Husky Union Building

Room 145

COLLABORATION VIA CTMS

July 30th, 2019

Oscar Cano

CTMS Product Manager

ocano@fredhutch.org

CTMS Program Office

CTMS_Office@fredhutch.org

AGENDA

- What is CTMS?
  - OnCore
  - CTMS Program Office
  - Current and Upcoming OnCore Features
- Activity
- Collaborating on a Clinical Trial - Discussion
- OnCore as a Collaboration Tool
- Debrief
- Q&A

WHAT IS CTMS?

Introduction to CTMS Program Office and OnCore

ONCORE

What is the OnCore CTMS?

- ❑ A Clinical Trials Management System (CTMS) is a data management software that stores clinical trial information.

- ❑ OnCore is the CTMS we use across Fred Hutch, University of Washington and Seattle Cancer Care Alliance.

OnCore

ONCORE

Who has access to OnCore?

- ❑ PI's
- ❑ Research Managers
- ❑ Study/Research Coordinators
- ❑ Data Managers
- ❑ SRC Reviewers
- ❑ Regulatory Coordinators/Managers
- ❑ Directors and VPs
- ❑ Research Scientists
- ❑ Project Managers
- ❑ Research Nurses
- ❑ Administrative Coordinators/Managers

CTMS PROGRAM OFFICE

Cross-Institutional Background

- The Fred Hutchinson/University of Washington Cancer Consortium is a research collaboration comprising Fred Hutch and its strong collaborators: the University of Washington, Seattle Children's, and the Seattle Cancer Care Alliance.
- The Consortium is recognized as an NCI-designated Comprehensive Cancer Center.
- The OnCore CTMS is currently used for all oncology studies in the consortium and for Fred Hutch non-oncology studies.
- The OnCore CTMS will also be used for UW non-oncology studies, which are part of our continuing implementation.

CTMS PROGRAM OFFICE

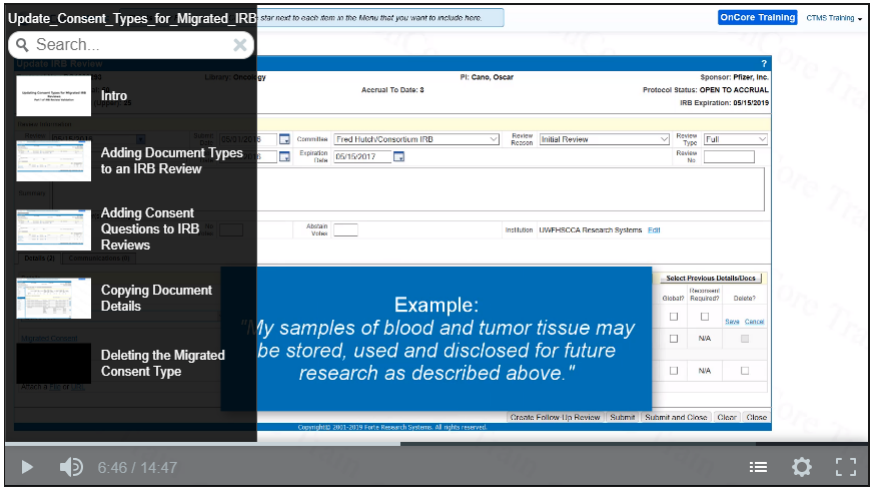
What is the CTMS Program Office?

- The CTMS Program Office is responsible for the implementation and ongoing operation of the CTMS and maintains neutrality across institutions.
- The CTMS Program Office aims to empower study teams to advance clinical research and enable administrators to gain insight on research data through collaboration across our institutions.

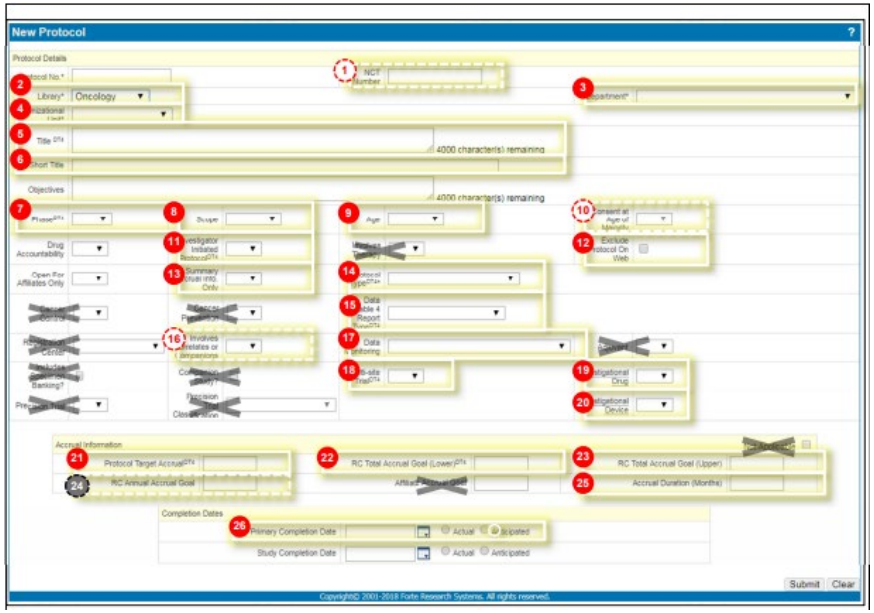
CTMS PROGRAM OFFICE

CTMS Program Office Services

- OnCore Training
  - On-demand, at your desk, video based training
  - In-person group training for ad-hoc topics available on request
- OnCore Support
  - Troubleshooting and live help for OnCore workflows
  - OnCore and access issue resolution



CTMS PROGRAM OFFICE



CTMS Program Office Services

- Quality Control of OnCore data
  - Monitoring of reportable fields for completion
  - Study team notification of missing or incomplete data

ACTIVITY

Build a Structure to Support the Cell

ACTIVITY

Scenario

- ❑ As a team, build the tallest structure possible that will support a 4oz cell toy.
- ❑ Each table is a team.
- ❑ Every person on the team will be assigned a building material.

Materials

- ❑ 10 Marshmallows
- ❑ 10 Pipe Cleaners
- ❑ 10 Building Blocks
- ❑ 10 Building Blocks
- ❑ 10 Poker Cards
- ❑ 10 Strips of Tape
- ❑ 2 Chopsticks
- ❑ 1 Small Tub of Putty

Rules

- ❑ Each person can only use their assigned building material.
- ❑ The building materials can be used and altered as needed, however only the provided materials can be used.
- ❑ Teams do not need to use all materials.
- ❑ A single 4oz cell toy will be floating around if the team would like to test their structure.
- ❑ 10 minute time limit
- ❑ At time, the height of each structure will be measured and the team will place the cell figure on the structure. If the structure doesn't fall, the team stays in. If the structure falls, the team is out. The team with the tallest structure that does not fall, wins.

ACTIVITY

Debrief

- ❑ How did it go?
- ❑ What went wrong?
- ❑ What went well?
- ❑ What would you do differently?

COLLABORATING ON A CLINICAL TRIAL

Discussion

COLLABORATING ON A CLINICAL TRIAL

- What are some common issues you've experienced collaborating within a study team?
  - What about collaborating across teams or with administrative offices?
  - What about across institutions?
- What are some parallels with issues you had collaborating during the activity?
- Recall some of the things that went well during the activity. How can some of those basic concepts be applied to collaboration on a clinical trial?
- What are some resources or tools that you wish you had that would help with collaboration?

ONCORE AS A COLLABORATION TOOL

One Piece of the Toolkit

"It is recognized that well designed trials are the basis for addressing important clinical questions, but science alone will not be sufficient to successfully deliver a trial…Clinical trials all require the same coordinated processes and systems, regardless of the size, scope, costs or duration."

- Farrell B, Kenyon S, Shakur H.
Managing clinical trials

ONCORE AS A COLLABORATION TOOL

The CTMS Program Office aims to empower study teams to advance clinical research and enable administrators to gain insight on research data through collaboration across our institutions.

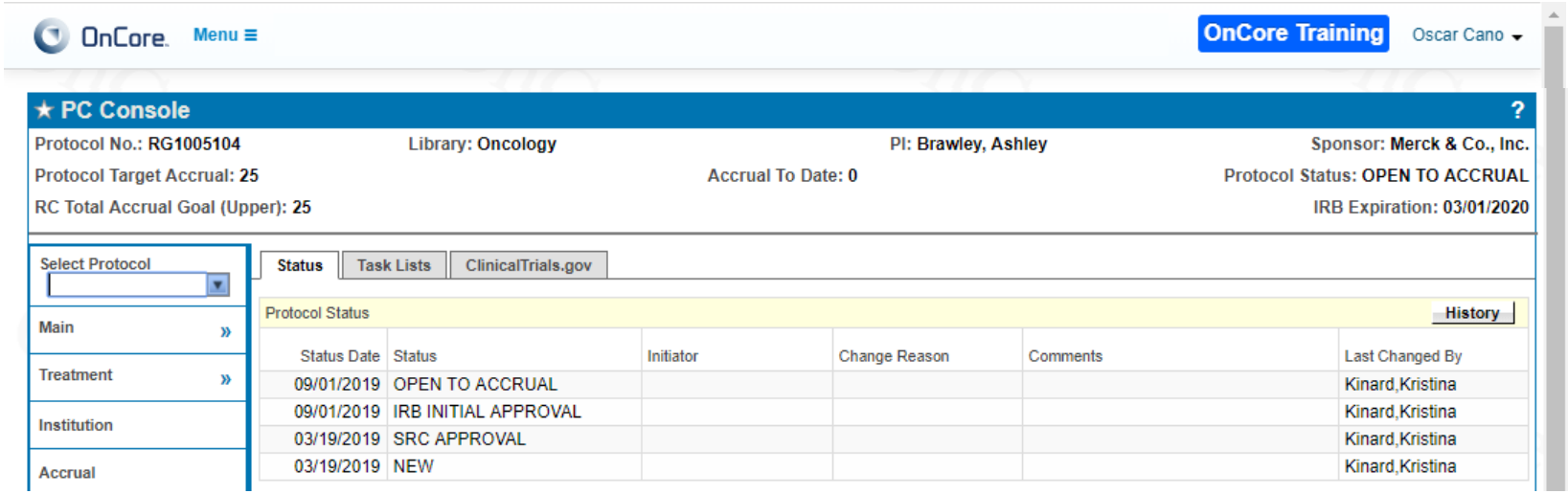
Current Scope:

- ❑ All cancer consortium studies and Fred Hutch non-oncology studies must be entered and managed in OnCore.
  - ❑ Human research studies only
  - ❑ Includes interventional, observational and ancillary/correlative studies

UW non-oncology studies will also use OnCore in the future as part of our continuing implementation.

Protocol Management

- Study details
  - Examples: Title, staff, sponsor, study sites, external protocol numbers
- Study status dates
  - Examples: Open to Accrual date, Closed to Accrual date



Protocol Management

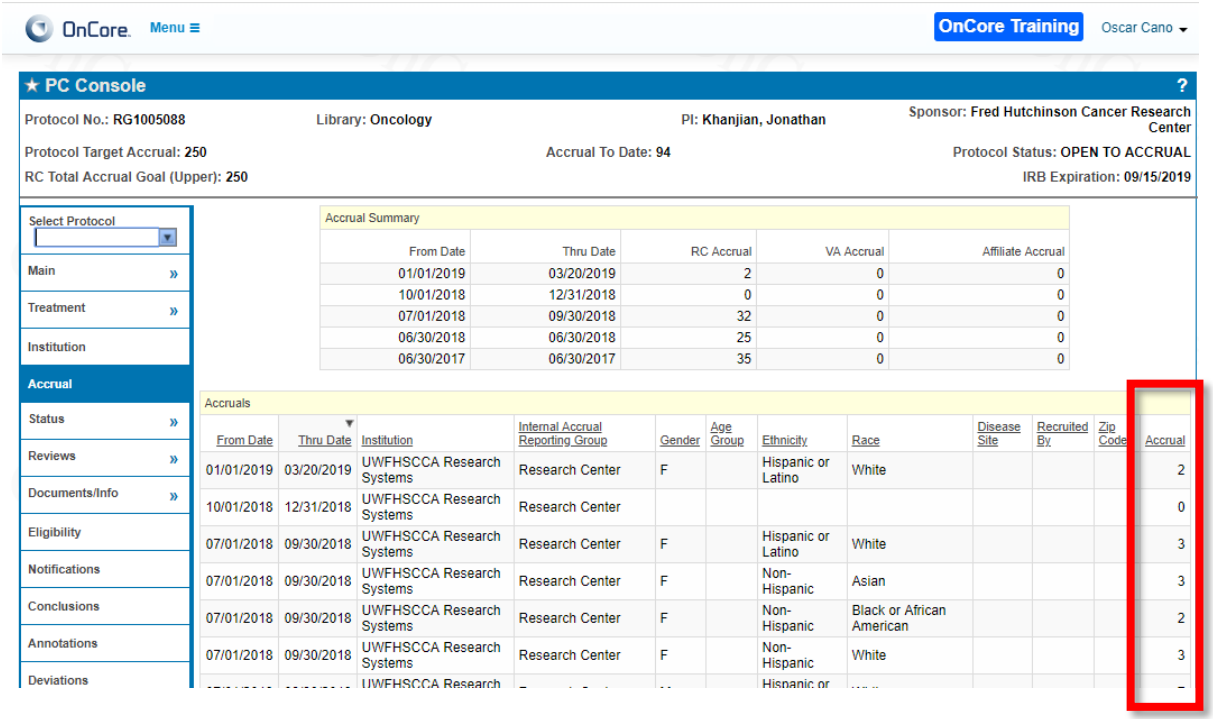
Collaboration Benefits

- Central place to enter, reference and report on high-level study details
  - Example: My team's Regulatory Coordinator enters an IRB Initial Approval in OnCore. This triggers a notification email to staff on that study, which can function as a trigger for additional tasks:
    - The Research manager can then complete the required tasks to Open to Accrual, which will trigger another notification to the team.
    - (Upcoming Feature) The subject coordinator can then go into OnCore and download the approved consent documentation.

DATA MANAGEMENT

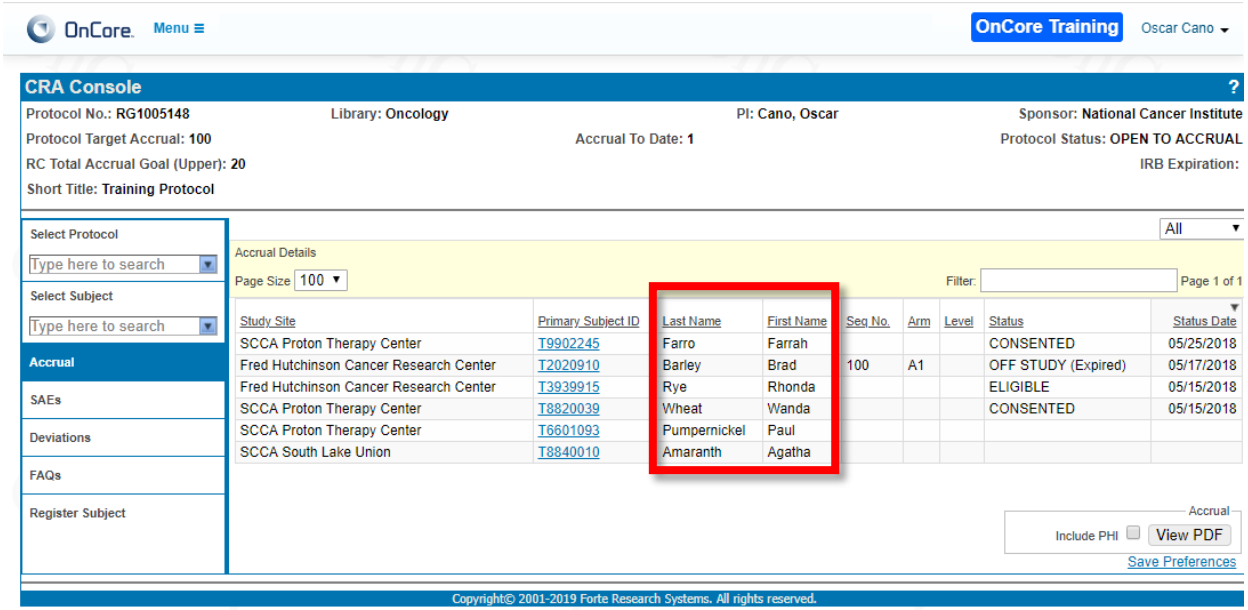
Subject Management

- Ability to record accruals at either:
  - Summary Level
    - Accrual numbers by demographic groups



Subject Management

- Ability to record accruals at either:
  - Summary Level
    - Accrual numbers by demographic groups
  - Granular Level
    - Individual subjects and subject statuses



Subject Management

Collaboration Benefits

- Central place to enter, reference and report on subject details
  - Example: I need to report accrual information for all the studies in my team or for all studies under a certain PI. Since subject milestone dates and statuses were entered as they occurred by various team members:
    - If I need subject level details, I can run a Subject Search out of OnCore and include/exclude which ever data points I need (Demographics, Study Site, Consent Date, On Study Date, Status, etc.). I can also filter by a certain field, such as only including Screen Failures.
    - If I just need an accrual number, I can run a Protocol Search out of OnCore and include Accrual numbers. This will allow me to choose what study details I want to include in addition to Accrual number (Title, IRB #, Study Sites, Protocol Status, etc.).

EPIC INTEGRATION

OnCore is integrated with our Electronic Medical Record (EMR) system, Epic.

- ❑ We receive subject demographic information from Epic
  - ❑ Epic is the source of truth for patient/subject demographics
- ❑ We send study data back to Epic
  - ❑ Protocol #, NCT #, Staff, etc.
- ❑ We also send subject data back to Epic
  - ❑ Protocol # subject is registered to, Subject Status, “Active Start/Stop Dates”, etc.

EPIC INTEGRATION

Collaboration Benefits

- Data entry occurs in the most appropriate system and is automatically updated in the other
  - Example: My study has billing implications that are driven out of Epic but I also need to maintain accruals and study details in OnCore.
    - I can search the EMR to register my subject directly through OnCore. If the subjects demographics are updated in Epic, that information will always flow back to OnCore without me taking any action (name or address change). If the subject expires, that date will automatically flow to OnCore and change the subject status.
    - The protocol details I enter in OnCore will transfer to Epic, including PI and Staff details.
    - This will trigger administrative offices to complete relevant billing tasks in Epic.
    - The Billing Contact I entered in OnCore will be visible in Epic so they can be sent the monthly study invoice.

DATA ACCESSIBILITY AND TRANSPARENCY

OnCore is a centralized tool which is accessible to clinical trial staff and administrative staff across teams and institutions.

- Information entered in OnCore can be viewed by approved staff directly in OnCore or automatically delivered via email report.
  - In general, your data is only viewable by your team and select administrative teams. Your approval is required if an outside study team member needs access to your studies.
- Administrative teams have updated their processes to get data from OnCore instead of via reach out to study teams, where possible.
- The CTMS Program Office proactively reaches out to teams when reportable fields are missing or incomplete.
  - Multiple cross-institutional teams collaborated and agreed on required data points. The CTMS Program Office is continuously working to streamline study team reach out and catch data gaps before they become an issue.

DATA ACCESSIBILITY AND TRANSPARENCY

Collaboration Benefits

- ❑ Where possible, OnCore and the CTMS Program Office act as a link between study teams, administrative offices and data consumers.

UPCOMING ONCORE FEATURES

Upcoming Features

- ❑ Subject calendars
  - ❑ When will a subject be seen, what will be done during each visit, what data will be recorded?
- ❑ Subject visit tracking
  - ❑ Record of what was actually done during a specific visit
- ❑ Financials functionality
  - ❑ Examples: Sponsor invoicing, coverage analysis, study budgeting
- ❑ Store and download most recent IRB reviewed documentation

DEBRIEF

- OnCore is the clinical trial management system (CTMS) we use across Fred Hutch, University of Washington and Seattle Cancer Care Alliance.
- The CTMS Program Office is responsible for the implementation and ongoing operation of the CTMS and maintains neutrality across institutions.
  - Responsible for OnCore training, support and data QC.
- Collaborating on a complex project is difficult
  - See: The tower activity and running a clinical trial
- Where possible, OnCore and the CTMS Program Office act as a link between study teams, administrative offices and data consumers in order to address some of the challenges presented when collaborating on a study.

For more information contact

CTMS Program Office
CTMS_Office@fredhutch.org
http://iths.org/ctms

Accelerating Study Initiation

Presented by Ashley Waldie, MA, CCRP

Tuesday, July 30

2:15pm-3:15pm

UW Husky Union Building

Room 145

Accelerating Study Initiation: Institutional Resources to Catalyze Study Design

FRED HUTCH
UNIVERSITY OF WASHINGTON
CANCER CONSORTIUM
ITHS Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

Ashley Waldie
Start-up Operations Manager
Clinical Research Support (CRS)

Learning Objectives

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

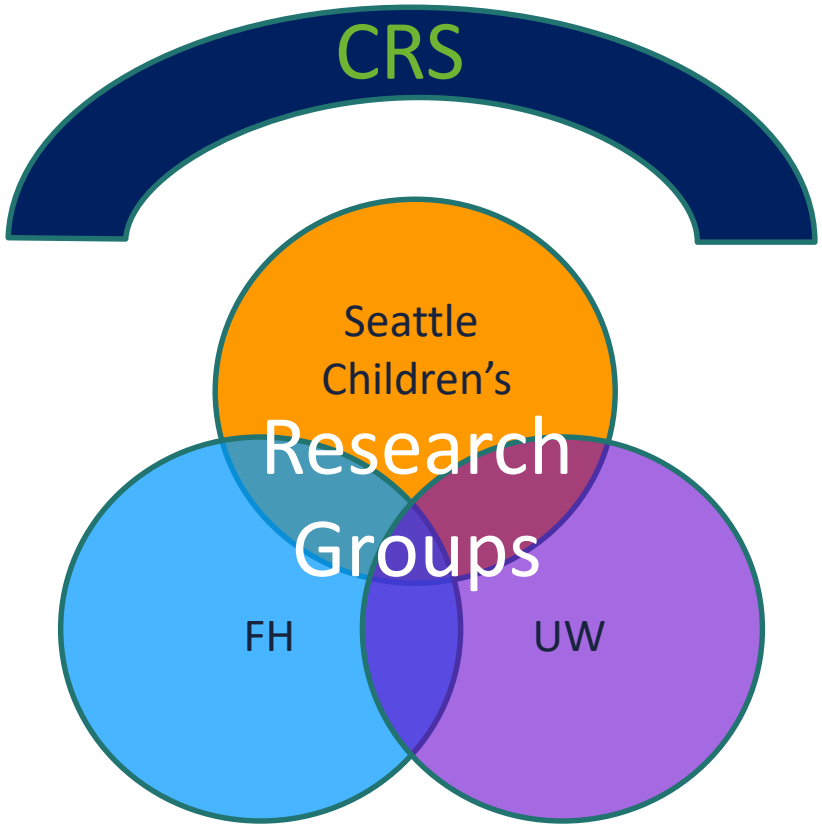
- Describe what minimum documentation or materials you will need from the sponsor
- Describe what feasibility considerations/concerns should be confirmed prior to initiating a new clinical trial
- Describe the timeline for study startup, relative dependencies and setting accurate expectations
- Identify the tools and resources needed for study initiation

Background: Fred Hutch/UW Cancer Consortium

- An NCI-designated Comprehensive Cancer Center
- A collaboration between:
  - Fred Hutch
  - UW
  - Seattle Children's
  - SCCA

Background: Cancer Consortium Clinical Research

- Clinical Research Support (CRS) is the Cancer Consortium's clinical trials office
- Consortium clinical research is organized into 14 Research Groups



14 Research Groups:

- Breast Oncology
- Gastrointestinal Oncology
- GU/Prostate Oncology
- Gynecologic Oncology
- Hematologic Malignancies
- Head & Neck Oncology
- Lung & Thoracic Oncology
- Renal Cell Carcinoma/Melanoma
- Neurologic Oncology
- Sarcoma
- Pediatric Oncology
- Stem Cell Transplantation
- Phase I
- T-Cell Immunotherapy

