The Study Start-Up Process

Presented by Emily Cox, PhD

10:50pm-11:50pm

UW Husky Union Building

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

The study start-up process

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

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Today's topics

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

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


Writing
Grant submission
Funding
Start-up

“Why does start-up take so long?”

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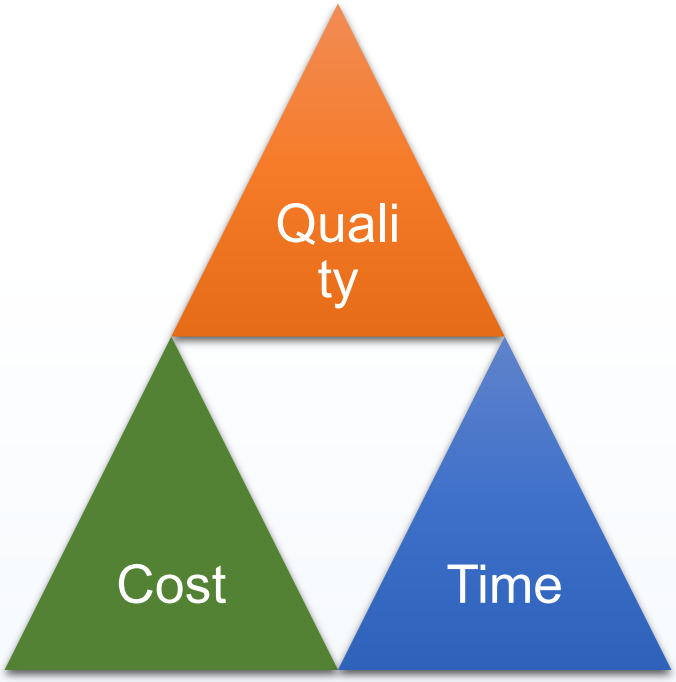
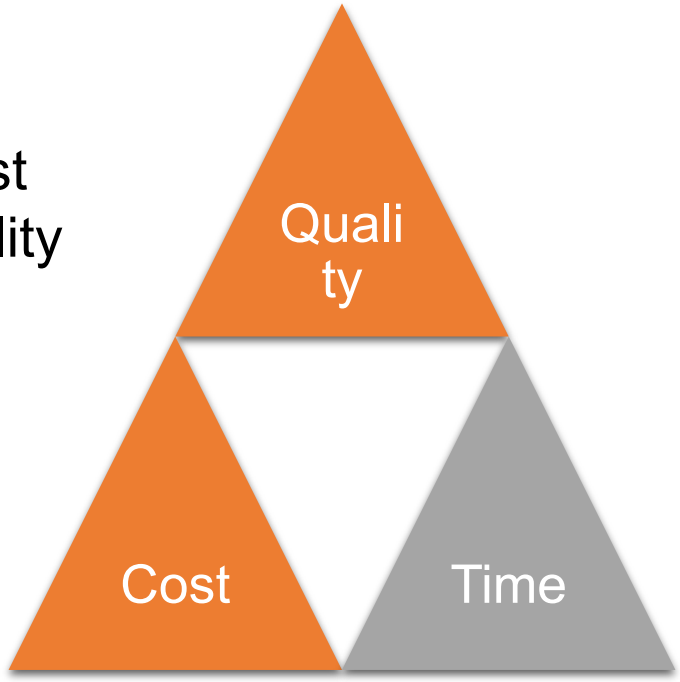
- Slow CRO responses
- Legal or compliance questions
- Sponsor acquisition
- Inexperienced sponsor team
- New hardware
- New software
- Contracting with 3rd party suppliers
- Staff PTO
- Insufficient feasibility assessment
- Regulatory disagreements
- Medical device purchasing
- Lack of subject injury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

Project management constraints

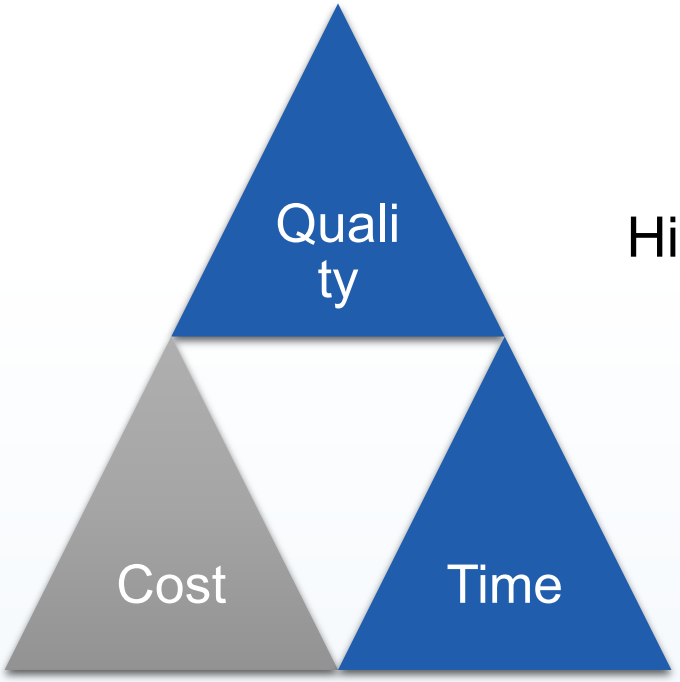


Project management constraints

Low cost
High quality
Slow

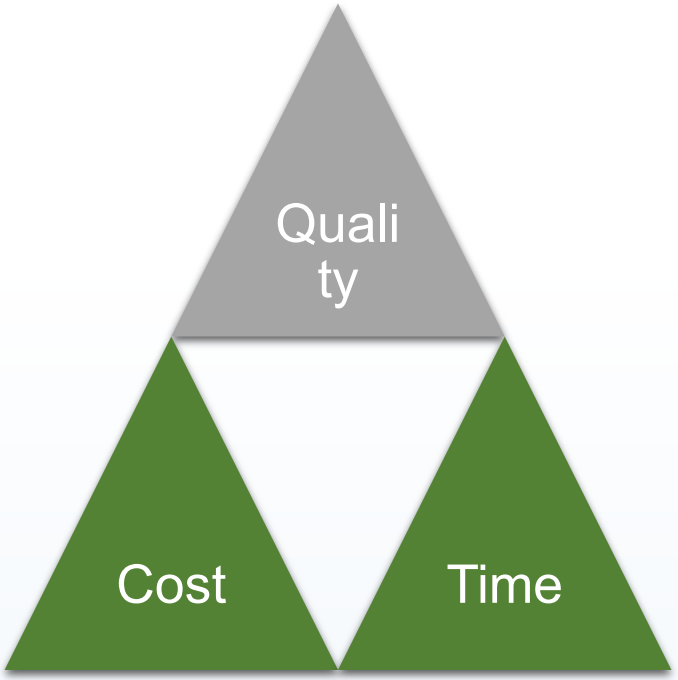


Project management constraints