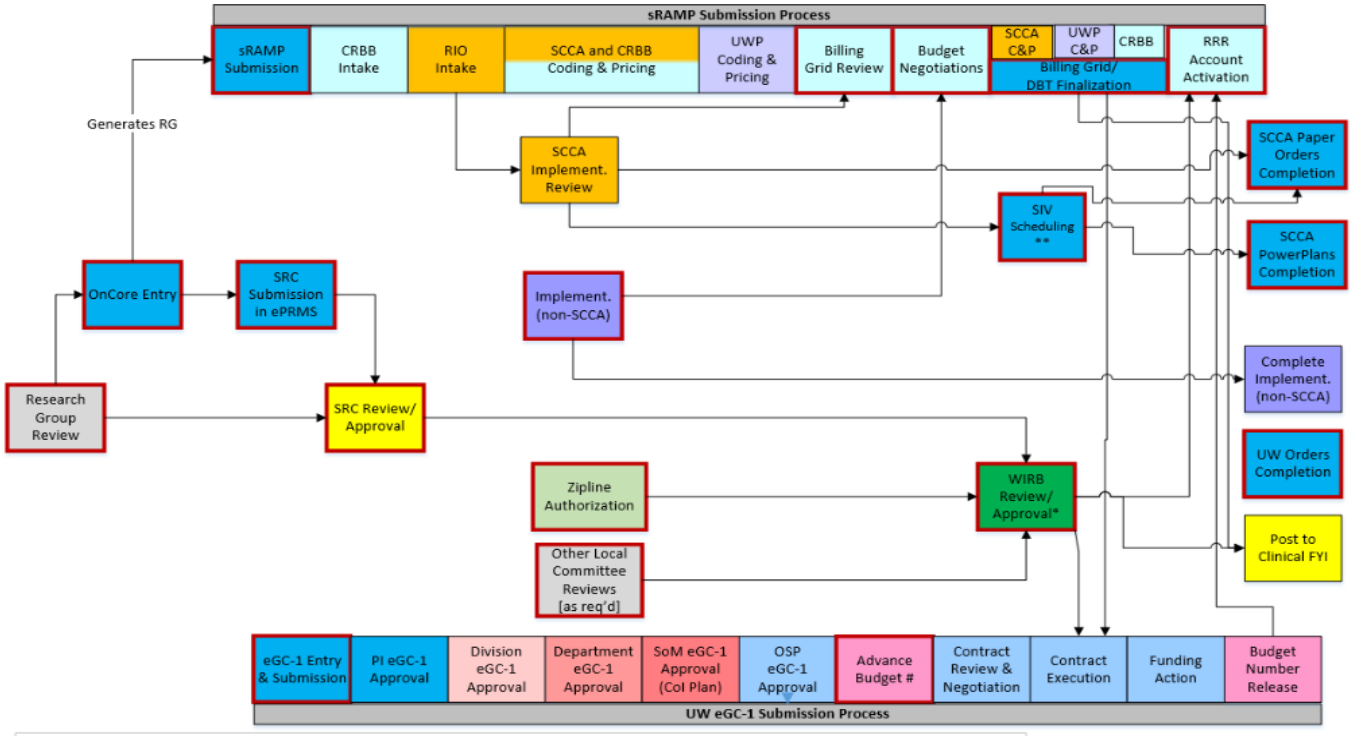
Background: Consortium Clinical Research Roles

- CRS implemented a central startup team with the goal of starting new trials in 100 days

	Study startup	Study Management	Oversight
CRS	• Scientific Review • Document management • FDA submissions • CT.gov registration/CTRP registration • FH Industry contracts	• NCI reporting • Document management • Training, tools & templates • NCTN trial management • FDA reporting	• Data & safety monitoring • Monitoring & auditing • Compliance Sub-committee review • Low accrual review • Staff training
CRS or Study Team	• **Study startup management** • **Review submissions** • **Clinic implementation** • **Regulatory submissions/ and finalization** • **Budget development & negotiation** • **Contract Finalization**	• Regulatory coordination • IND management	• Staff onboarding
Study Team	• Study-specific training	• Subject management • Data coordination • Budget management	• PI oversight • Study staff management

Background: UW-WIRB Study Startup Map

- It is a complicated process involving many departments
- Requires dedicated staff and a plan to navigate efficiently



CRS Study Startup Team Roles

Project Management

- Intake Process
- Timeline creation/monitoring
- Milestone tracking
- Review coordination
- Communications

Budget/Implementation Specialist

- Budget development
- Budget negotiation
- Clinic operations liaison
- Post award management tools
- SIV coordination and facilitation

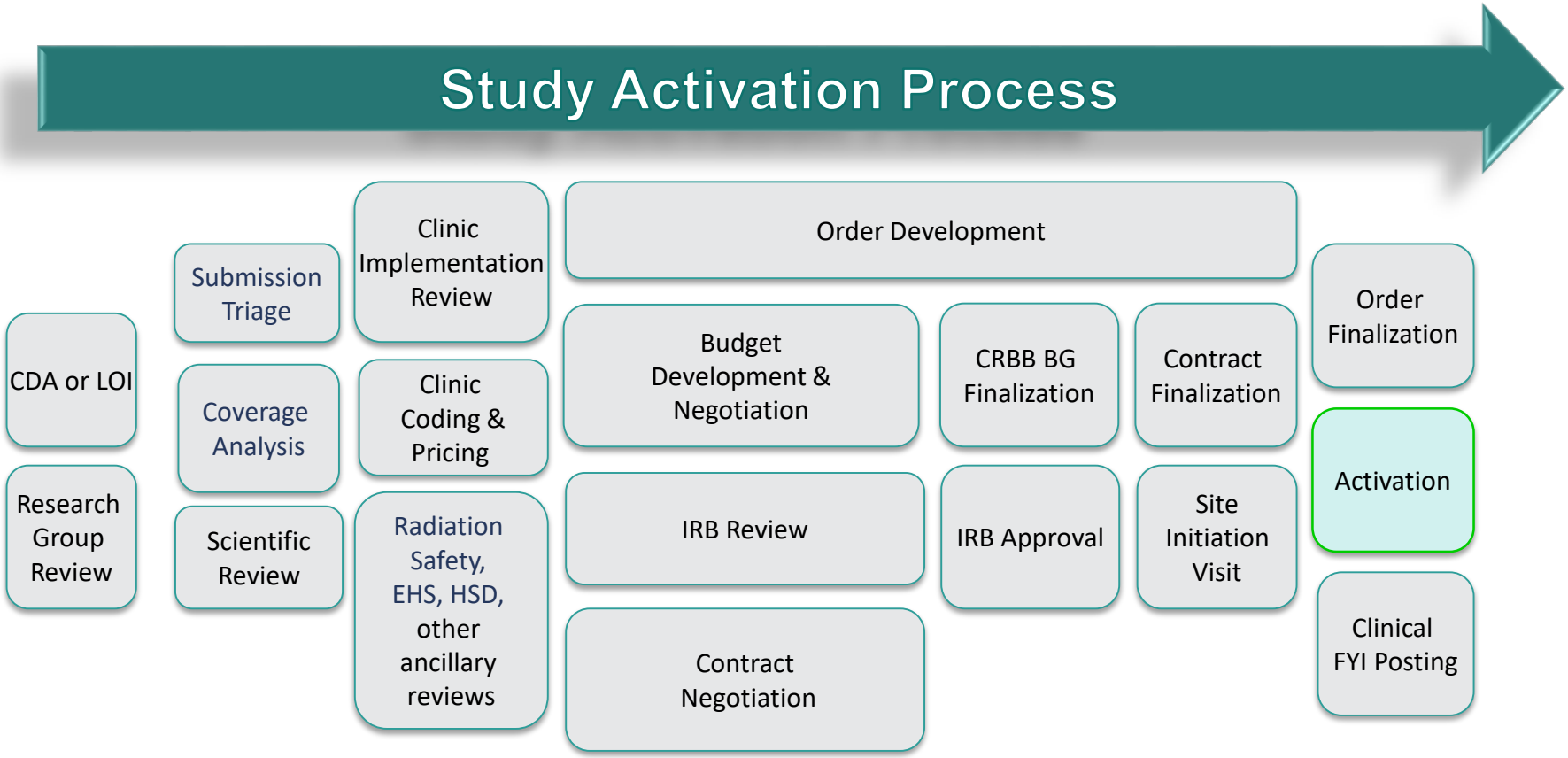
Regulatory Coordination

- Ancillary review submissions/approvals
- ICF writing/finalization
- IRB submission/approval
- Site documentation (training logs, CVs, licenses, Delegation of Authority Log, etc.)

Site Staff Coordination

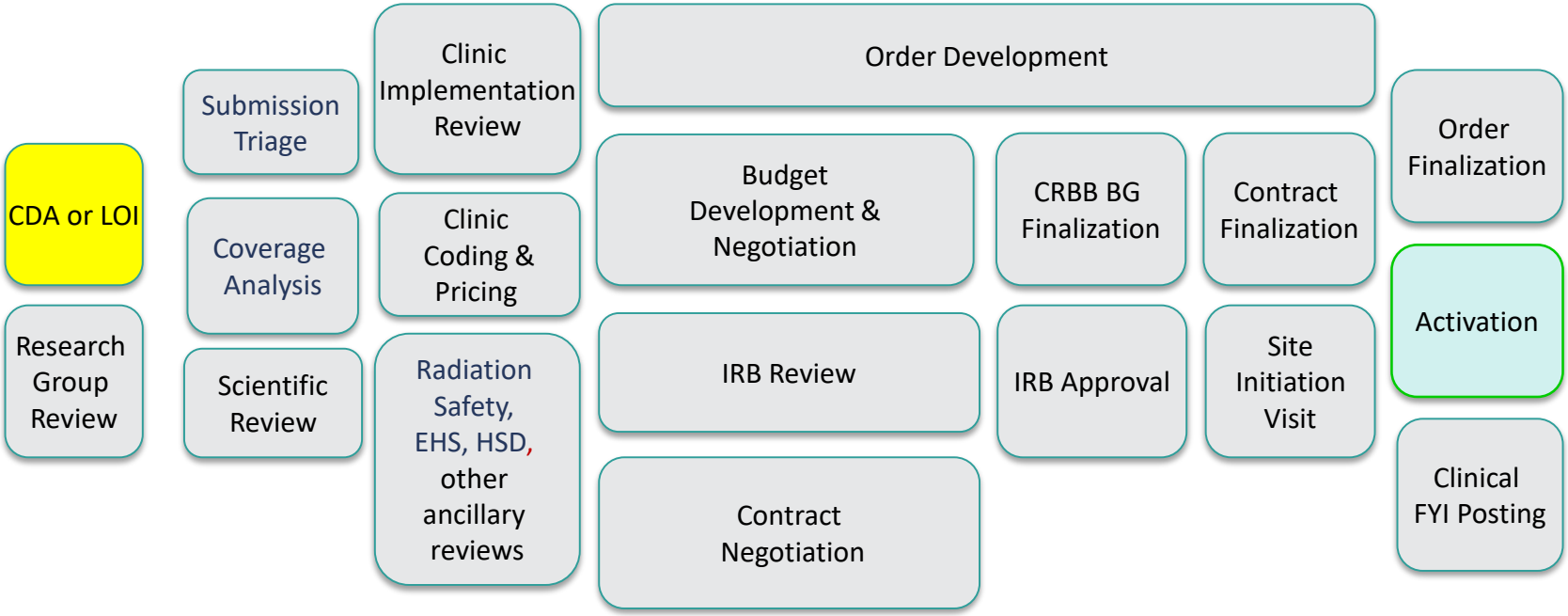
- Vendor certs/portal access
- Coordinator tools/resources
- Supplies and equipment
- Internal registry with required service areas (pathology, specimen processing, disease assessment, etc.)

Background: Consortium Study Startup Overview



Site Selection

Q: How have your site and/or investigator(s) typically been identified and selected to conduct a clinical trial?



Site Selection: Fundamental Requirements

Site Selection: Investigators and Institutions

- ✓ Qualified and experienced investigators
- ✓ Adequate site resources to properly conduct the trial
- ✓ Investigators/Institutions agreeance to conduct the trial in compliance with GCPs, regulatory requirements and IRB/EC-approved protocol requirements.
- ✓ Verify that potential investigator(s) are not listed on FDA's Debarment List or Disqualification Proceedings List
- ✓ Absence of Financial Conflict -or- Existing bias minimization plan in place

Site Selection: Other Considerations

Other Site Selection Considerations:

- ❑ Relevant authorship
- ❑ Previous study participation
- ❑ Known similar clinical trial portfolio (i.e. ClinicalTrials.gov)
- ❑ Specialty clinics or sites
- ❑ Presentations or attendance at scientific meetings
- ❑ Referrals
- ❑ Familiarity with investigational product

Site Selection: Site Qualification

Site Qualification Visits and Questionnaires

Q: Does anyone have any recent experiences with site qualification they may be willing to share?

Site Selection: Site Qualification Processes

Common Types

1. Meeting remotely - by phone or email with questionnaire(s)
2. Meeting in-person (onsite with facility tours)

Which is better?

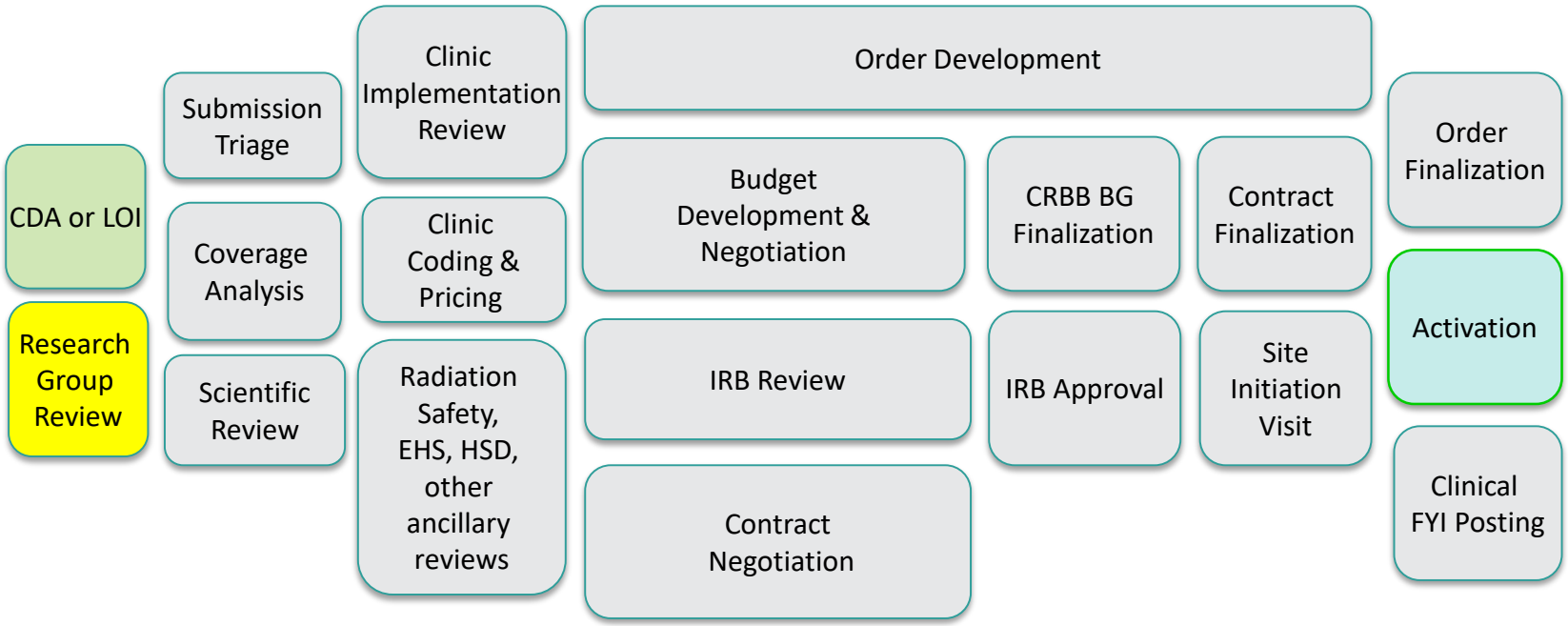
✓ The one that is THOROUGH

Tips:

- Provide as many applicable Institutional SOPs as possible
- Get the right people in the room
  - ✓ Service Area Managers
  - ✓ Clinic/Nurse Managers
  - ✓ IT team (NO GUESSING)
  - ✓ Safety officers

Study Selection

Q: How does your investigator, research team, site or department decide to do a study?



Study Selection: Discussion

Group Session Part I:

QI. What are the minimum requirements of your site or institution to initiate the study startup process?

- Site and institutions often vary in their minimum requirements for initiating study startup activities. What are your site's requirements?

Study Selection: Discussion

Group Session Part II:

QII. What documents are required to evaluate clinical trial feasibility?

- What documents you would like to review from an Industry Sponsor to evaluate the feasibility of a new clinical trial? Why?

Other Considerations…

Are the documents required by your site or institution to start the startup process the same or different than what you would like to review for feasibility?

Does the your site or institution ensure a study is feasible before you can initiate study startup process?

Study Selection: Create Intake Requirements

★ Set Minimum Requirements with Sponsors

Study Information	
Internal Study ID #	
Sponsor Protocol ID #	
Priority in research group portfolio	
Sponsor Name	
CRO Name (if applicable)	
PI Name / Appointment	
PI Administrative Coordinator Name	
NCT #	
Site Qualification Visit (SQV) Date	
Does this study permit enrollment of subjects < 18 years of age?	
Minimum Requirements	**Completion Date**
*Sponsor Pre-approval of coverage analysis and required Institutionally Required Fees	
Fully Executed CDA	
Signed RGR Form (approved by disease group director/designee)	
Final Protocol	
Investigator Brochure(s) (if applicable)	
Sponsor ICF(s)	
Draft Budget	
Draft Contract	
Final Pharmacy/Product Handling & Administration Manuals	
Final Lab Manual	
*CRS SSU Team Requirement	

Study Selection: Investigator Perspective

Investigator Considerations in Study Selection:

- Scientific interest
- Authorship
- Scientific collaborators
- Study design
- Patient population and anticipated accrual (Recruiting/Retention)
- Treatment/Competing trials

Study Selection: Conduct a Feasibility Review

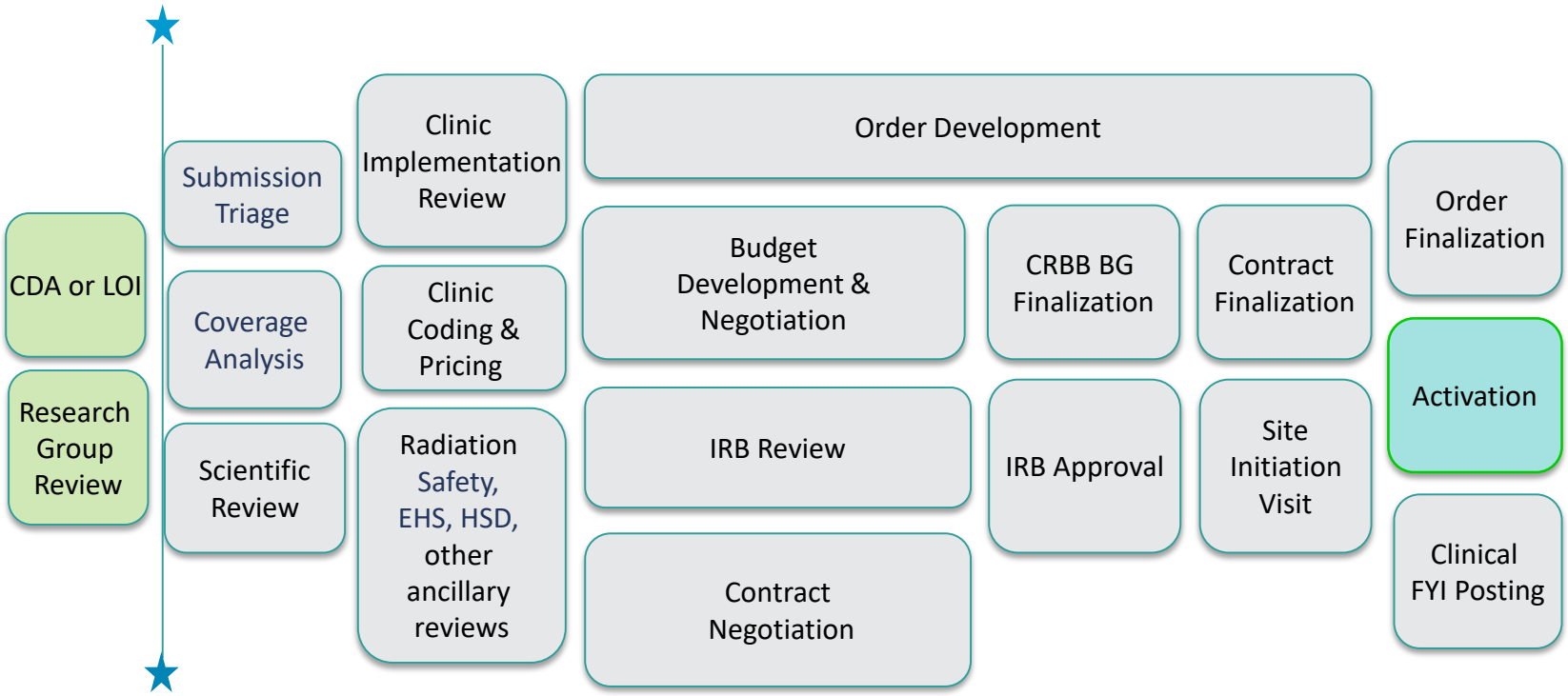
★ **Ensure feasibility before committing time, money and institutional resources to a clinical trial.**

Study Team/Clinic Operational Feasibility Considerations:

- Send Service Area SOPs to sponsor for review/approval EARLY
- Clinic requirements
- Product or Devices requirements
- Schedule requirements
- Reporting/data collection requirements
- Site services/equipment/resources
- Research staff resources
- Budget/financial support
- Previous experience with sponsor

Creating a Plan

★ **Create a plan and timeline for completion of each required activity and review so that you can communicate accurate expectations**



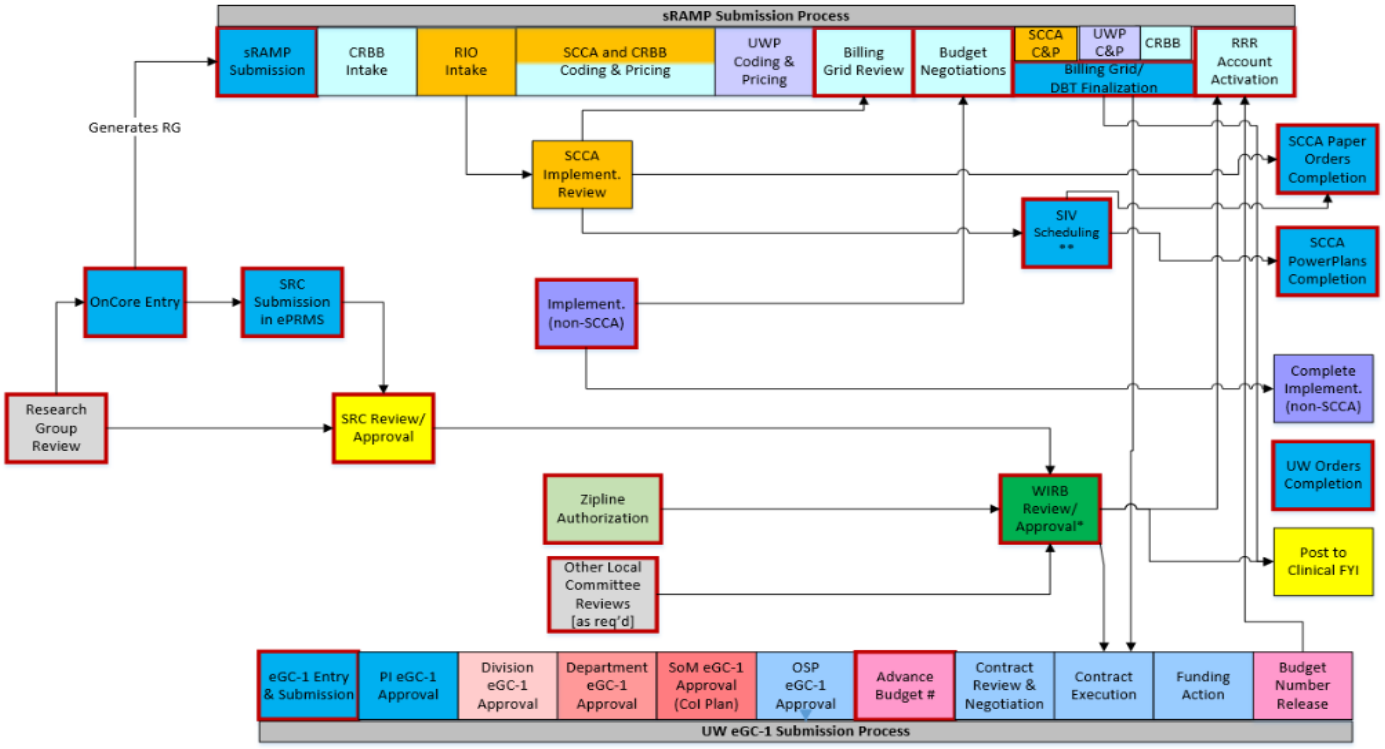
Creating a Plan: Considerations

Steps to Creating a Plan

- ❑ What does your site or institution require to open a clinical trial
- ❑ What internal reviews will be required by your institution
- ❑ What are the financial requirements of opening and running a study
- ❑ What are the regulatory requirements for a clinical trial
- ❑ Map the required activities and milestones into a realistic timeline

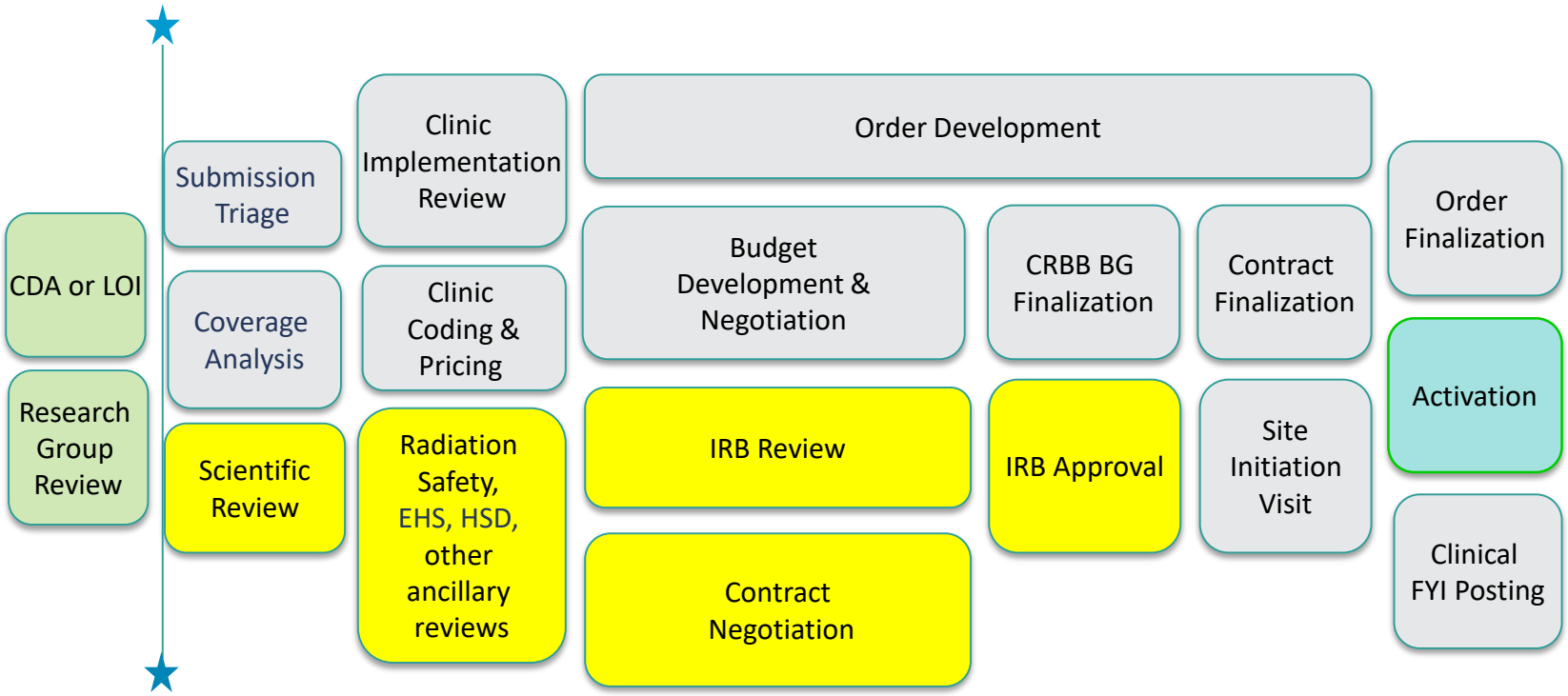
Creating a Plan: Institutional Requirements

✓ **Understand what is required by your institution to open a clinical trial**



Creating a Plan: Regulatory Requirements

★ **Understand what internal reviews will be required for the study, what dependencies exist between these reviews and when these reviews take place**



Creating a Plan: Regulatory Requirements

Internal/External Reviews

- ❑ **Scientific Review Committee (SRC)**
  Required for clinical intervention study involving cancer or relating to cancer.
- ❑ **Human Subjects Division (HSD)**
  Required for clinical intervention study involving cancer or relating to cancer prior to IRB submission.
- ❑ **Environmental Health and Safety (EHS)**
  - □ Biological
  - □ Chemical
  - □ Environmental
  - □ Radiation
  - □ Research & Lab
- ❑ **Institutional Review Board Approval (IRB)**
  Required for clinical trials involving intervention on human subjects prior to activation.

Creating a Plan: Regulatory Requirements

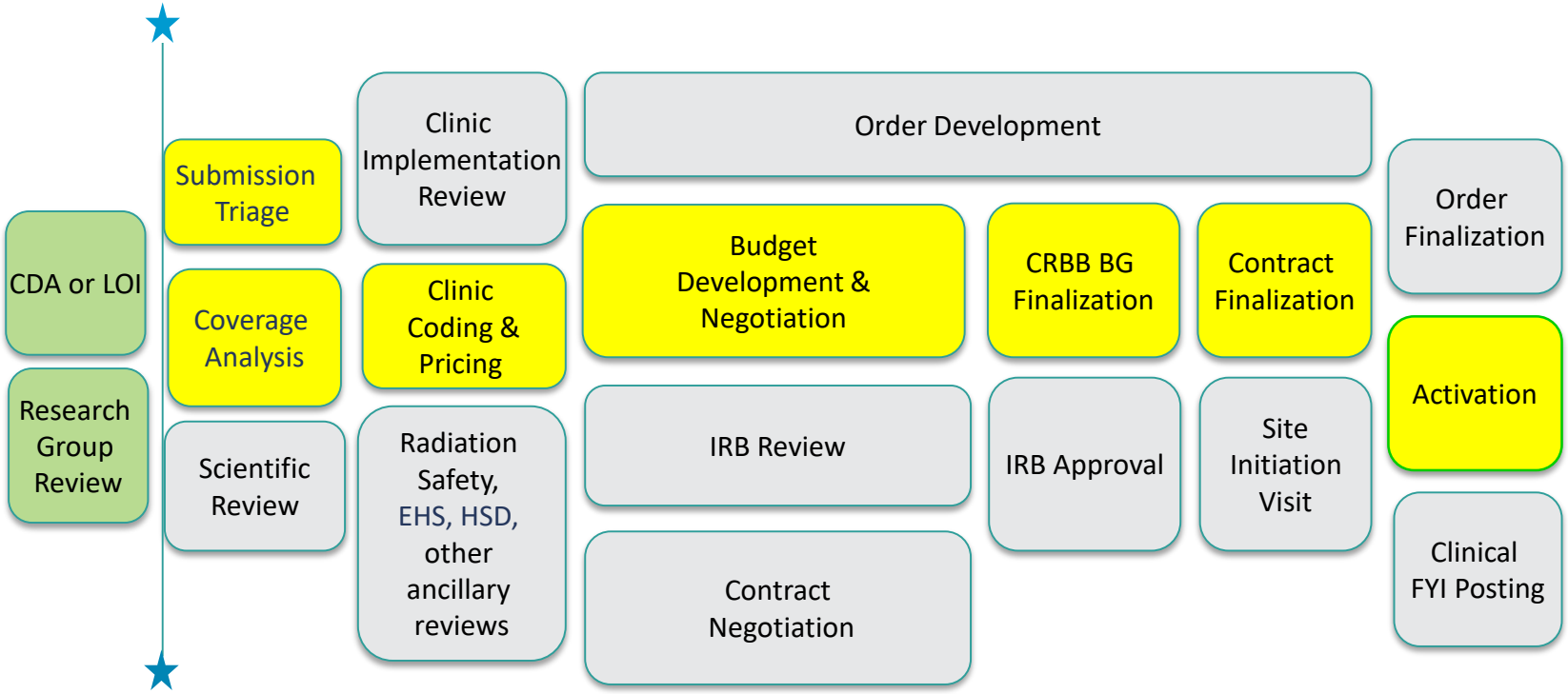
★**Understand the regulatory requirements for opening a clinical trial**

Regulatory Requirements

- ❑ **Essential Regulatory Documents**
  Including but not limited to: 1572, FDFs, PI Signature pages, GCP, DOA, MLs, CVs, CAPs/CLIAs, etc.)
- ❑ **ICF(s)**
- ❑ **Training documentation**
  Always required

Creating a Plan: Budget Development & Implementation

★ **Understand relevant institutional fees, research billables items/procedures, and other administrative costs for opening and operating a clinical trial.**



Creating a Plan: Budget Development & Implementation

Budget Development

- ❑ **Coverage Analysis**
  Required for all therapeutic trials with procedures potentially billable to the patient or the patient's insurance provider in order to maximize institutional compliance with the Medicare Clinical Trial Policy.

- ❑ **Clinic Implementation Review**
  Required to determine patient flow and resolve internal inquiries regarding protocol requirements.

- ❑ **Coding and Pricing**
  Required prior to Billing Grid Finalization

- ❑ **Budget Development and Negotiation**
  Required prior to Contract Execution and SIV scheduling

- ❑ **Clinical Research and Billing Office (CRBB) Billing Grid Finalization**
  Required to ensure research budget and consent align with coverage analysis prior to contract execution.

- ❑ **Office of Sponsored Programs (UW) or CRS Contracts Fiscal Management (FH)**
  Required to negotiate and facilitate execution of clinical trial agreements.

- ❑ **Activation**
  Requires institutional approval to confirm all required startup activities are complete.

Creating a Plan: Budget Development

Relevant Costs

- ❑ **Institutional Fees**
  - □ Indirect rate
  - □ Human Subjects Division (HSD) Fee
  - □ Protocol Office Fee
  - □ IRB Fee(s)
  - □ Technology Fee
  - □ Work-day Fee
  - □ Department Fee(s)
  - □ Service Area Fees
  - □ Pathology Fees
  - □ Investigational Drug Services Fees
  - □ Archive/Record Management Fees
  - □ Specimen Processing Lab Fees
  - □ Disease Assessment Fees
- ❑ **Staff Effort**
  - □ Principle Investigator
  - □ Sub-Investigators
  - □ Research Staffing
- ❑ **Research Items/Procedures**
  - □ Coverage Analysis Outcome (per NCD/LCD guidelines)
- ❑ **Research Administration Costs**
  - □ Site Activation
  - □ Pre-Screening
  - □ Serious Adverse Event (SAE) Reporting
  - □ Unscheduled Visits
  - □ Third Party Safety Reports
  - □ Protocol/ICF Amendments
  - □ Administrative Modification
  - □ IBC Renewal
  - □ IRB Renewal
  - □ Study Maintenance
  - □ Contract/Budget Amendments
  - □ External “Not for Cause” Audits
  - □ Monitor Visits (per monitor/day)
  - □ Monitor Changes
  - □ Data/Image Transfer
  - □ Site Closeout

Creating a Timeline

★Map the required activities and milestones into a realistic timeline

Target Completion Week	**Wks __-__**	**Wks __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**Wk __ -__**	**TARGET OPEN DATE**
Date Completed																		__ / __
	SAGE/eGC1 (UW Only)	Sponsor outstanding questions answered	Submit study in sRAMP / 3rd Party Coverage Analysis	Submit / Obtain SRC Approval	IBC Submission / Approval	Final 3rd Party Coverage Analysis Approval	Hutch Grants Submission (FH studies only)	Radiation Safety submission / approval	Submit / Obtain UWHSD Auth (if applicable)	Draft Budget review / approval by Study Team	Clinic Implementation Review(s) Meeting	Final Pricing/Costs Received	Complete Budget Negotiations	IRB Submission / Approval	Internal Billing Office Apprroval(s)	Contract Execution	SIV	Site Activation/ / Open to Accrual

COMPLETE
SUBMITTED; PENDING APPROVAL
PAST DUE, NOT STARTED
REQUIRES STUDY TEAM/PI ACTION

Using a Timeline to Communicating Status

★Timelines may be used throughout the startup process to create transparency with investigators & external partners

Example weekly status report:

Study Start-Up Progress Tracking

Week 0 12/30/16	Week 1 1/12	Week 1-2 submitted for review 1/12; anticipate 2/15 review date	Week 2 1/22	Week 2-5 1/23	Week 5	Week 5-7	Week 5-7 **SRC review 2/14**	Week 10-13	Week 5-11 **2/10: In progress**	Week 12-13
Administrative & Contract Review *pending receipt of needed study documents & manuals*	Pricing & Budget Review	In-Clinic Implementation Review by Service Area Staff	Budget Negotiations w/ Sponsor - Start-Date	Budget review with Study Team	Budget Negotiations w/Sponsor - End-Date	Final Budget Submission Approved by UW CRBB[1]	Submit/ Obtain WIRB Approval (SRC[2], UWHSD[3])	OSP[4] will Negotiate Terms & Execute Contract With Sponsor	Reg Docs Submission	SIV *(Site requires 30 days notice to coordinate SIV date)*

3/31 TARGET OPEN

1. Clinical Research Budget & Billing Office (CRBB)
2. Scientific Review Committee (SRC)
3. University of Washington Human Subjects Division (UWHSD)
4. Office of Sponsored Programs (OSP)

- SITE START-UP REQUIREMENTS
- SITE & SPONSOR REQUIREMENTS
- SPONSOR REQUIREMENT
- COMPLETE
- SUBMITTED; PENDING REVIEW & FINAL APPROVAL

Setting a Study up for Success

- **Comprehensive, accurate budgets and payment terms**
- **Complete, organized and accurate regulatory records**
- **Research Staff Implementation Resources**
  - — Study tools
  - — Checklists
  - — Templates
- **SIV Coordination**

Tips for Success: Partnering with Sponsor

- **Identify points of contact**
  - create study contact sheet
- **Set accurate expectations**
  - minimum requirements to initiate startup process
  - internal process and review dependencies
  - identify implementation challenges/questions early
- **Communicate regularly**
  - create/maintain a timeline
  - send regular timeline updates
  - create response time expectations
- **Be Professional**
- **Be Responsive**

Tips for Success: Partnering with Clinic

- **Identify points of contact**
  - create study contact sheet
- **Set accurate expectation**
  - what activities and/or procedures will occur
  - provide relevant materials
  - identify challenges/questions early
  - ordering/scheduling needs
  - timeline
- **Identify Training/Access Needs**
  - facilitate Sponsor-Clinic
  - facilitate Investigator-Clinic
- **Be Proactive**
- **Be Gracious**

UW Resources, Templates & Checklists

CRBB Main https://depts.washington.edu/crbb/

Department of Laboratory Medicine http://depts.washington.edu/labweb/

Environmental Health and Safety (EHS) http://www.ehs.washington.edu/

EHS - IBC
http://www.ehs.washington.edu/biological/institutional-biosafety-committee-ibc
EHS – HSRAC
http://www.ehs.washington.edu/radiation/use-radiation-human-subjects-research
http://www.ehs.washington.edu/system/files/resources/hsracform1.pdf
http://www.ehs.washington.edu/system/files/resources/HSRAC-Approved-Risk-Language-For-Consent-Forms.pdf

GCA Main http://finance.uw.edu/gca/

HSD Main https://www.washington.edu/research/hsd/

HSD - Clinical Trials
https://www.washington.edu/research/hsd/clinical-trials/#reg

Institute of Translational Health Sciences: https://www.iths.org/

NW BioSpecimen Services: https://depts.washington.edu/nwbios/

OSP Main https://www.washington.edu/research/osp/

Office of Research (OR) http://www.washington.edu/research/?page=or

OR - Research Forms/Templates
https://www.washington.edu/research/forms-and-templates/

Office of Research Information Services (ORIS) https://www.washington.edu/research/oris/

OncoRad/TIMC https://rad.washington.edu/research/uw-oncoradtumor-imaging-metrics/

Other Resources, Templates & Checklists

Seattle Cancer Care Alliance

Research Staff Resources https://www.seattlecca.org/research-staff-resources

IBC
https://www.seattlecca.org/sites/default/files/page_content/2017-10/SCCA-IBC-Submission-Form.doc

Fred Hutch

Clinical Research Support (CRS) http://www.cancerconsortium.org/en/support.html

CRS Study Tools and Templates
http://www.cancerconsortium.org/en/support/forms/study-document-templates.html

IRB https://extranet.fredhutch.org/en/u/irb.html

Radiation Safety
https://extranet.fredhutch.org/en/u/irb/radiation-safety-review.html

Other Resources, Templates & Checklists

Seattle Cancer Care Alliance

Research Staff Resources https://www.seattlecca.org/research-staff-resources

IBC
https://www.seattlecca.org/sites/default/files/page_content/2017-10/SCCA-IBC-Submission-Form.doc

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CRS Study Tools and Templates
http://www.cancerconsortium.org/en/support/forms/study-document-templates.html

IRB https://extranet.fredhutch.org/en/u/irb.html

Radiation Safety
https://extranet.fredhutch.org/en/u/irb/radiation-safety-review.html

Regulatory and Clinical Research Institute, Inc

https://www.rcri-inc.com/clinical-research/

Learning Objectives

- Describe what minimum documentation or materials you will need from the sponsor
- Describe what feasibility considerations/concerns should be confirmed prior to initiating a new clinical trial
- Describe the timeline for study startup, relative dependencies and setting accurate expectations
- Identify the tools and resources needed for study initiation

Questions:

Ashley Waldie, MA, CCRP

amwaldie@fredhutch.org

FRED HUTCH
UNIVERSITY OF WASHINGTON
CANCER CONSORTIUM

An Ethical Framework for Clinical Research

Presented by Ben Wilfond, MD

3:25pm-4:25pm

UW Husky Union Building

Room 145

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

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

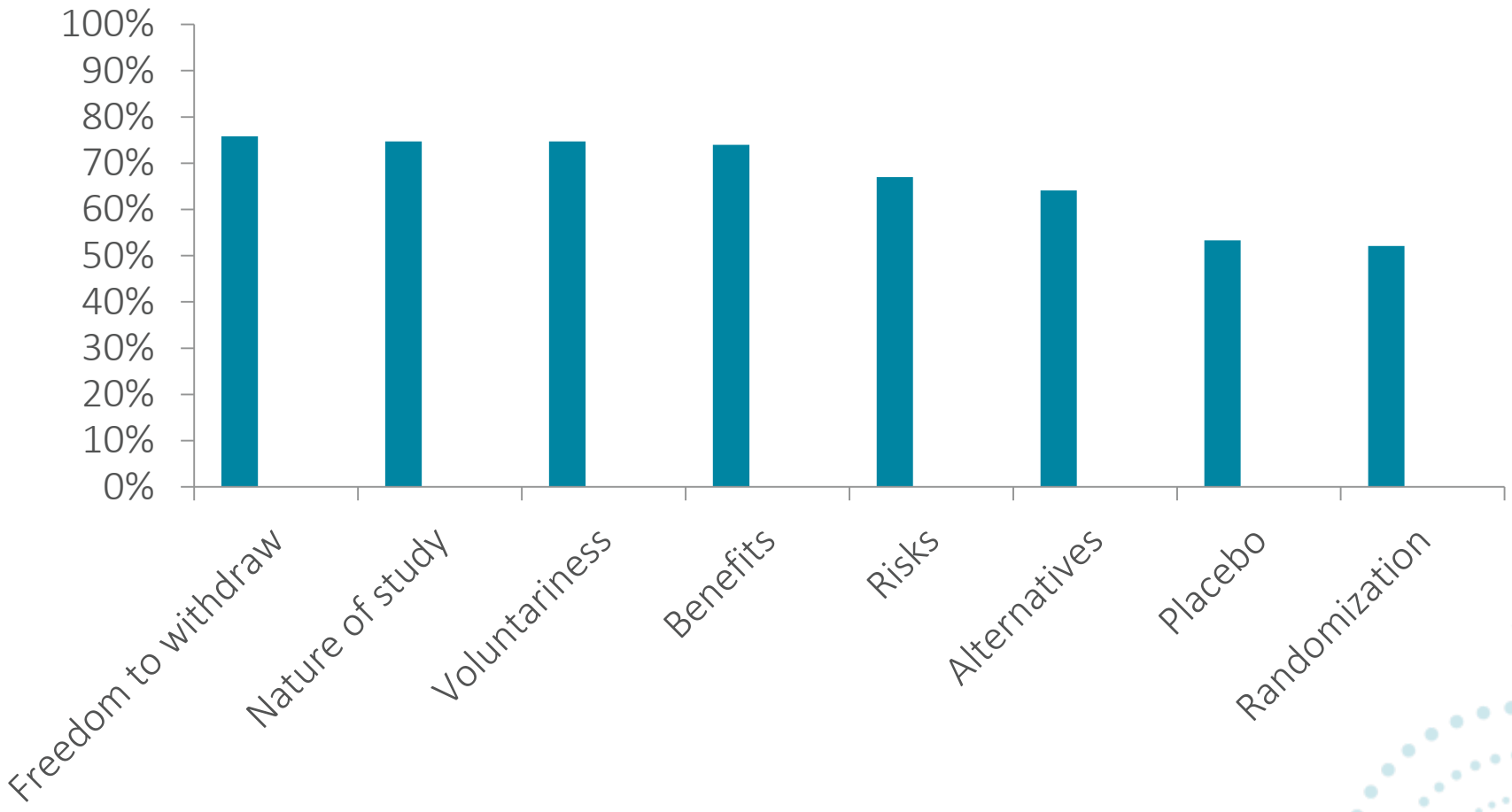
Elements of Informed Consent

- Capacity
- Disclosure
- Understanding
- Voluntariness
- Authorization

Elements of Informed Consent – Empirical Data

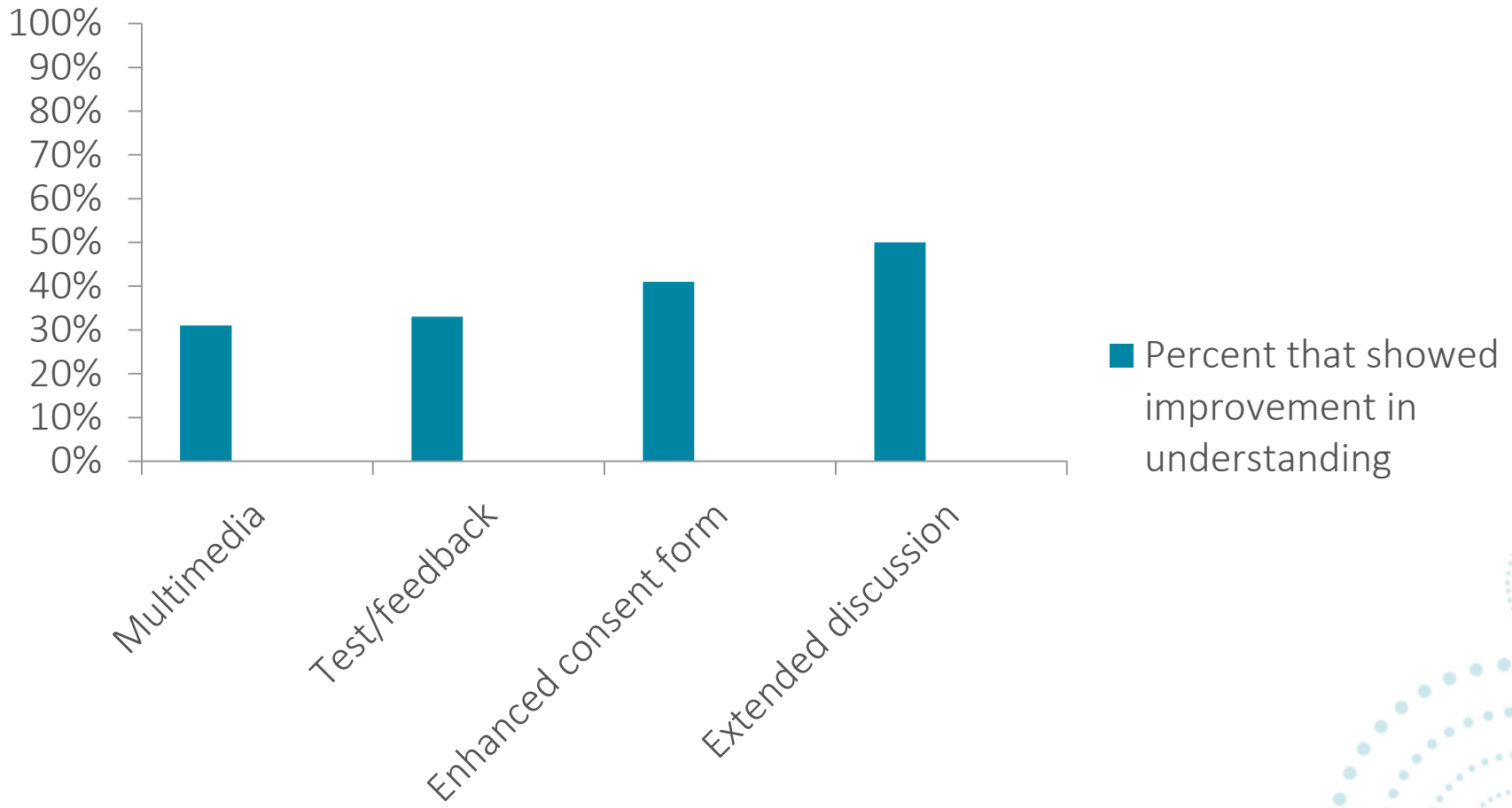
- Capacity
- Disclosure
- Understanding
- Voluntariness
- Authorization

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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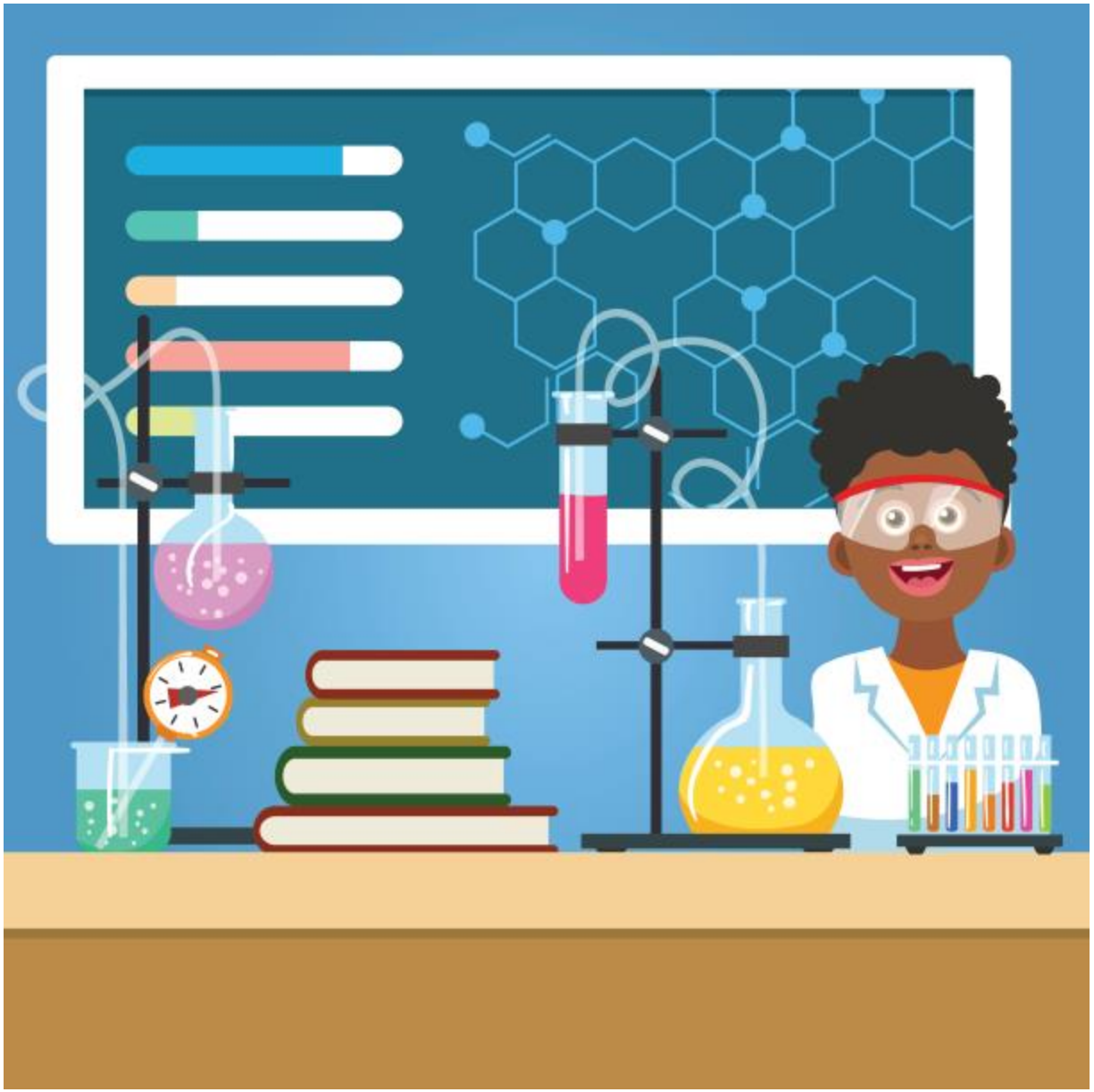
2. Social Value

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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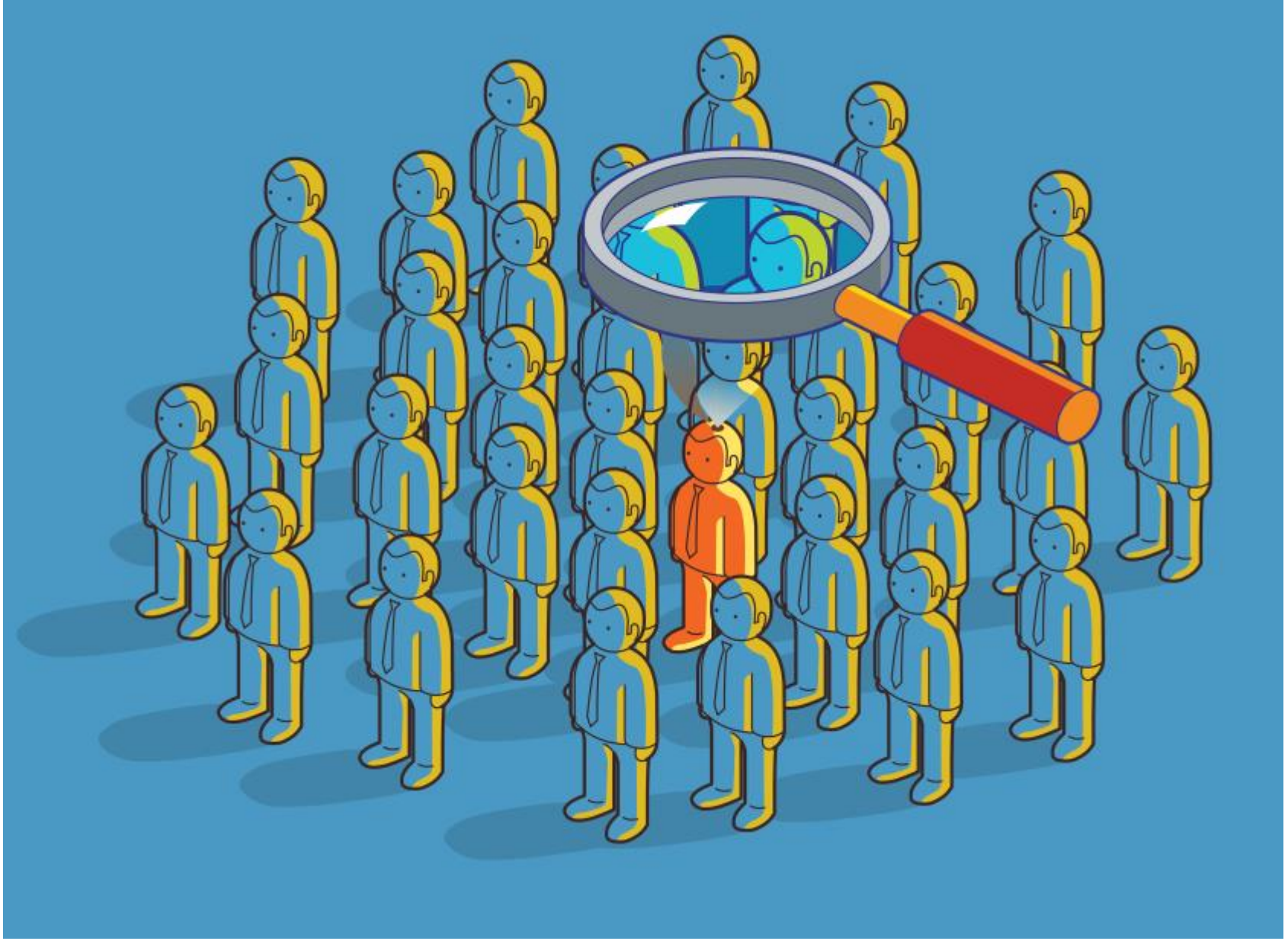
Scientific Validity

- 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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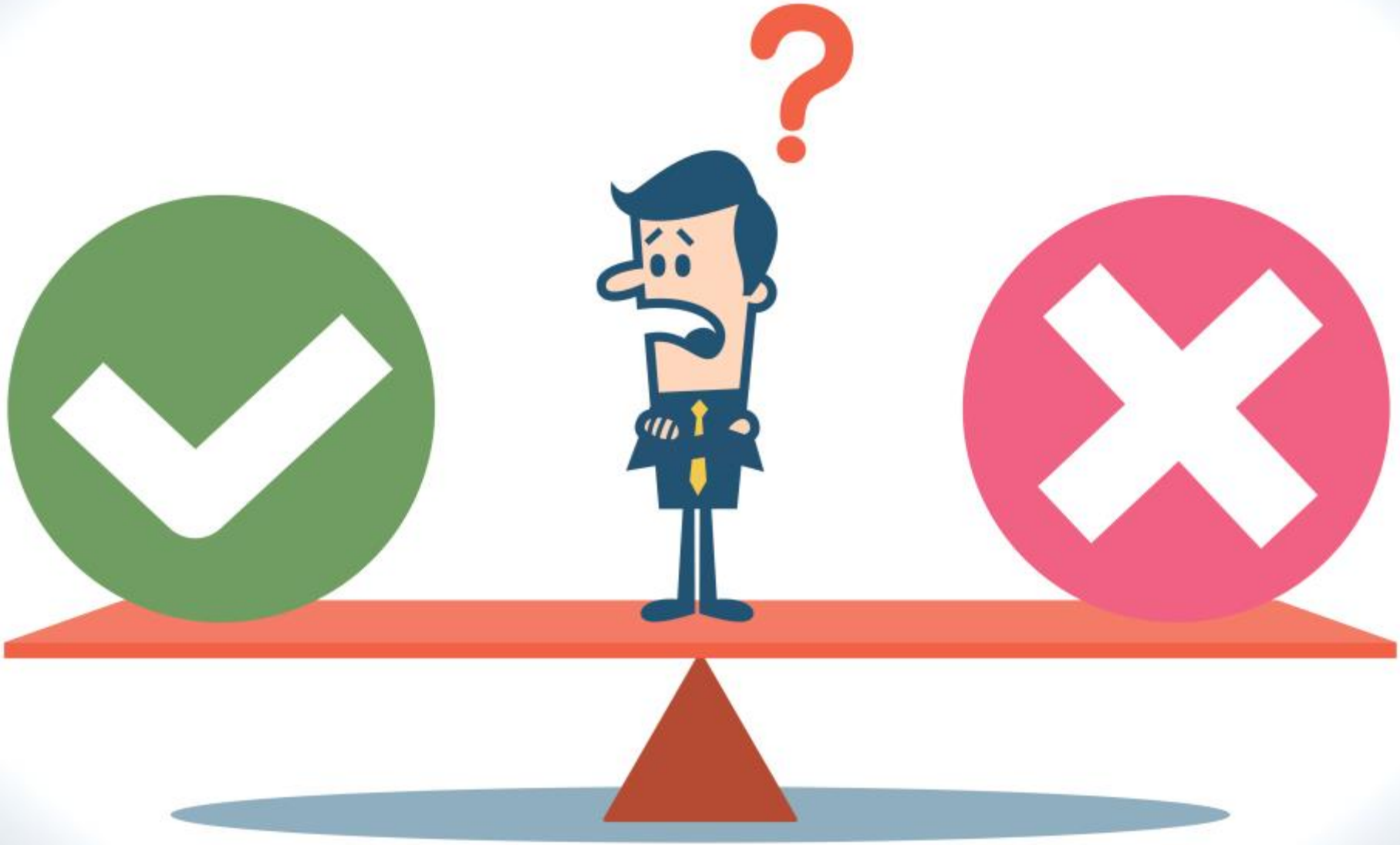
4. Fair Subject Selection

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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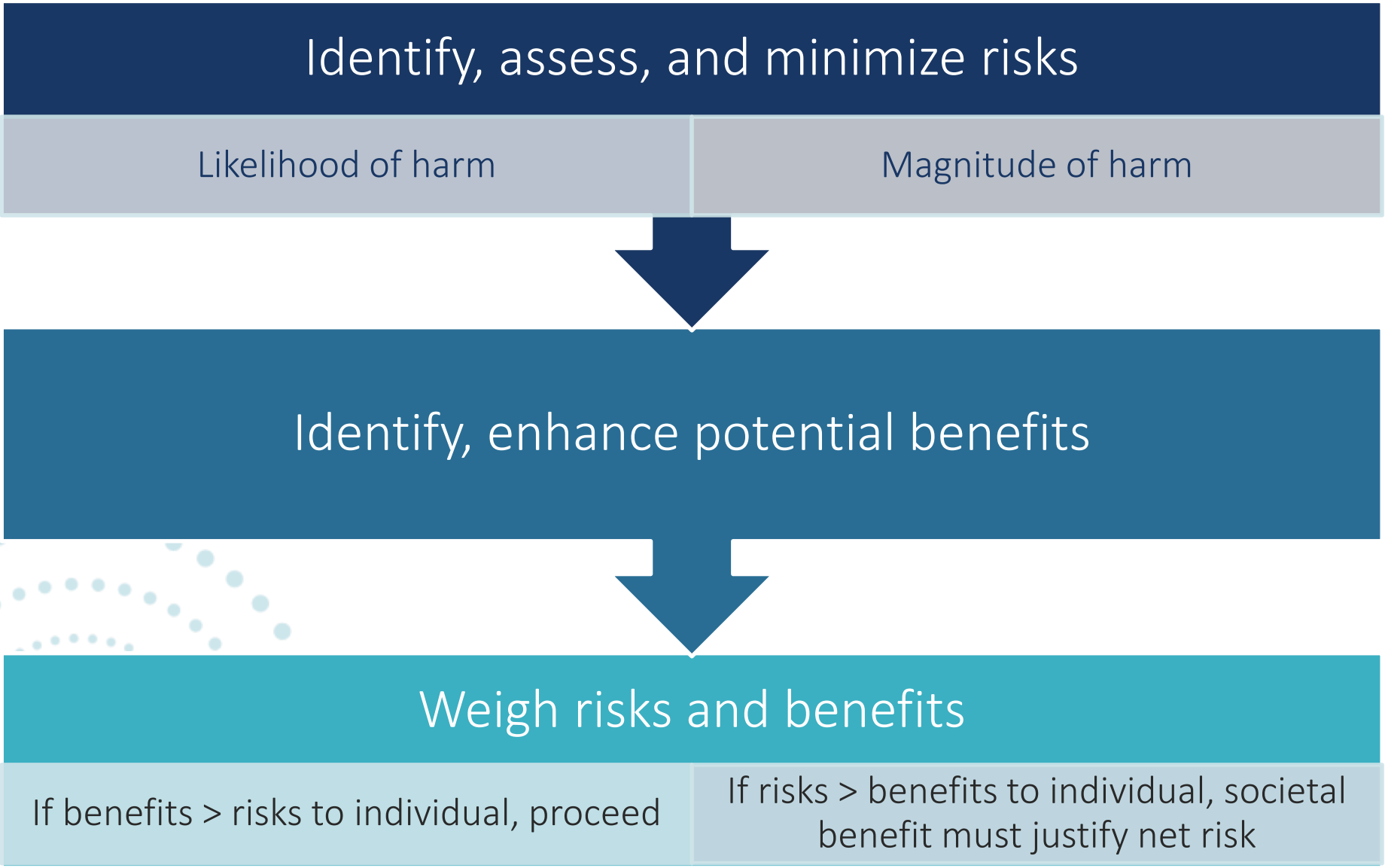
5. Favorable Risk/Benefit Ratio

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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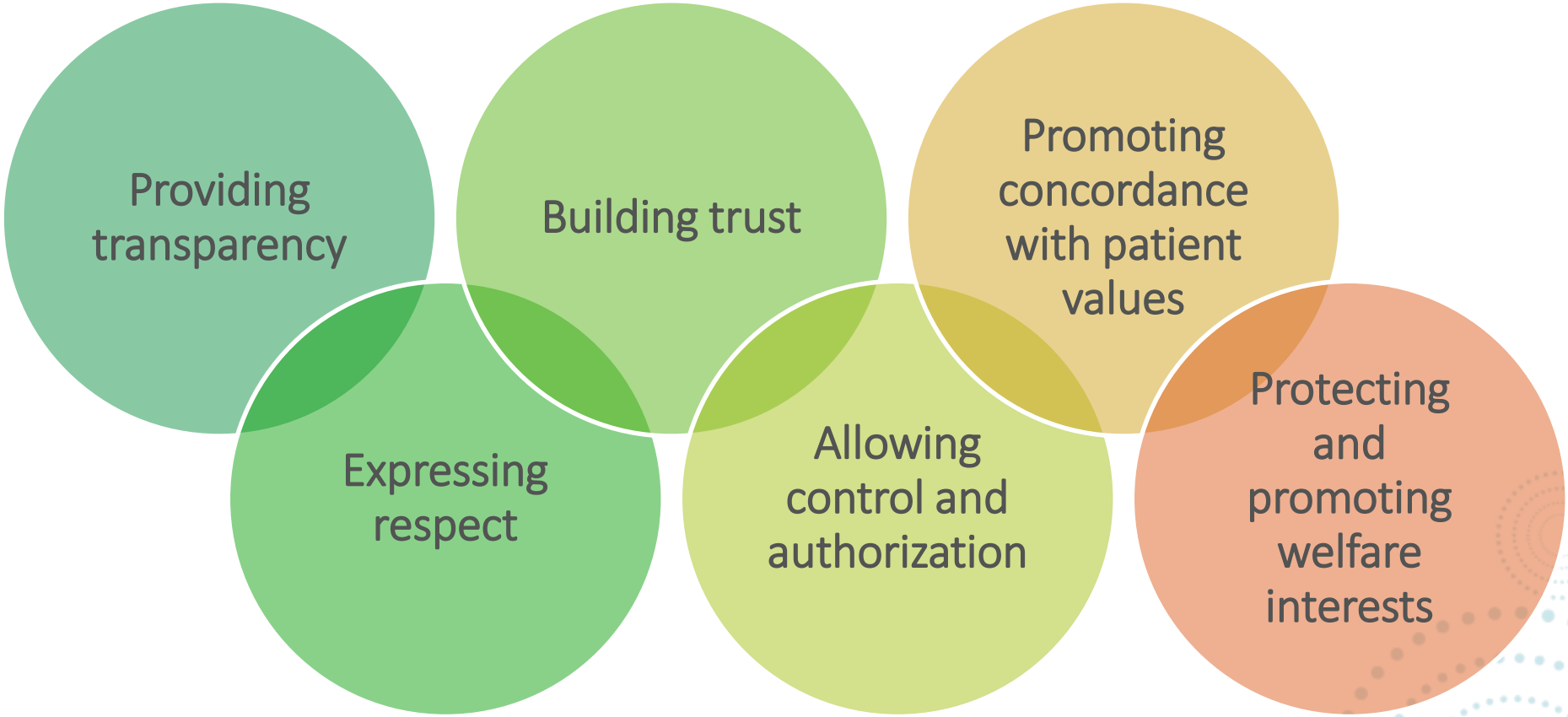
7. Informed Consent

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?

benjamin.wilfond@seattlechildrens.org
stephanie.kraft@seattlechildrens.org
kathryn.porter@seattlechildrens.org

www.iths.org/bioethics

Introduction to Clinical Research Boot Camp 2019

Staff Track -Tuesday, July 31

UW Husky Union Building

Room 145

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

The Protocol Review

Presented by Amy Good, PhD

8:30am-9:30am

UW Husky Union Building

Room 145

THE PROTOCOL REVIEW:

How to Read for Both the Big Picture and Your Responsibilities in Implementing a Study

Amy B. Good, PhD
Manager, Research Coordination Center
UW Clinical Trials Office/Institute of Translational Health Sciences

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Learning Objectives

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

- Describe your role as the liaison between the study and the public
- Discuss which components of the protocol are most relevant for study execution by study staff
- Identify components in the protocol that facilitate the creation of study checklists

Protocols

- Industry vs grant funded protocols
- For today, focus is on time of implementation; start-up and approvals are completed

Protocols

Why is the protocol important?

- Road map, source of information for study execution.
- The big picture: you are the liaison between the study team and the participants, and between the study and the public.

Table of Contents

The Why of the Protocol

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3. OBJECTIVES/STUDY AIMS

- Primary objective
- The primary objective of this study is to evaluate the effect of a dietary supplement, given as an oral tablet, on muscle energetics as measured by a muscle fatigue test in elderly subjects.

- Secondary objective
- The secondary objectives of the study are to assess the safety and tolerability of a single oral dose of the supplement in elderly subjects.

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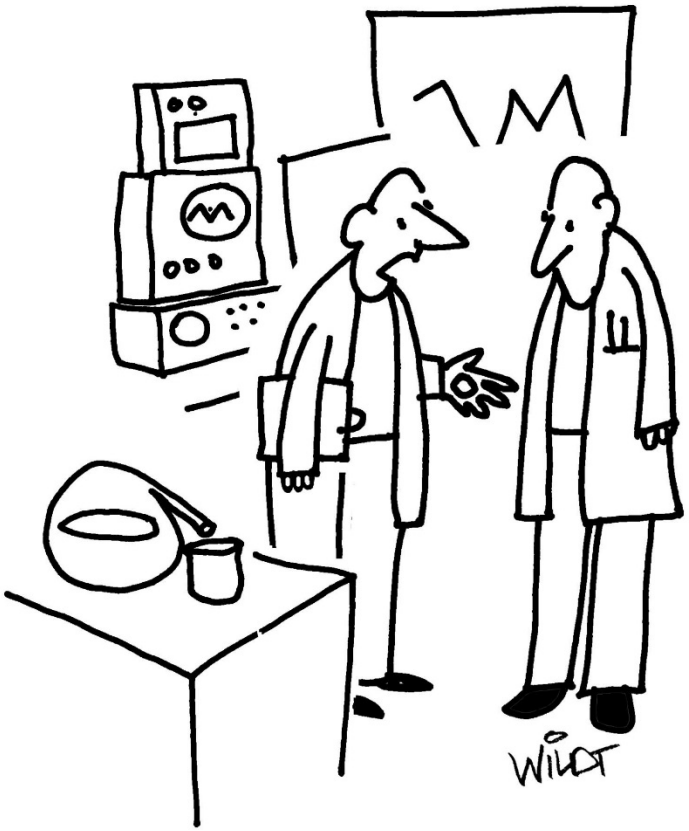
The How of the Protocol

4. STUDY DESIGN



"They want us to double check our methodology.
Your turn to flip."

CartoonStock.com

The How of the Protocol

STUDY DESIGN

- A Phase 2 randomized, double-blind, placebo-controlled study to evaluate the impact of a dietary supplement on muscle function in the elderly

Table of Contents

The Who of the Protocol

5. PARTICIPANT SELECTION

- Participant Inclusion Criteria
- Participant Exclusion Criteria

6. RECRUITMENT PLAN

Table of Contents

The When, What, and Where

7. **STUDY INTERVENTION**
8. **VISIT SCHEDULE AND ASSESSMENTS**

Assessment specifics

- Familiarize yourself with these
- Can you experience the assessments yourself?
  - Diaries
  - Questionnaires
  - 6-minute walk test
  - Neurocognitive assessments
  - Procedures: can you observe?

Schedule of Events

Parameters	Screening	Baseline Visit 1[a]	Visit 2 (Day 21)	Visit 3 (Day 60)
Informed consent	X			
Pulmonary Function Tests	X			X
6 minute walk test	X			X
Inclusion and exclusion criteria	X			
Medical history	X			
Physical examination	X			X
Height and Weight	X			X
Laboratory – CBC, chemistry panel	X			X
Laboratory – serum biomarkers[b]		X	X	X
Laboratory – liver function tests		X		X
ECG	X			X
Vital Signs[c]	X	X	X	X
Study Product Dispensed		X	X	
Peak Flow Meter[d]	X	X	X	X
Review Exercise Diary		X	X	X
Quality of Life Questionnaires		X		X
Concomittent Medications	X	X	X	X
Adverse Events		X	X	X

a Should occur no more than 14 days after screeing visit
b Participant should be fasting
c To include heart rate, blood pressure, temperature, and respiratory rate
d Peak flow meter dispensed at screening visit for home use; reviewed at study visits

The When, What, and Where

Labs and specimen processing

- Lab medicine vs research testing service (RTS)
- Watch out for aggregate labs
  - Comprehensive metabolic panel

Table of Contents

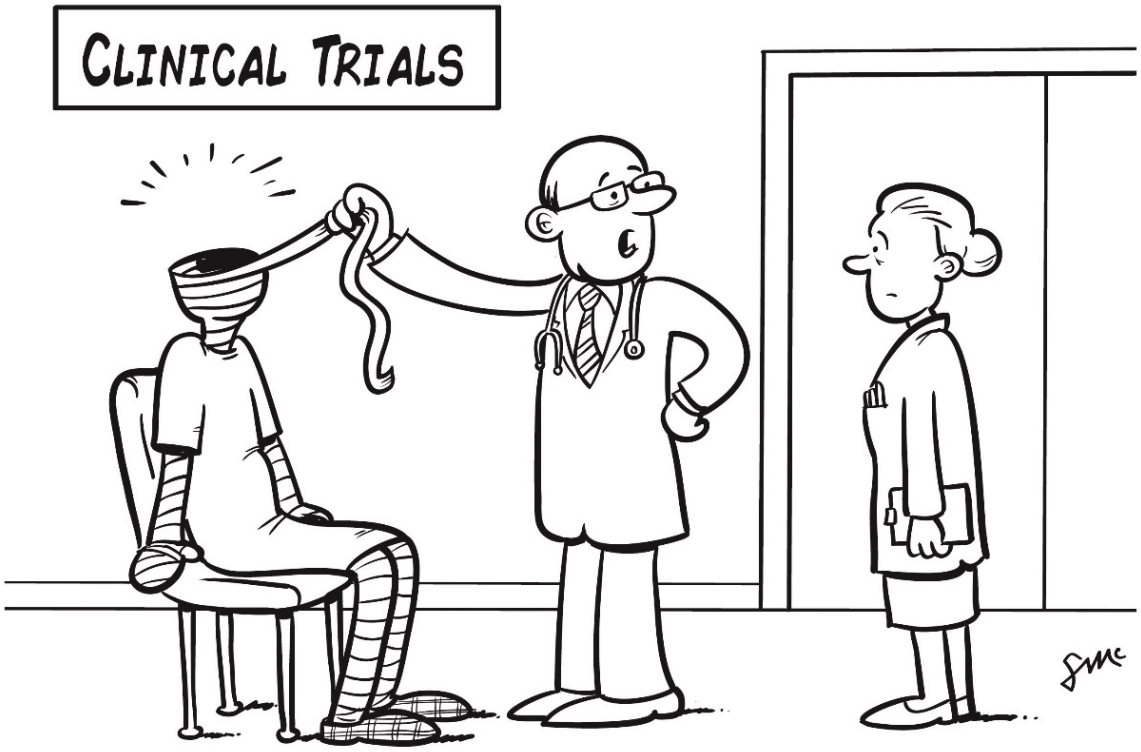
Safety

9. ASSESSMENT OF SAFETY

- **Adverse Event**
- **Serious Adverse Event**

Reporting requirements

- To whom
- By when
- Requirements vary



"So I guess this probably counts as an adverse event."

CartoonStock.com

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Appendices

13. APPENDICES

- Schedule of events
  - Footnotes!

- Lab manual
  - Processing times

Participant Visits

What, who, when, and where?

Mental run-through; think it through.

Where do you start?

- Checklists
- Participant binders
- Equipment, questionnaires, study assessments

Participant Visits

Traveling kit

- Checklists
- Protocol
- Schedule of events
- Extra consent forms
- Post-its and pens
- Assessments/questionnaires
- Lab manual

Learning Objectives

- Describe your role as the liaison between the study and the public
- Discuss which components of the protocol are most relevant for study execution by study staff
- Identify components in the protocol that facilitate the creation of study checklists

Increase Study Success Through Integration of Team Science

Presented by Jennifer Sprecher & Nicole Summerside

9:40am-10:40am

UW Husky Union Building

Room 145

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
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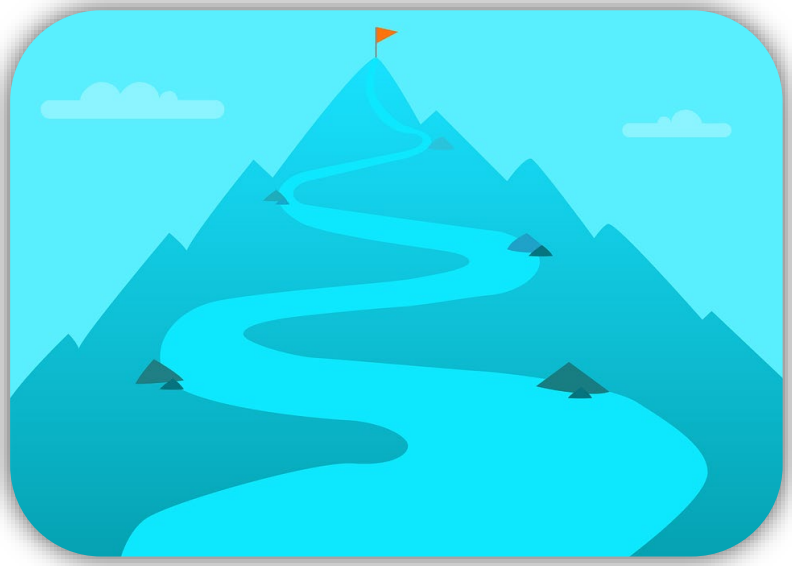
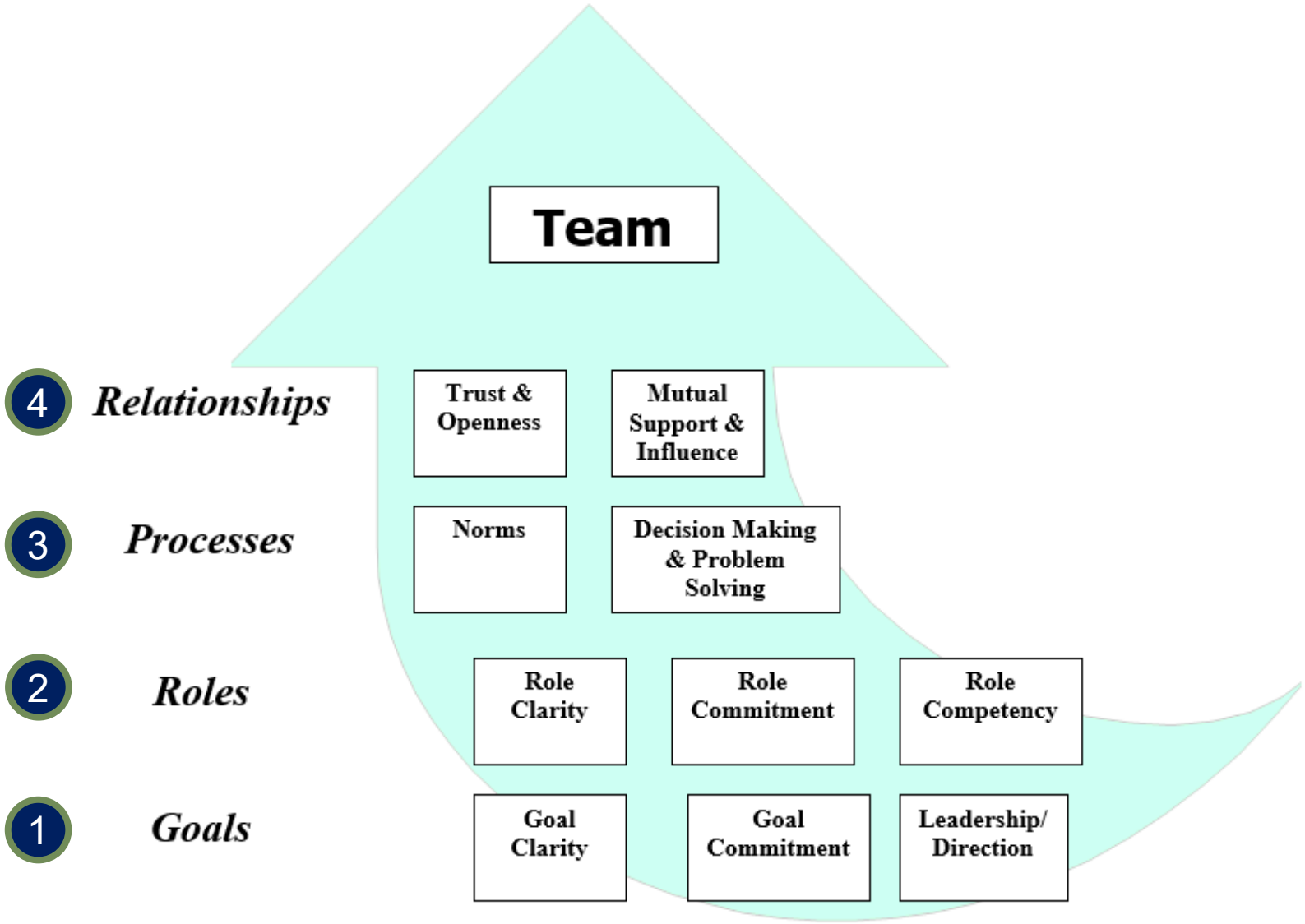
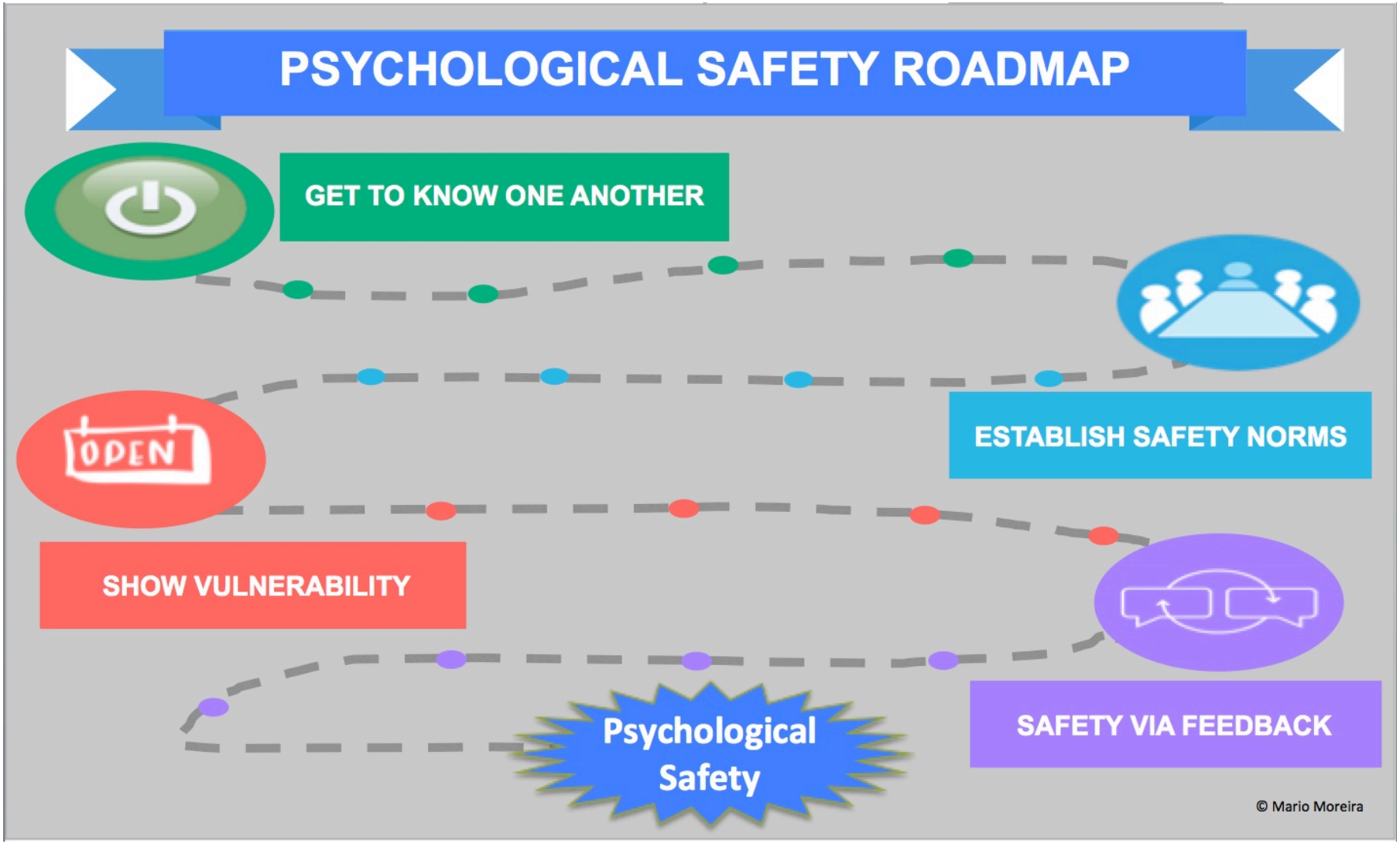
Learning Objectives

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

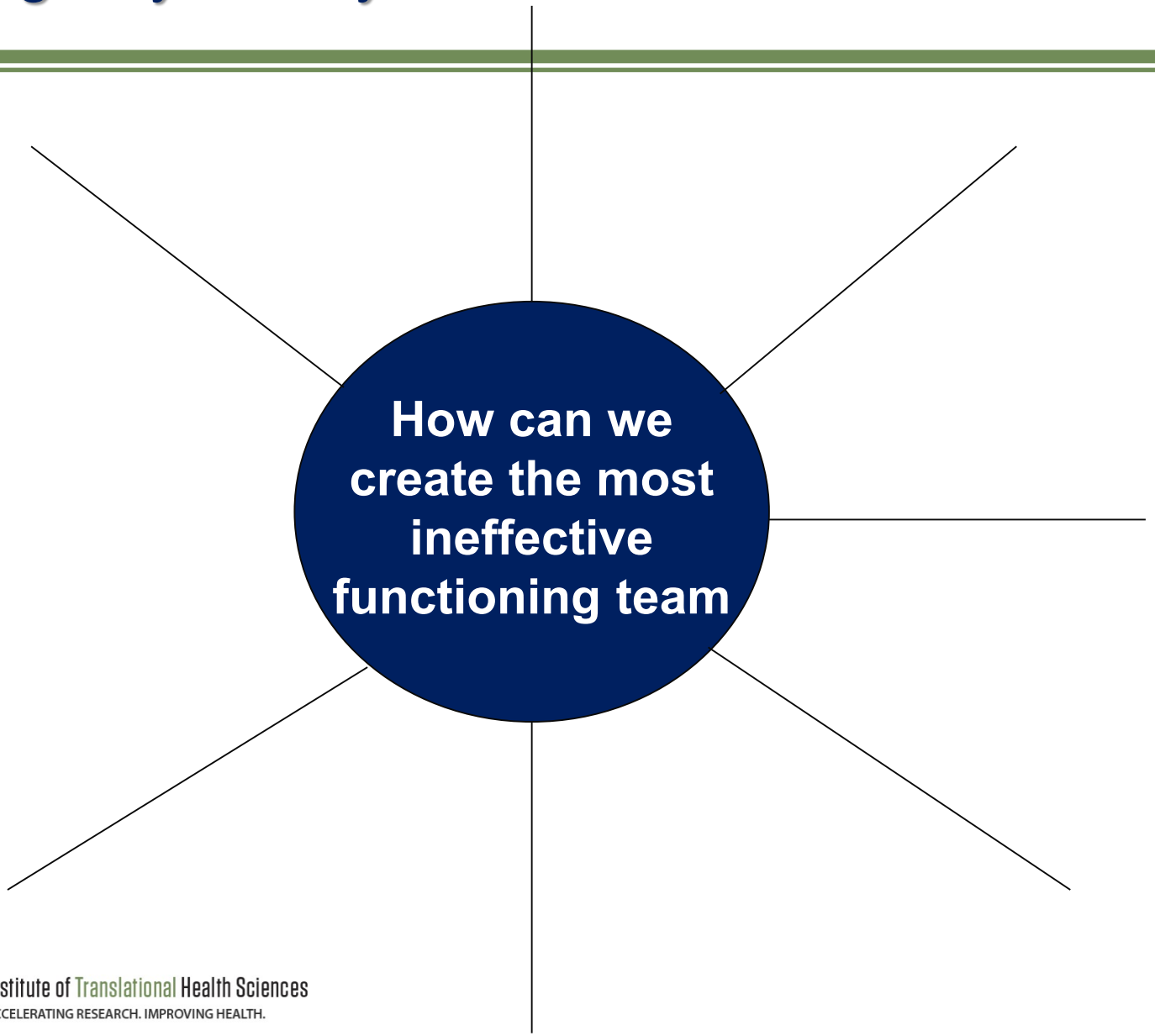


Managing Teamwork




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

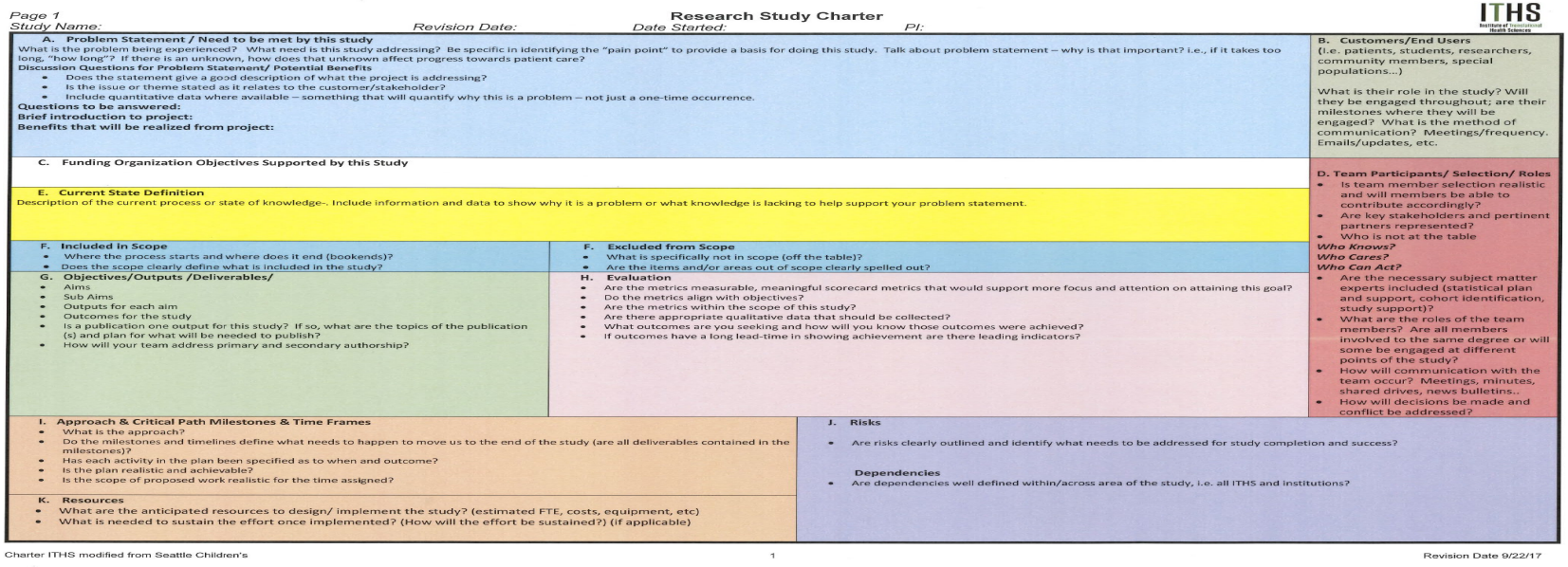
1. Suspend Assumptions
2. Listen, Don't Re-load
3. Balance Advocacy with Inquiry
4. Attribute Positive Intent
5. Minimize Interruptions
6. Strive to Participate

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:

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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?

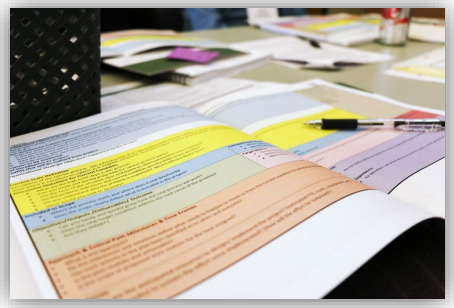
The Team (Section D)

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

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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.

Leveraging the EMR: Tools & Rules

Presented by Bas de Veer

10:50pm-11:50pm

UW Husky Union Building

Room 145

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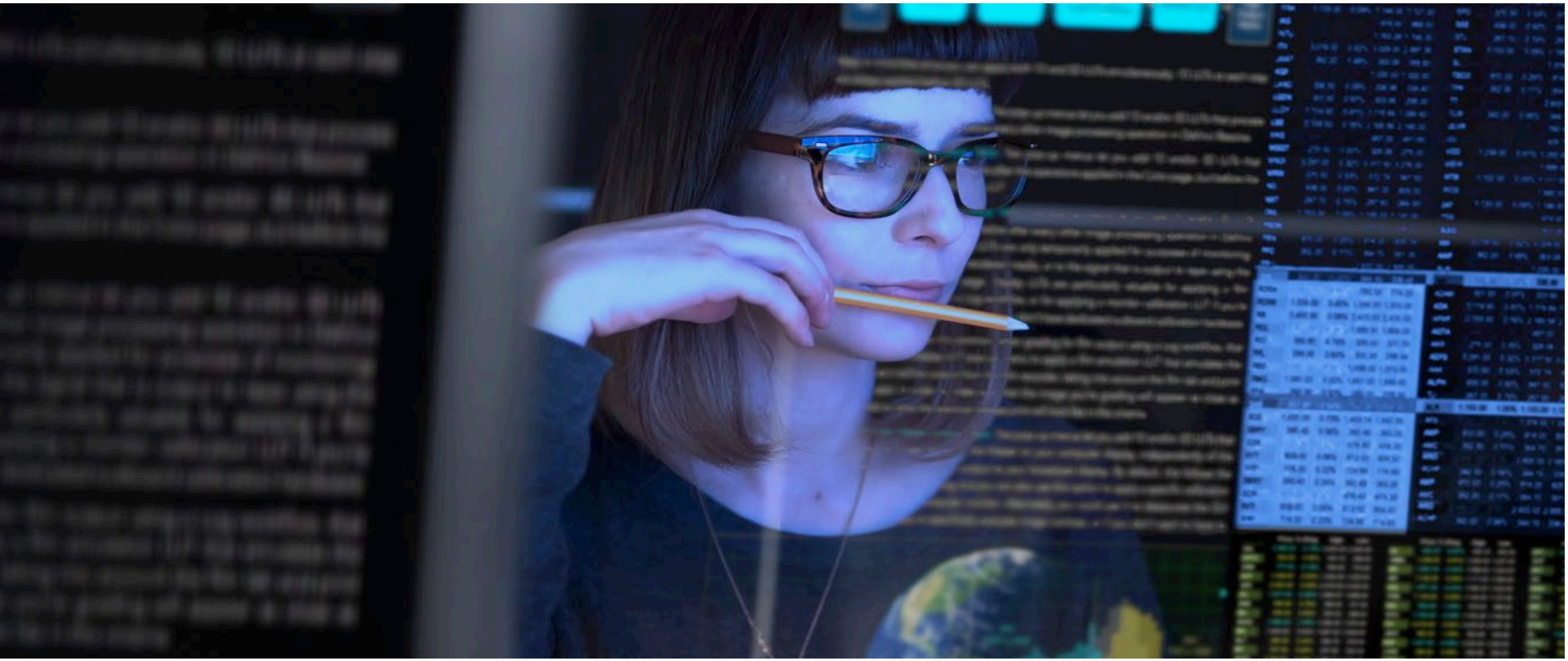
UW MEDICINE | Analytics

Leveraging the EMR:

Tools & Rules for EMR Research Data Acquisition



Presented by: Bas de Veer, Bio-Medical Informatics Services Manager

UW Medicine

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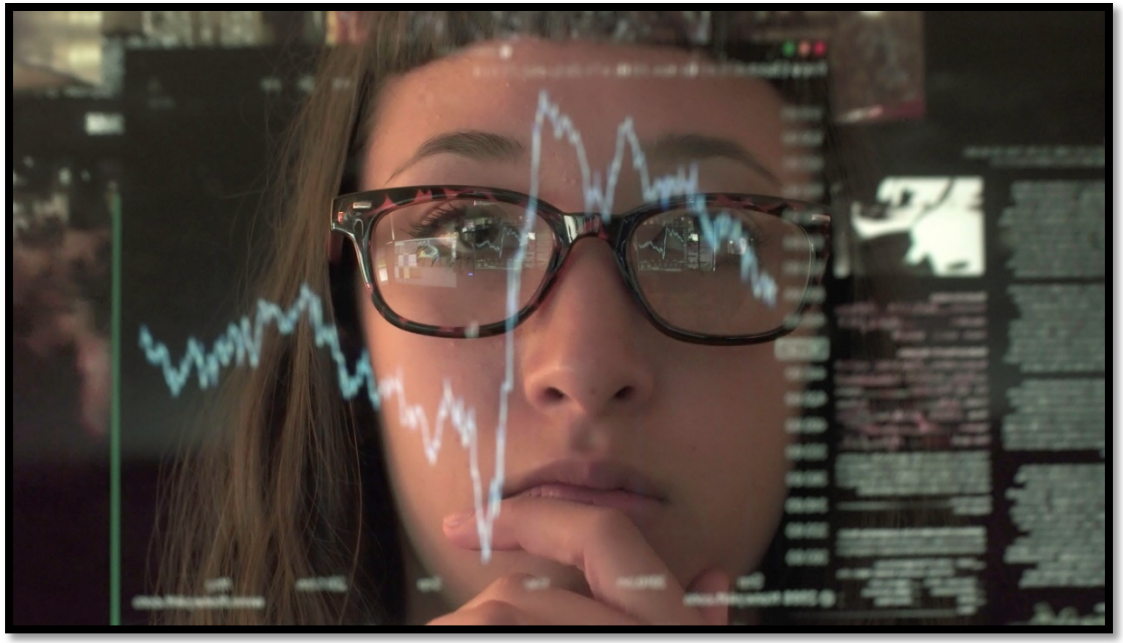
Learning Objectives

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

- Discuss the important information needed about your research question in order to effectively navigate the data access process
- Discuss the concepts of risks involved in the accessing of data
- Describe the various pathways or approaches to accessing different types of data
- Discuss the importance of data quality and validation, to be able to answer the question: Do you really have the cohort you need?

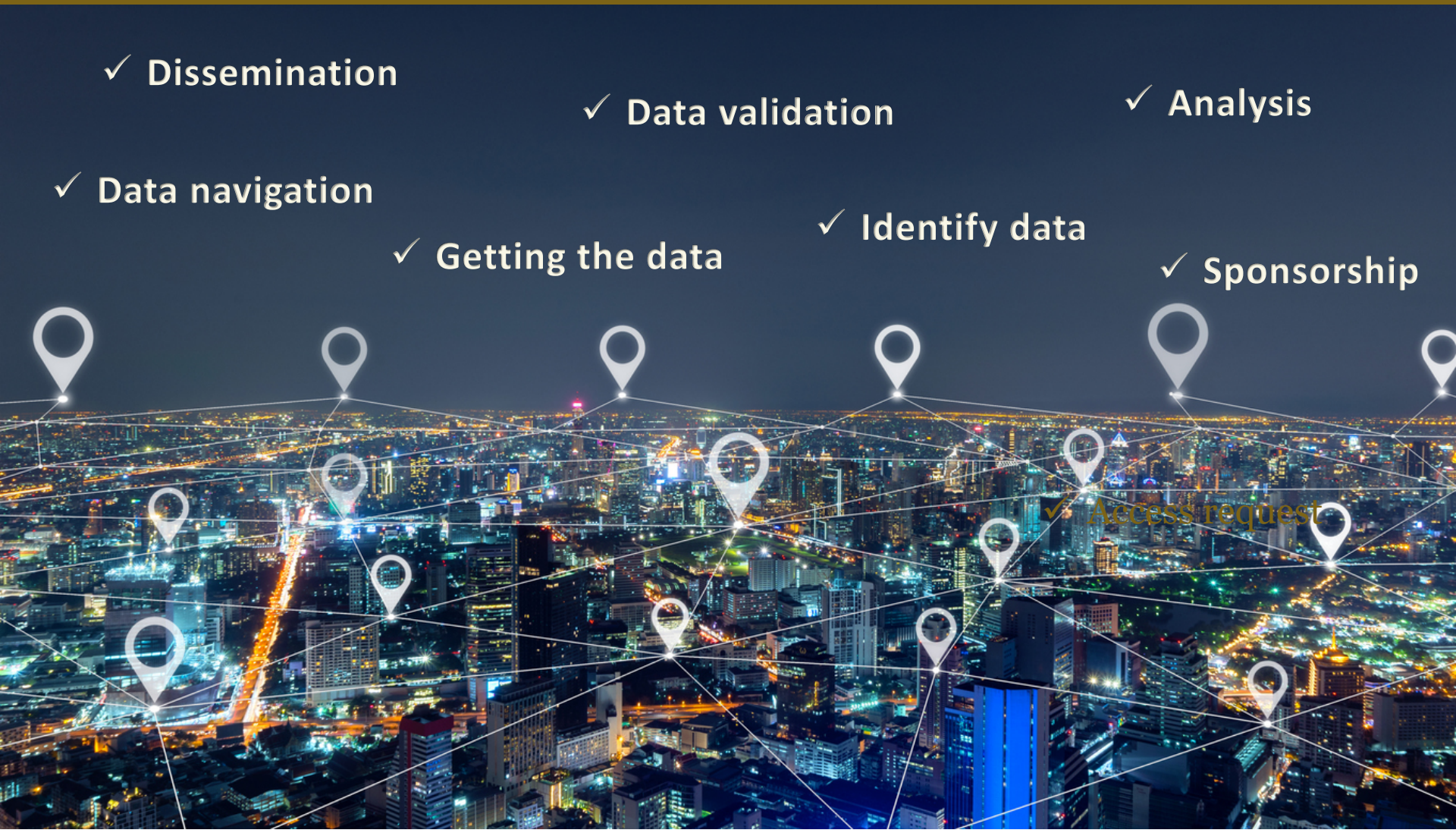
Assignment

Think about a research question you may have that will need health data…



(We'll come back to this in a few minutes)

How Do I Get Data to Support My Research?



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Worksheet

- Write down your research question and we will work through the areas together.

Identify Data

- What data do you need to answer your research question?
- Where does this data live?
- Is it structured or in notes? Data in notes is much harder to locate.
- Do you require Protected Health Information (PHI)? De-identified* patient data will be easier to obtain.
- A “limited data set” is another option if you absolutely must have dates.
- There are federal and state regulations that apply to health data, with substantial civil and criminal penalties for mishandling.

* Safe-Harbor method for de-identification requires removal of all of the following, without exception: Names, street address, city, zip (may keep first three digits of zip), all dates (may keep year), all ages > 89, telephone numbers, emails, any identifiers (SSN’s, MRN’s, IP addresses, health plan beneficiary numbers, etc.), Photos, fingerprints

Sponsorship

- This data is typically protected; ideally you will have a sponsor inside the organization.
- You may need to follow an IRB* process.
- You likely will need to follow an internal process as well.

NOTE: Obtaining an IRB does not grant you the right to access the data. The data is owned by the institution which has its own policies and processes for data release.

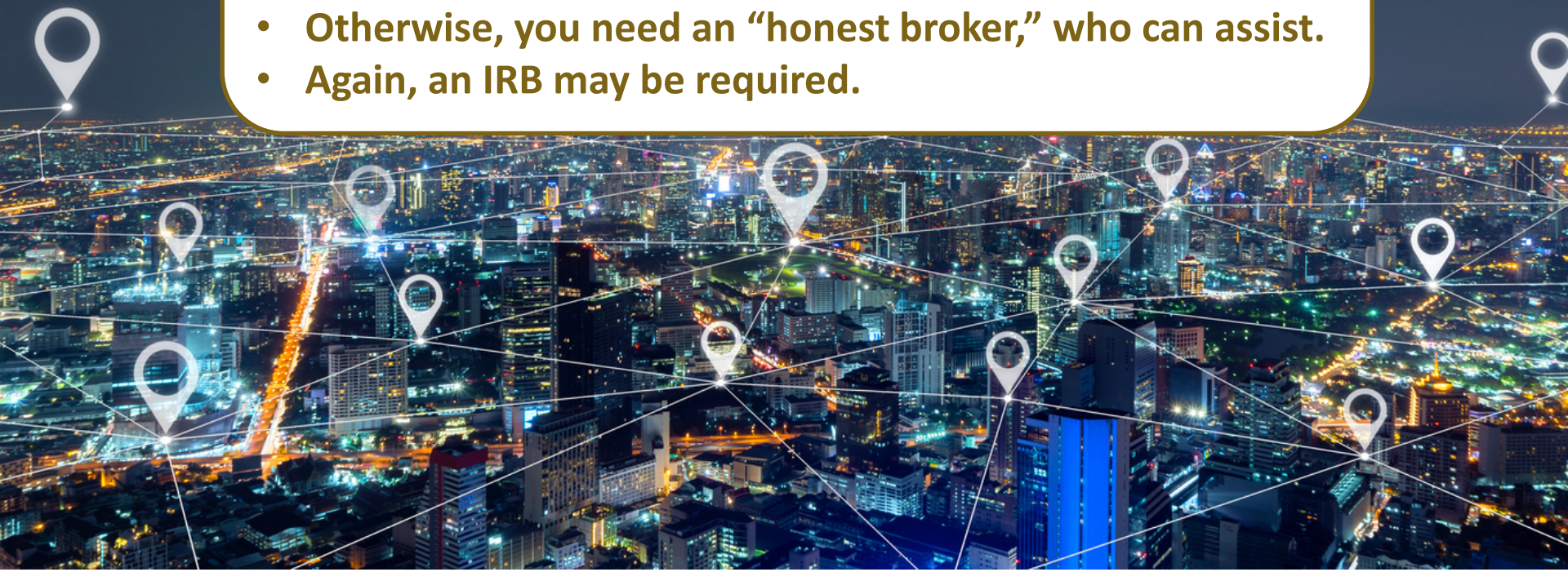
*IRB — Internal/Institutional Review Board. An IRB is a board, committee, or other group formally designated by an institution to review research involving humans as subjects. Typically, use of PHI for research requires human subject review.

Getting the Data

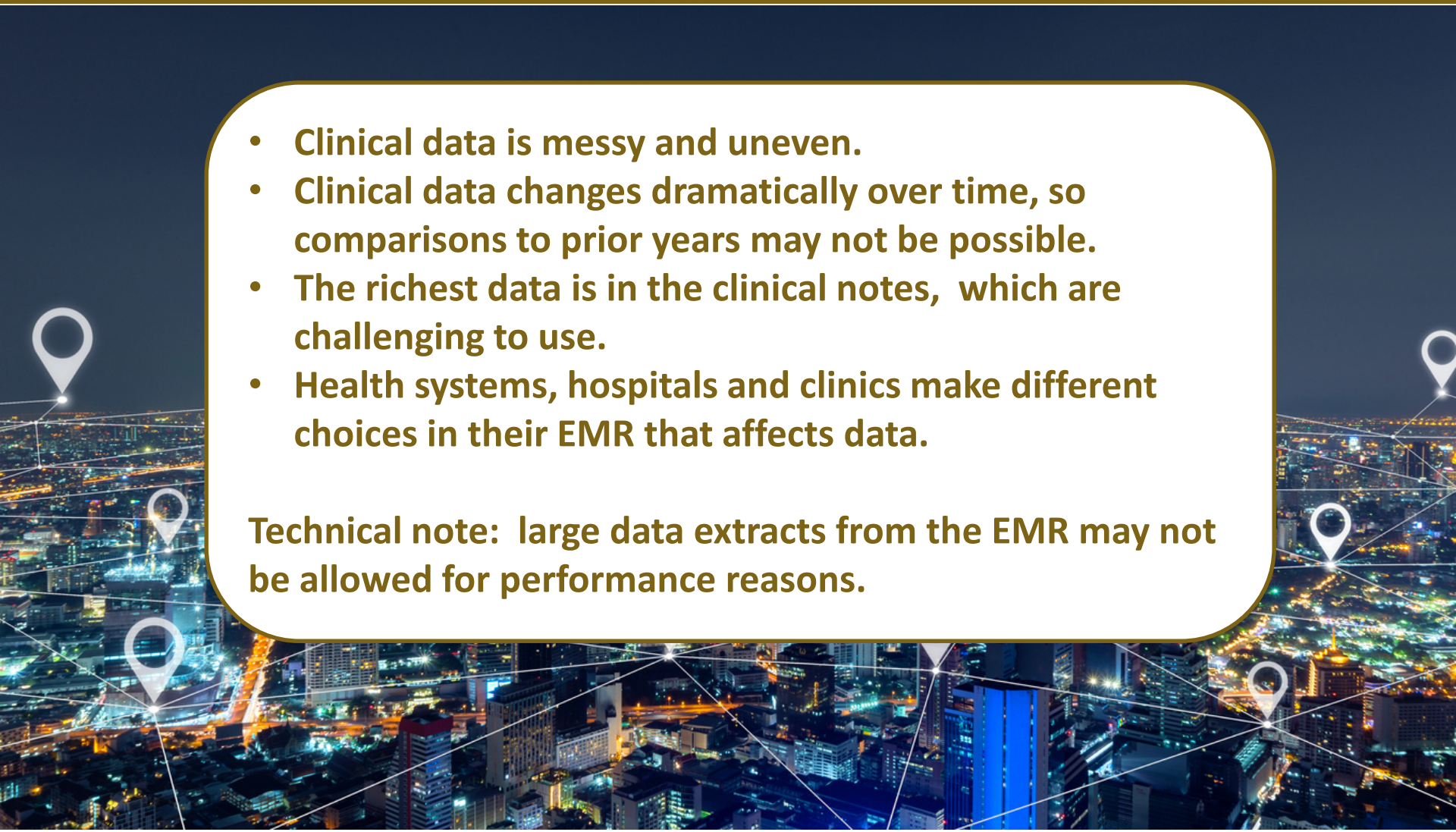
- If the data is in the EMR, you may need to write reports; if elsewhere, you may need SQL or other skills to extract.
- Locating the data you need is difficult (see data navigation) – you will likely need guidance on this from experts as well.
- You may also need training on EMR use, in order to understand the data entry process/scenario.
- At UW Medicine, we recommend partnering with an Affiliated Developer or Research IT.

Access Request

- You need to identify the system that has your data, and acquire access to that system.
- For direct access, you will need user login permission and access to the functions/data you've identified.
- Otherwise, you need an "honest broker," who can assist.
- Again, an IRB may be required.



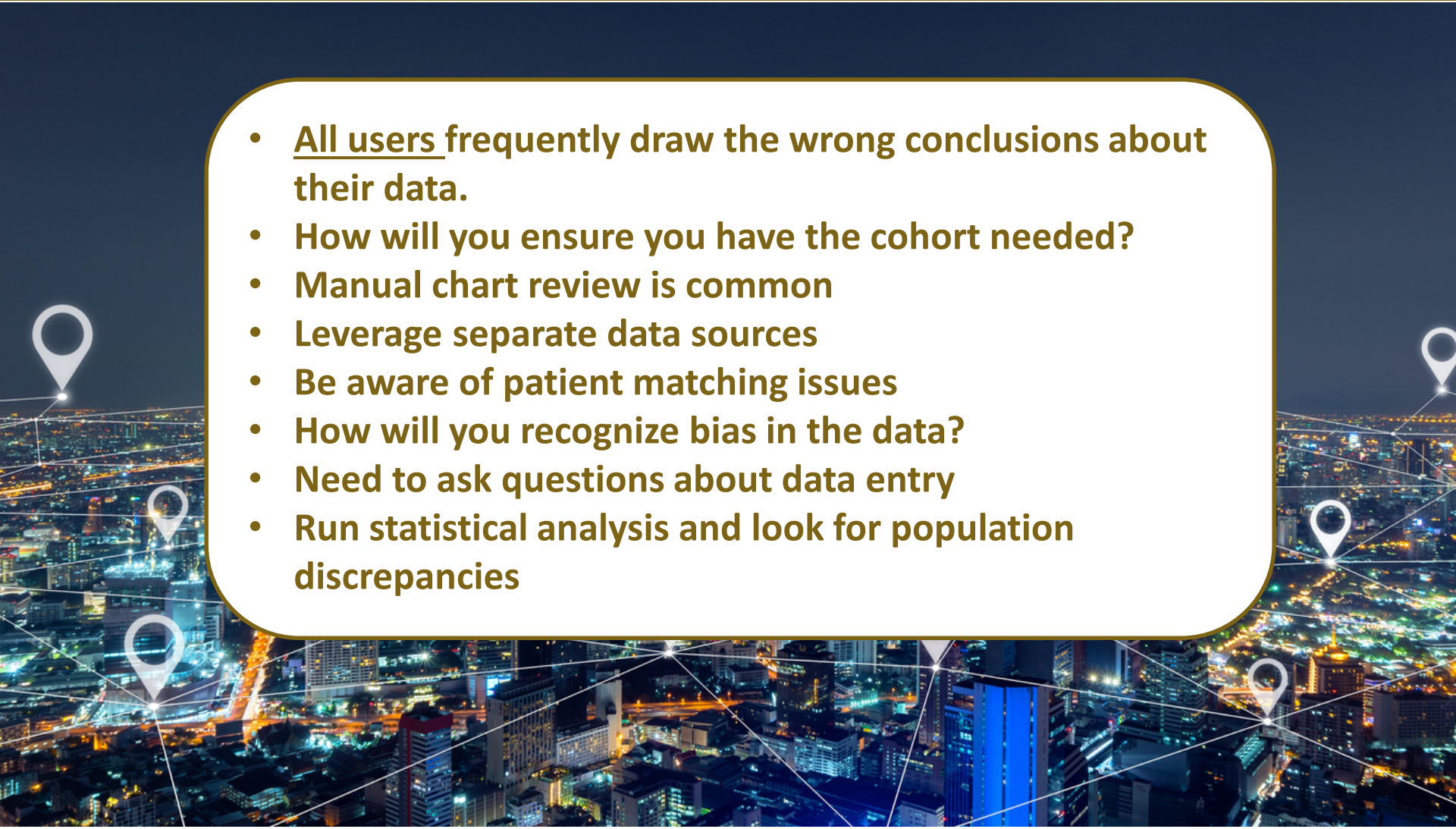
Data Navigation



- Clinical data is messy and uneven.
- Clinical data changes dramatically over time, so comparisons to prior years may not be possible.
- The richest data is in the clinical notes, which are challenging to use.
- Health systems, hospitals and clinics make different choices in their EMR that affects data.

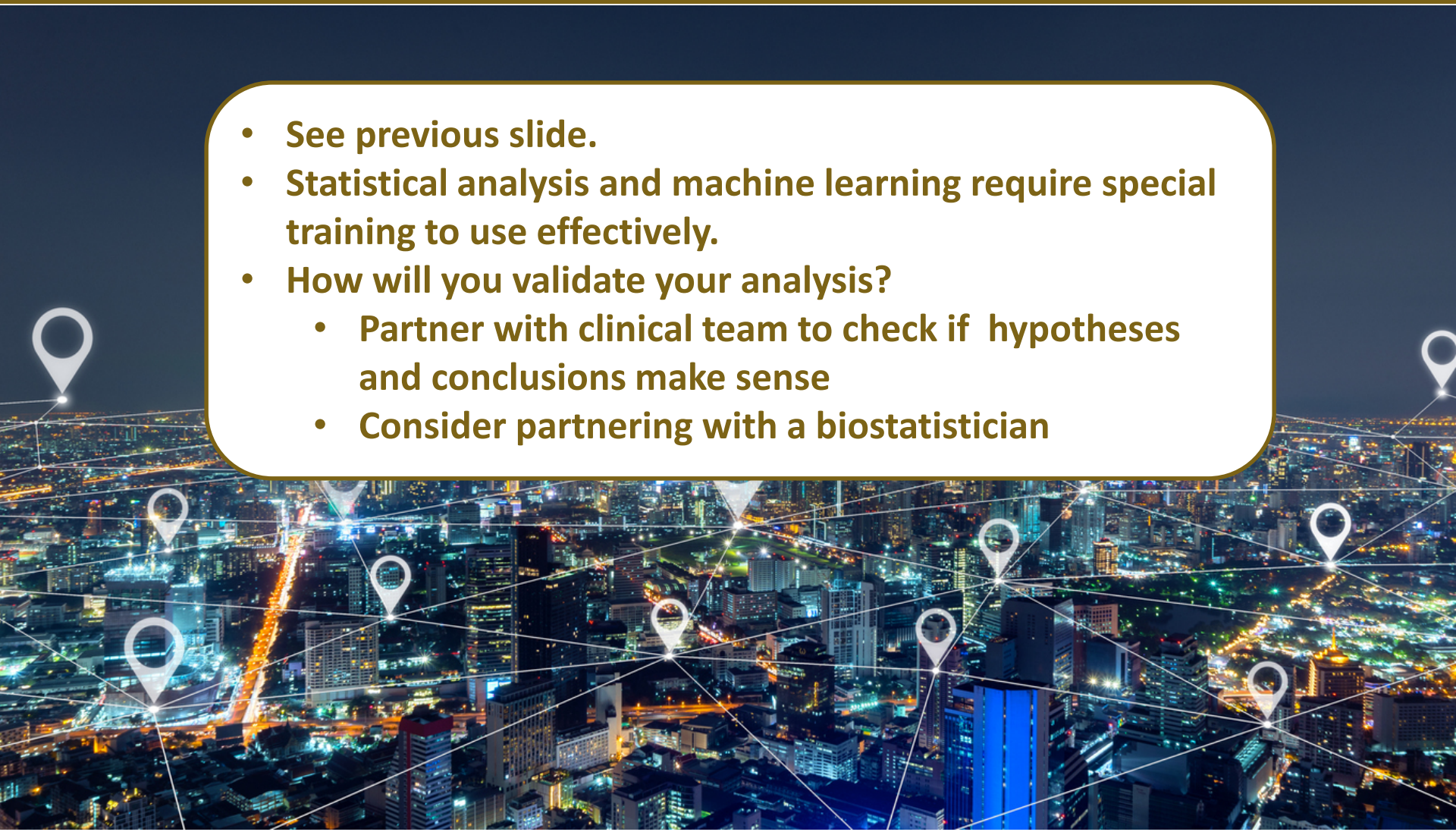
Technical note: large data extracts from the EMR may not be allowed for performance reasons.

Data Validation



- All users frequently draw the wrong conclusions about their data.
- How will you ensure you have the cohort needed?
- Manual chart review is common
- Leverage separate data sources
- Be aware of patient matching issues
- How will you recognize bias in the data?
- Need to ask questions about data entry
- Run statistical analysis and look for population discrepancies

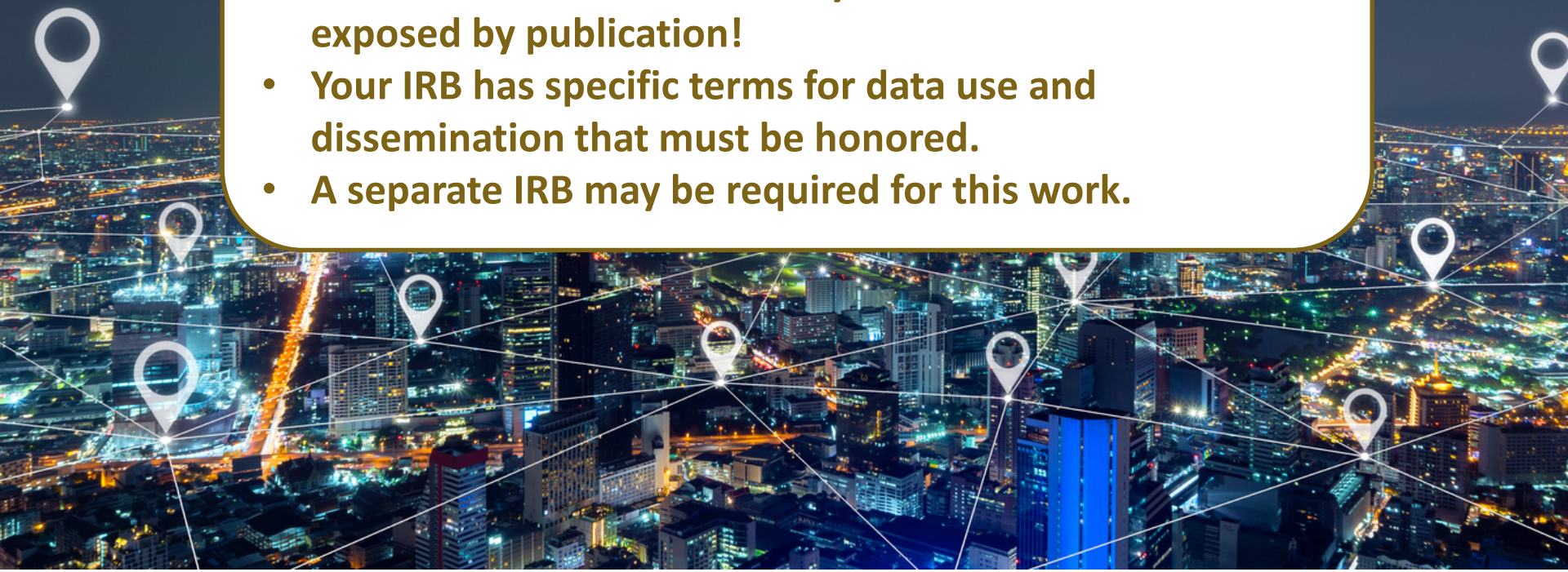
Analysis



- See previous slide.
- Statistical analysis and machine learning require special training to use effectively.
- How will you validate your analysis?
  - Partner with clinical team to check if hypotheses and conclusions make sense
  - Consider partnering with a biostatistician

Dissemination

- Data used for publication becomes part of public domain! You need to ensure this is permissible and may need to replicate research with publishable data.
- PHI and confidential health system data should never be exposed by publication!
- Your IRB has specific terms for data use and dissemination that must be honored.
- A separate IRB may be required for this work.



Learning Objectives

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ClinicalTrials.gov: Increasing the Transparency of Clinical Research

Presented by Diana Nelson Louden, MLIBR

12:45pm-1:45pm

UW Husky Union Building

Room 145

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

ClinicalTrials.gov: Increasing the Transparency of Clinical Research

Diana Nelson Louden
Biomedical & Translational Sciences Librarian
University of Washington Health Sciences Library
July 31, 2019

UNIVERSITY of WASHINGTON

HEALTH SCIENCES LIBRARY
UNIVERSITY of WASHINGTON
University Libraries

Why is a Librarian Talking About Clinical Trials.gov?

- We provide support throughout the biomedical research lifecycle.
- We help people find relevant public biomedical information.
- ClinicalTrials.gov is hosted by the National Library of Medicine.

ARNOLD LIBRARY
a Fred Hutch Shared Resource

HEALTH SCIENCES LIBRARY
UNIVERSITY of WASHINGTON
University Libraries

Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

Action figure from Archie McPhee

Goals for this Session

- Learn about the contents of ClinicalTrials.gov and how this data is used by researchers and the public.
- Describe legal, NIH, and publisher requirements for submitting data.
- Understand the role of ClinicalTrials.gov in increasing the transparency of clinical research.

- Contents
  - Clinical trial registry (starting in 2000)
  - Trial results (starting in 2008)
- Submitters
  - Trial sponsors, both private and public
- Audiences
  - Patients and families
  - Researchers and clinicians
  - Study record managers

Contents of ClinicalTrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
2	☐	Recruiting NEW	Veterans Nature Therapy (Vet Hike)	• Posttraumatic Stress Disorders	• Behavioral: Group nature hikes • Behavioral: Group urban hikes	• VA Puget Sound Health Care System Seattle, Washington, United States
3	☐	Not yet recruiting NEW	XperGuide in Sacroiliac Joint Injection	• Sacroiliitis • Sacroiliac Joint Pain	• Other: sacroiliac joint injection	• UW Center for Pain Relief Seattle, Washington, United States
4	☐	Not yet recruiting NEW	Inotuzumab Ozogamicin and Chemotherapy in Treating Patients With Recurrent or Refractory B-cell Acute Lymphoblastic Leukemia	• Blasts 5 Percent or More of Bone Marrow Nucleated Cells • Blasts 5 Percent or More of Peripheral Blood White Cells • CD22 Positive • (and 4 more...)	• Drug: Etoposide • Drug: Doxorubicin • Drug: Doxorubicin Hydrochloride • (and 6 more...)	• Fred Hutch/University of Washington Cancer Consortium Seattle, Washington, United States
5	☐	Not yet recruiting	Developing Low-Cost Universal Malnutrition Screening for Low Income Countries - the MAMMS Trial	• Child Malnutrition	• Other: Maternal Administered Malnutrition Monitoring System (MAMMS)	
6	☐	Recruiting	Harm Reduction for Tobacco Smoking With Support of Tobacco-Replacing Electronic Nicotine Delivery Systems	• Smoking, Tobacco	• Other: HaRTS-TRENDS • Other: Standard Care (SC)	• University of Washington - Harborview Medical Center Seattle, Washington, United States

Thrive, a Computerized Cognitive Behavior Therapy Program to Treat Depression Among Rural Montanans

- > Study design
- > Outcome measures
- > Inclusion & Exclusion criteria
- > Status and relevant dates

ClinicalTrials.gov Identifier: NCT03244878

Study Design

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	464 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Participants are randomized to either the wait-list controlled group or intervention group. Intervention period is 8 weeks. Data collection occurs at baseline, 4 weeks, and 8 weeks, with longer-term follow-up assessments.
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Randomized Controlled Trial of a Culturally-adapted Version of Thrive, a Computerized Cognitive Behavior Therapy (cCBT) Program to Treat Depressive Symptoms, Syndromes, and Disorders Among Rural Montanans
Actual Study Start Date :	May 1, 2017
Actual Primary Completion Date :	January 31, 2018
Actual Study Completion Date :	January 31, 2018

Benefits to the Public

- Meet ethical obligation to human subjects, i.e., that results will be used to help others/inform science
- Enhance patient access to enrollment in clinical trials
- Increased transparency of clinical research being conducted by pharmaceutical companies and with federal funding
- May contribute to increased public trust in clinical research

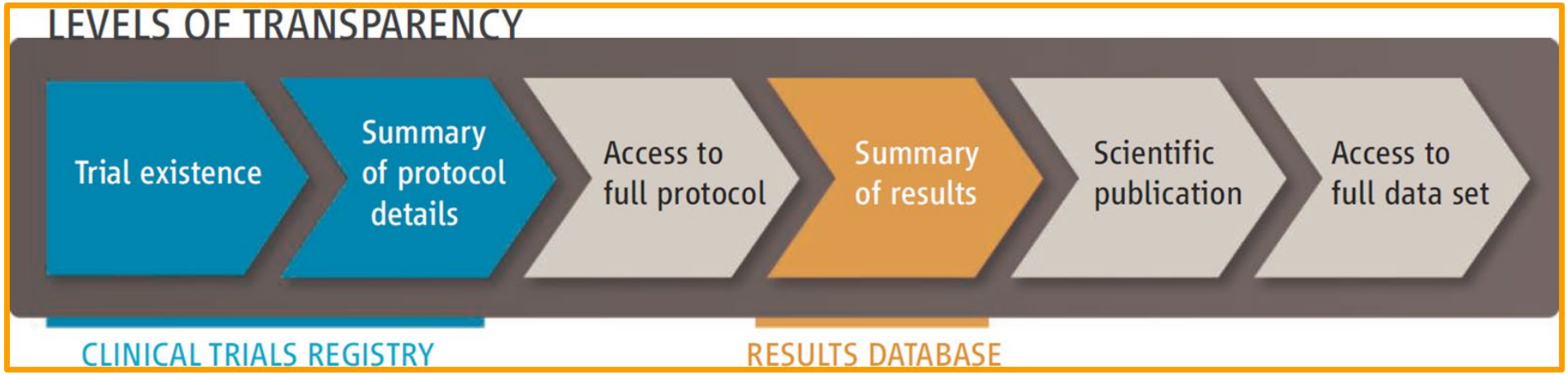
U.S. Air Force photo/Airman 1st Class Kyle Johnson

Benefits to the Clinical Research Process

- Inform future research and research funding decisions
- Mitigate information bias (e.g., non-publication)
- Evaluate research integrity (e.g., adherence to protocol)
- Prevent duplication of trials of unsafe or ineffective interventions
- Provide access to data to support evidence-based medicine

Levels of Transparency

"Transparency exists along a continuum from documentation that a trial exists to full disclosure of the results data set at the end of the trial."



Zarin DA, Tse T. Moving toward transparency of clinical trials. Science. 2008 Mar 7;319(5868):1340-2

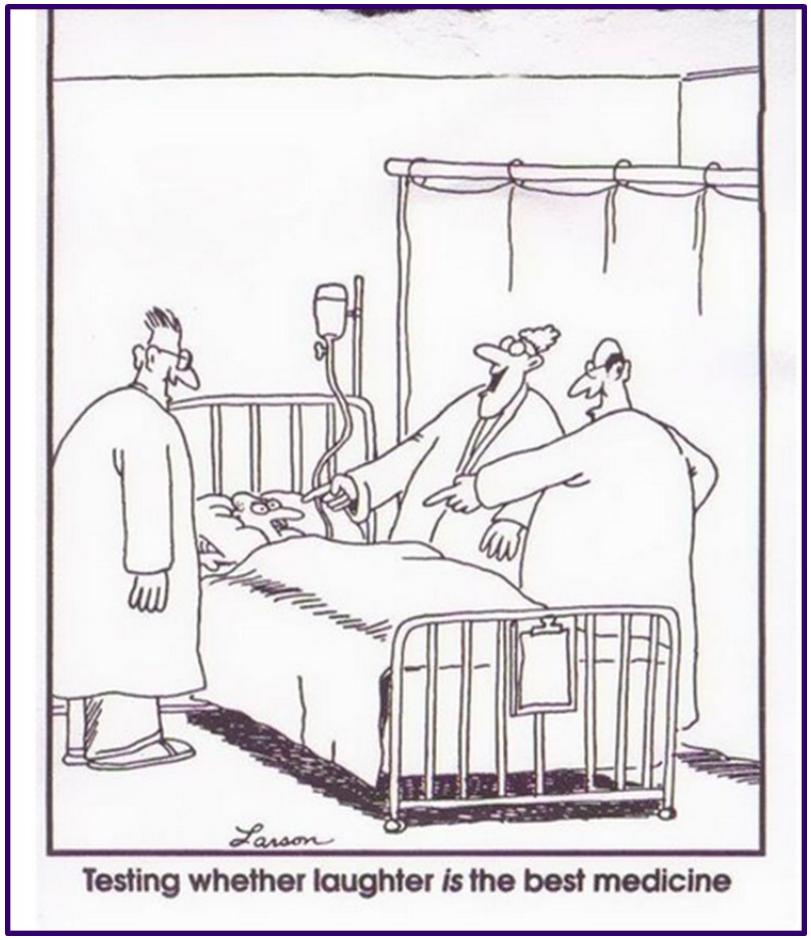
Illustrating the Benefits of a Trial Registry and Results Database

Assuming this is an IRB-Approved, NIH-funded trial involving multiple patients and a control group…

How does registration of this trial benefit the clinical research process?

How does registration of this trial benefit the public?

If this trial shows no benefit to patients, what is the benefit of documenting the results in ClinicalTrials.gov?



Testing whether laughter *is* the best medicine

ClinicalTrials.gov Fulfills its Purpose if the Information is Complete and Discoverable

- Data needs to be high quality.
- Record formats and terminology need to be standardized.

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	464 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Participants are randomized to either the wait-list controlled group or intervention group. Intervention period is 8 weeks. Data collection occurs at baseline, 4 weeks, and 8 weeks, with longer-term follow-up assessments.
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Actual Study Start Date :	May 1, 2017
Actual Primary Completion Date :	January 31, 2018
Actual Study Completion Date :	January 31, 2018

- All relevant studies need to be included.

Who Requires Trial Registration and, in Some Cases, Results Reporting?

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

- ICMJE policy applies to many scientific journals, such as American Journal of Nursing, Pediatrics, & Transplantation
- Trial registration is a condition of consideration for publication.

FDA

- FDAAA 801 and 42 CFR Part 11 "The Final Rule" require that Applicable Clinical Trial data be submitted no later than 21 days after enrollment of 1st participant.
- Results must be reported no later than 1 year after primary completion date.

NIH National Institutes of Health
Turning Discovery Into Health

- Trial registration and results reporting are requirements for NIH-funded trials, whether or not they are FDA regulated.

BILL & MELINDA GATES foundation

- Organizations such as the Gates Foundation, Wellcome Trust, & PATH require trial registration & results reporting.

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

- Trials submitting claims to the Centers for Medicare & Medicaid Services must include the NCT number from ClinicalTrials.gov

ICMJE = International Committee of Medical Journal Editors
FDAAA 801 = Section 801 of the Food and Drug Administration Amendments Act of 2007

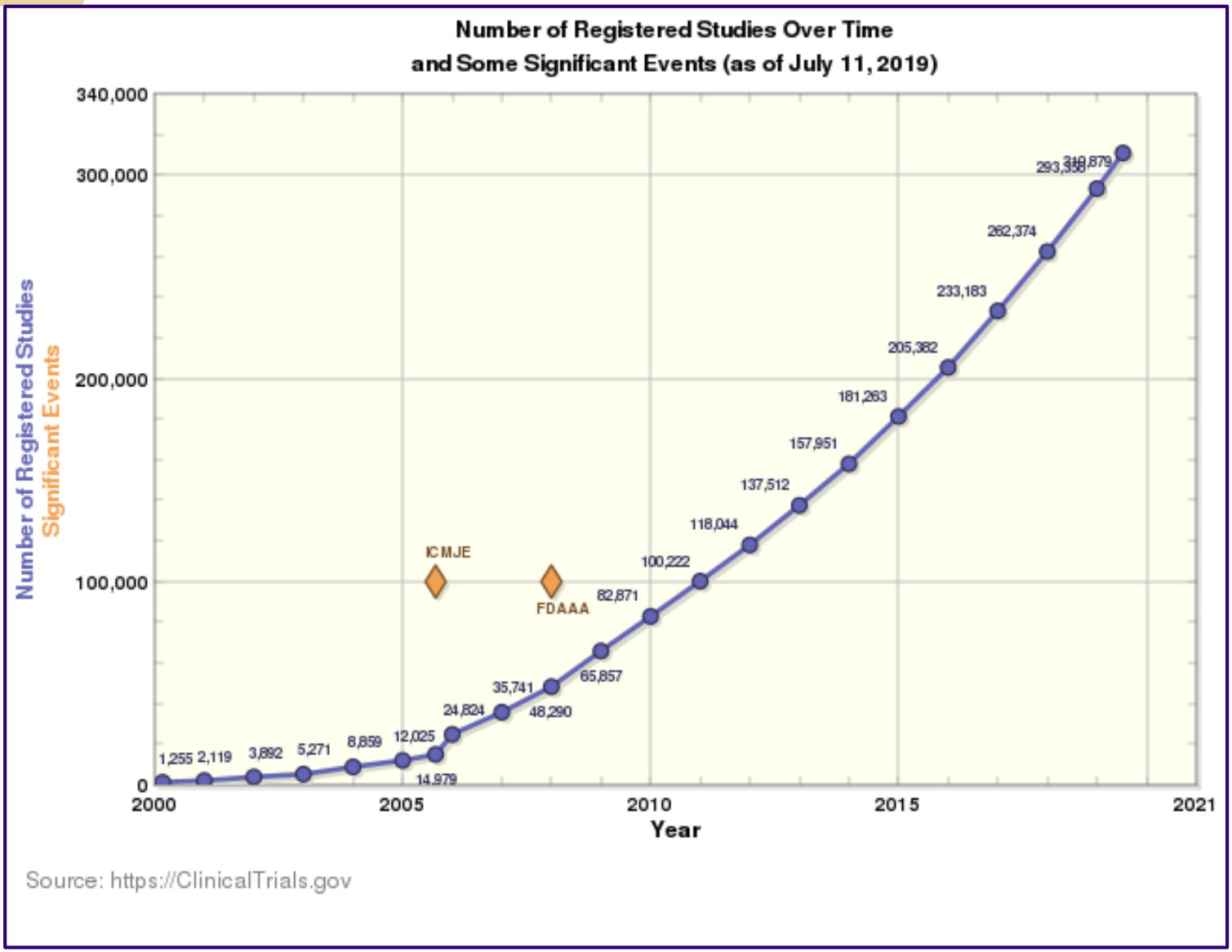
Joint Statement on Public Disclosure of Results from Clinical Trials (2017)

"In addition to the ethical imperative, poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are based on only a subset of all completed clinical trials."

who.int/ictrp/results/jointstatement/en/

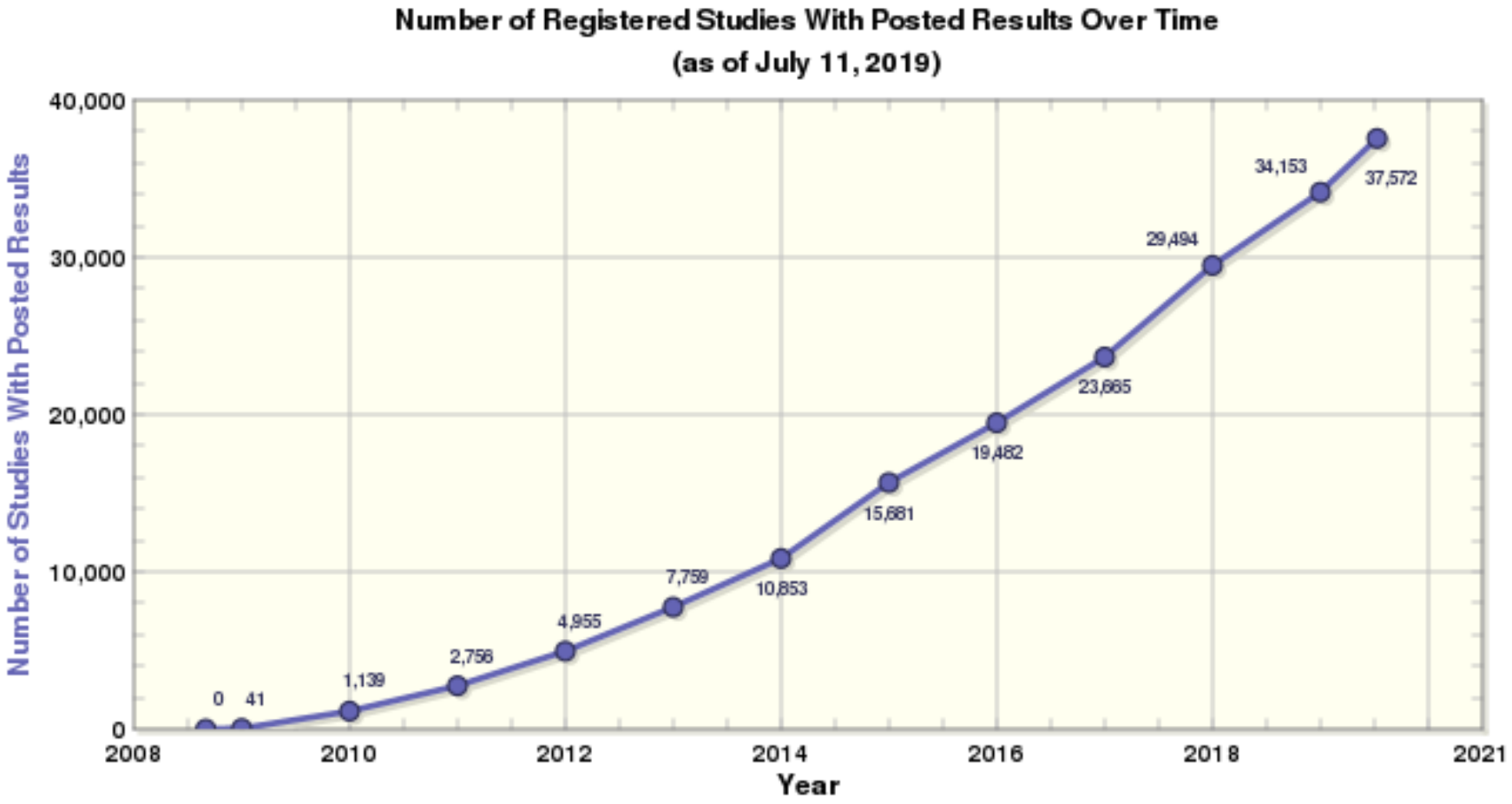
Are 100% of Applicable Clinical Trials Entered in Clinical Trials.gov?

No, but…



Source: https://ClinicalTrials.gov

Trials With Results Data



Source: https://ClinicalTrials.gov

Significant Changes in Trial Registration as of 2017: Expanded FDA Regulation and New NIH Policy

A summary table describes the changes. Three especially noteworthy changes (highlighted by the UW Human Subjects Division) are:

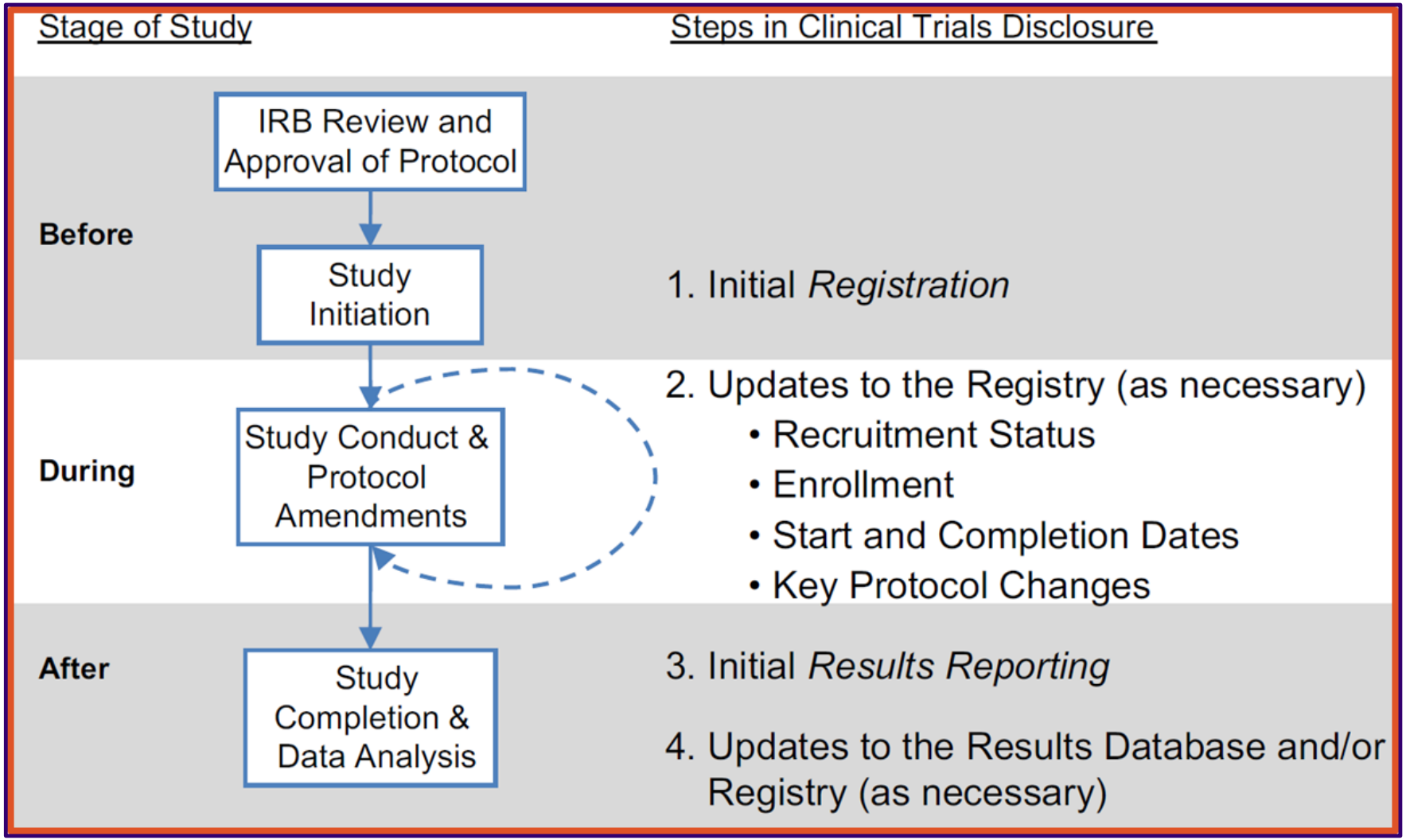
1. All clinical trials funded in whole, or in part, by NIH must be registered, regardless of study phase or type of intervention.
2. Study consent forms must contain a sentence about the trial registration, using the words provided by the FDA and NIH.
3. Penalties for non-compliance may include:
   - Identifying the clinical trial record as non-compliant in ClinicalTrials.gov
   - Suspension or termination of grant or contract funding, if required registration and reporting cannot be verified
   - Consideration of the non-compliance in future funding decisions
   - Civil monetary penalties to the "responsible party" (PI) of up to $10,000/day

Roles & Legal Responsibilities at UW

Who	What	Why
Lead PI	• Register the trial • Update the record • Report the results • Consent statement	42 CFR 11 NIH Policy
Site PI	Consent statement	42 CFR 11 NIH Policy
IRB	Consent form has the statement	21 CFR 50.25(c) 21 CFR 56.111(a)(4,5)
UW ↳ HSD	• Institutional contact for ClinicalTrials.gov • Help with researcher account	ClinicalTrials.gov requirement

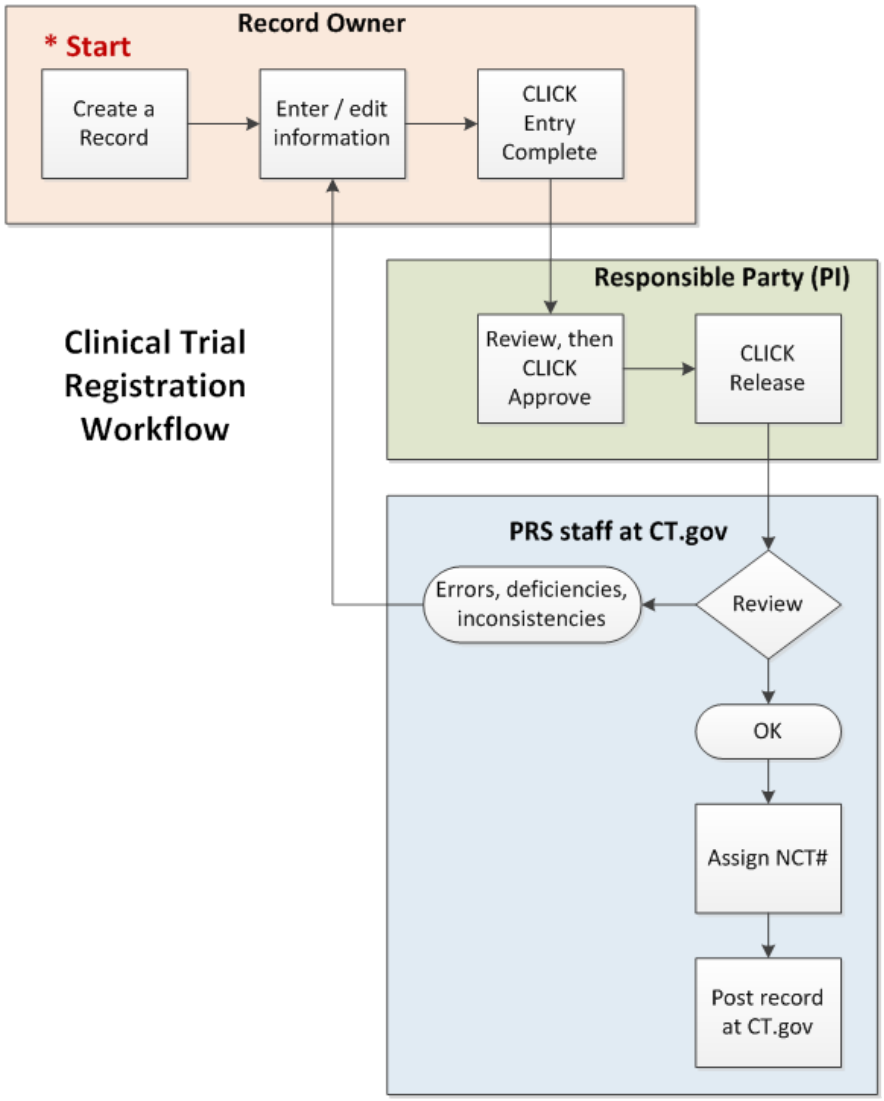
Thank you to the UW Human Subjects Division

When Do Registration & Results Reporting Occur?



Tse T, Zarin DA, Williams RJ, Ide NC. The Role and Importance of Clinical Trial Registries and Results Databases. In: Gallin JI, Ognibene FP, editors. Principles and Practice of Clinical Research. London: Academic Press; c2012. p. 171-181.

Clinical Trial Registration Workflow



Record Owner

Responsible Party (Principal Investigator)

PRS Staff at ClinicalTrials.gov

washington.edu/research/forms-and-templates/clinical-trial-registration-work-flow

Help is Available

- Help from your institution's human subjects department.
- Tools to help you determine if your study is considered a clinical trial under the NIH's revised definition.
- Possible to upload study data to ClinicalTrials.gov from within the NIH's eRA Human Subjects System
- ClinicalTrials.gov user support materials.
  - "How to" information
  - Policies of VA, National Cancer Institute, PCORI, etc.

Submitting High Quality Information: Specificity and Consistency

- > Required Data Elements
- > Internal Consistency
- > Appropriate Level of Specificity
- > Standardized Terminology When Appropriate

Outcome Measure Type *
Definition: The type of outcome measure. Select one.

- Primary
- Secondary
- Other Pre-specified
- Post-Hoc

ClinicalTrials.gov Results Data Element Definitions for Interventional and Observational Studies
prsinfo.clinicaltrials.gov/results_definitions.html

Outcome Measure Title *
Definition: Name of the specific outcome measure.
Limit: 255 characters.

Outcome Measure Description [*]
Definition: Additional information about the outcome measure, including a description of the metric used to characterize the specific outcome measure, if not included in the Outcome Measure Title.
Limit: 999 characters.

Outcome Measure Time Frame *
Definition: Time point(s) at which the measurement was assessed for the specific metric used. The description of the time point(s) of assessment must be specific to the outcome measure and is generally the specific duration of time over which each participant is assessed (not the overall duration of the study).
Limit: 255 characters.

ClinicalTrials.gov Protocol Registration Quality Control Review Criteria - Examples

- Interventions are referred to by the same name throughout the study record.
- If more than one name is used for the same drug (e.g., a generic name and a brand name), the study record clearly indicates that the drugs are the same.
- The Arm Description or Group/Cohort Description include details about the intervention strategies administered (e.g., dosage, dosage form, frequency of administration, duration of administration) or groups evaluated.
- Use, if available, appropriate descriptors from NLM's Medical Subject Headings (MeSH) thesaurus.

*Quality Control Review Criteria for **Registration** and **Results***

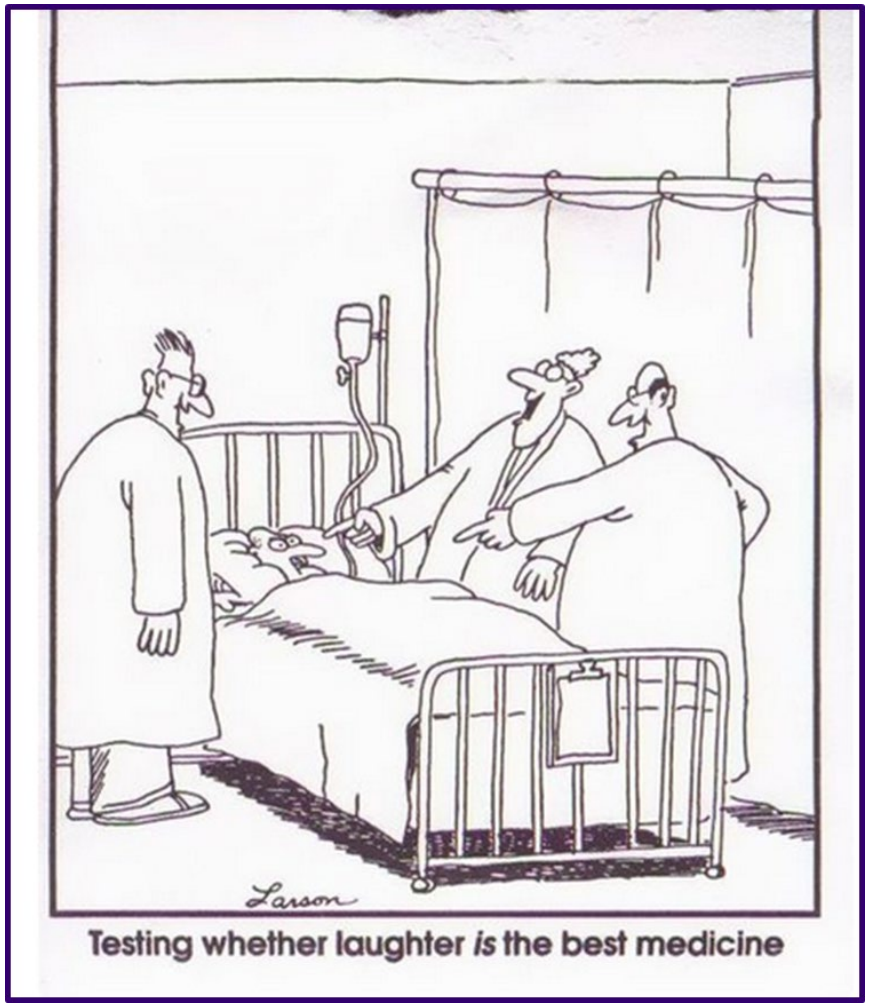
Effectiveness of laughter in alleviating postoperative pain following colorectal resection

Population: hospitalized patients who have undergone colorectal resection for colon cancer.

Study design: 48 patients, randomized to laughter + usual treatment or usual treatment.

Treatment protocol: Laughter administered 3 times a day for 3 days.

Outcomes: Pain measured with the 2010 Revised American Pain Society Patient Outcome Questionnaire



Some Required Data Elements for Trial Registration

Study Description Go to

Brief Summary:

This prospective, randomized, double-blind study will enroll nonsmoking female subjects undergoing laparoscopic bariatric surgery under general anesthesia. The hypothesis of this study is that female nonsmokers who receive nicotine via nasal spray immediately before waking up from anesthesia will need less pain medications 24 hours after the surgery compared to the subjects who receive placebo spray.

Condition or disease	Intervention/treatment	Phase
Pain, Postoperative	Drug: Nasal Nicotine Spray Drug: Nasal Normal Saline Spray	Phase 4

Outcome Measure Title and Time Frame Fields Are Highlighted

Primary Outcome Measures :

1. Postoperative Opioid Use During the Postanesthesia Care Unit (PACU) Stay, and the First 24 Hours Postoperatively [Time Frame: During PACU stay (approximately 94 minutes after operation), 24 hours after operation]

   Opioid use was calculated in intravenous morphine equivalents (iv MEQ) according to the Mayo Clinic Pharmacy opioid conversion calculator based on the recommendations from the American Pain Society. Specifically, the following conversion was used: 10 mg in MEQ=100mcg iv fentanyl=1.5 mg iv hydromorphone=20mg oral oxycodone=30mg oral hydrocodone.

More Suitable Documentation: A or B?

Data Element: Primary Disease or Condition Being Studied in the Trial

A	B
Surgical Pain	Pain, Postoperative [a Medical Subject Heading]

More Suitable Documentation: A or B?

Data Element: Study Description: Brief Summary

A	B
Objective: evaluate the effectiveness of laughter in alleviating postoperative pain following colorectal resection	Objective: evaluate the effectiveness of laughter in alleviating postoperative pain following colorectal resection

Data Element: Arm Title (Used for Interventional Studies)

A	B
Experimental Arm 1: Chuckling administered 3 times/day	Experimental Arm 1: Laughter administered 3 times/day

More Suitable Documentation: A or B?

Data Element: Outcome Measure Title

A	B
Pain	Mean Change from Baseline in Scores on the 2010 Revised American Pain Society Patient Outcome Questionnaire

Data Element: Outcome Measure: Time Frame

A	B
Daily through study completion	2 hours post-surgery; then daily during hospitalization, approximately 3 days.

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BMC Med Genet. 2013 Jan 11;14:6. doi: 10.1186/1471-2350-14-6.

Effects of smoking on the genetic risk of obesity: the population architecture using genomics and epidemiology study.

Fesinmeyer MD[1], North KE, Lim U, Bůžková P, Crawford DC, Haessler J, Gross MD, Fowke JH, Goodloe R, Love SA, Graff M, Carlson CS, Kuller LH, Matise TC, Hong CP, Henderson BE, Allen M, Rohde RR, Mayo P, Schnetz-Boutaud N, Monroe KR, Ritchie MD, Prentice RL, Kolonel LN, Manson JE, Pankow J, Hindorff LA, Franceschini N, Wilkens LR, Haiman CA, Le Marchand L, Peters U.

Author information

1 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024, USA.

Abstract

BACKGROUND: Although smoking behavior is known to affect body mass index (BMI), the potential for smoking to influence genetic associations with BMI is largely unexplored.

METHODS: As part of the 'Population Architecture using Genomics and Epidemiology (PAGE)' Consortium, we investigated interaction between genetic risk factors associated with BMI and smoking for 10 single nucleotide polymorphisms (SNPs) previously identified in genome-wide association studies. We included 6 studies with a total of 56,466 subjects (16,750 African Americans (AA) and 39,716 European Americans (EA)). We assessed effect modification by testing an interaction term for each SNP and smoking (current vs. former/never) in the linear regression and by stratified analyses.

RESULTS: We did not observe strong evidence for interactions and only observed two interactions with p-values <0.1: for rs6548238/TMEM18, the risk allele (C) was associated with BMI only among AA females who were former/never smokers (β = 0.018, p = 0.002), vs. current smokers (β = 0.001, p = 0.95, p(interaction) = 0.10). For rs9939609/FTO, the A allele was more strongly associated with BMI among current smoker EA females (β = 0.017, p = 3.5 x 10(-5)), vs. former/never smokers (β = 0.006, p = 0.05, p(interaction) = 0.08).

CONCLUSIONS: These analyses provide limited evidence that smoking status may modify genetic effects of previously identified genetic risk factors for BMI. Larger studies are needed to follow up our results.

CLINICAL TRIAL REGISTRATION: NCT00000611.

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A systematic mapping approach of 16q12.2 and BMI in more than 20,000 [PLoS Genet.

Interaction of FTO and physical activity leve adiposity in African [Obesity (Silver Spring).

BMI loci and longitudinal BMI from adolesce to young adulthood in a [Int J Obes (Lond).

Influence of common variants in FTO and n INSIG2 and MC4R on gro [Eur J Epidemiol.

Review Genetic association studies of obes Africa: a systematic review. [Obes Rev.

See rev

Se

Data for Large-Scale Analysis

Table. Sex Bias in Clinical Studies Determined From Published Articles and Clinical Trial Records[a]

Disease Category	Global Female Prevalence Fraction	Measurement Unit	Published Articles			AACT Records		
			Studies or Participants, No.	Female Participant Fraction	Sex Bias (95% CI)	Studies or Participants, No.	Female Participant Fraction	Sex Bias (95% CI)
Cardiovascular	0.51	Studies	14 371	0.37	−0.14 (−0.14 to −0.13)[b]	2164	0.41	−0.10 (−0.11 to −0.09)[b]
		Participants	540 050 700	0.49	−0.02 (−0.06 to −0.01)	2 229 071	0.39	−0.12 (−0.15 to −0.08)[b]
Diabetes	0.48	Studies	3727	0.45	−0.03 (−0.03 to −0.02)[b]	1420	0.46	−0.03 (−0.03 to −0.02)[b]
		Participants	38 420 434	0.48	0.00 (−0.05 to 0.04)	4 823 058	0.47	−0.01 (−0.08 to 0.02)
Digestive	0.60	Studies	1282	0.49	−0.11 (−0.12 to −0.10)[b]	348	0.54	−0.06 (−0.08 to −0.04)[b]
		Participants	8 519 928	0.51	−0.09 (−0.13 to −0.07)[b]	147 821	0.56	−0.03 (−0.06 to −0.01)
Hepatitis A, B, C, and E	0.44	Studies	1131	0.34	−0.09 (−0.10 to −0.09)[b]	632	0.37	−0.06 (−0.07 to −0.05)[b]
		Participants	1 833 724	0.37	−0.06 (−0.17 to 0.06)	243 846	0.39	−0.05 (−0.07 to −0.03)[b]
HIV/AIDS	0.50	Studies	1741	0.33	−0.17 (−0.18 to −0.16)[b]	387	0.27	−0.23 (−0.25 to −0.21)[b]
		Participants	30 459 386	0.53	0.02 (−0.09 to 0.06)	155 531	0.35	−0.15 (−0.20 to −0.11)[b]
Kidney, chronic	0.57	Studies	2554	0.40	−0.17 (−0.17 to −0.16)[b]	476	0.42	−0.15 (−0.16 to −0.13)[b]
		Participants	18 747 970	0.44	−0.13 (−0.18 to −0.09)[b]	201 763	0.42	−0.15 (−0.17 to −0.12)[b]
Mental	0.48	Studies	3635	0.47	−0.01 (−0.02 to 0.00)[b]	1650	0.44	−0.04 (−0.05 to −0.03)[b]
		Participants	58 097 584	0.48	−0.01 (−0.19 to 0.07)	463 645	0.49	0.00 (−0.01 to 0.02)
Musculoskeletal	0.56	Studies	2418	0.66	0.10 (0.09 to 0.11)[b]	983	0.70	0.14 (0.13 to 0.15)[b]
		Participants	5 898 338	0.60	0.03 (0.00 to 0.08)	438 112	0.65	0.09 (−0.05 to 0.18)
Neoplasms	0.51	Studies	11 121	0.40	−0.11 (−0.11 to −0.11)[b]	3179	0.41	−0.10 (−0.11 to −0.10)[b]
		Participants	54 377 430	0.49	−0.03 (−0.04 to −0.01)[b]	2 946 236	0.50	−0.02 (−0.09 to 0.03)
Neurological	0.59	Studies	3431	0.50	−0.09 (−0.10 to −0.09)[b]	1338	0.52	−0.07 (−0.08 to −0.06)[b]
		Participants	10 576 242	0.53	−0.06 (−0.09 to −0.03)[b]	497 964	0.65	0.06 (−0.01 to 0.12)
Respiratory, chronic	0.48	Studies	2800	0.43	−0.04 (−0.05 to −0.04)[b]	1161	0.44	−0.03 (−0.04 to −0.02)[b]
		Participants	116 410 829	0.48	0.00 (−0.05 to 0.02)	1 231 162	0.47	−0.01 (−0.04 to 0.01)
Total[c]	0.54	Studies	48 211	0.42	−0.12 (−0.12 to −0.11)[b]	13 738	0.45	−0.09 (−0.09 to −0.08)[b]
		Participants	883 392 565	0.49	−0.05 (−0.06 to −0.03)[b]	13 378 210	0.48	−0.06 (−0.09 to −0.03)[b]

Feldman S et al. Quantifying Sex Bias in Clinical Studies at Scale With Automated Data Extraction. *JAMA Netw Open.* July 03, 20192(7):e196700.

Improved Access to Information for Patients & Families

9 Studies found for: **Recruiting, Not yet recruiting Studies | Crohn Disease | Washington, United States | Child**

Applied Filters: ☑ **Recruiting** ☑ **Not yet recruiting** ☑ **Child (birth–17)**

Saved	Status	Study Title	Conditions	Interventions	Locations
☐	Recruiting	Reverse Engineering of Exclusive Enteral Nutrition	• **Crohn Disease**	• Other: Nutritional therapy	• Seattle Children's Hospital Seattle, **Washington**, **United States**
☐	Recruiting	A Study of the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active **Crohn's Disease**	• **Crohn's Disease**	• Drug: placebo for risankizumab • Drug: risankizumab IV • Drug: risankizumab SC	• Phoenix VA Healthcare /ID# 162267 Phoenix, Arizona, **United States** • HonorHealth Research Institute - Shea /ID# 161783 Scottsdale, Arizona, **United States** • Physician's Research Group /ID# 211883 Tempe, Arizona, **United States** • (and 471 more...)

"Access to more information about clinical trials is good for patients, the public and science. The final rule and NIH policy…will help maximize the value of clinical trials…and help us honor our commitments to trial participants, who do so much to help society advance knowledge and improve health."

~NIH Director Francis Collins

nih.gov/news-events/news-releases/hhs-takes-steps-provide-more-information-about-clinical-trials-public

Resources and Further Reading

- PRS User's Guide: Instructions for using the Protocols Registration & Results System (PRS) to submit clinical study information to ClinicalTrials.gov
- Quality Control Review Criteria for Registration and Results. ClinicalTrials.gov.
- Frequently Asked Questions on ClinicalTrials.gov & FDAAA. National Institutes of Health.
- FDAAA 801 and the Final Rule. Summary of Food and Drug Administration (FDA) requirements relating to ClinicalTrials.gov
- Summary Table of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information. National Institutes of Health.
- NIH Definition of Clinical Trial Case Studies.
- Steps to Compliance for NIH Awardees.
- Clinical Trial Registration Policy. International Committee of Medical Journal Editors
- ClinicalTrials.gov staff email: register@clinicaltrials.gov

Resources and Further Reading, p.2

- University of Washington Human Subjects Division: Clinical Trials Registration and Reporting
- Fred Hutch Clinical Research Support: CTRP & ClinicalTrials.gov
- Seattle Children's Clinical Research Support Office: Registration of Clinical Research Trials on ClinicalTrials.gov
- Friedman, L., Furberg, Curt, DeMets, David L., Reboussin, David, & Granger, Christopher B. (2015). Fundamentals of clinical trials (Fifth ed.). New York: Springer. Chapter 20 "Reporting and Interpreting of Results." [*ebook version available to UW affiliates*]
- FDAAA Trials Tracker. Evidence Based Medicine DataLab, University of Oxford.

Acknowledgements

- Kristina Elliott, MLS, Web Content and Outreach Coordinator, ClinicalTrials.gov
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- Emily Patridge, MLS, Assistant Director of Clinical Research & Data Services, University of Washington Health Sciences Library
- University of Washington Human Subjects Division Staff

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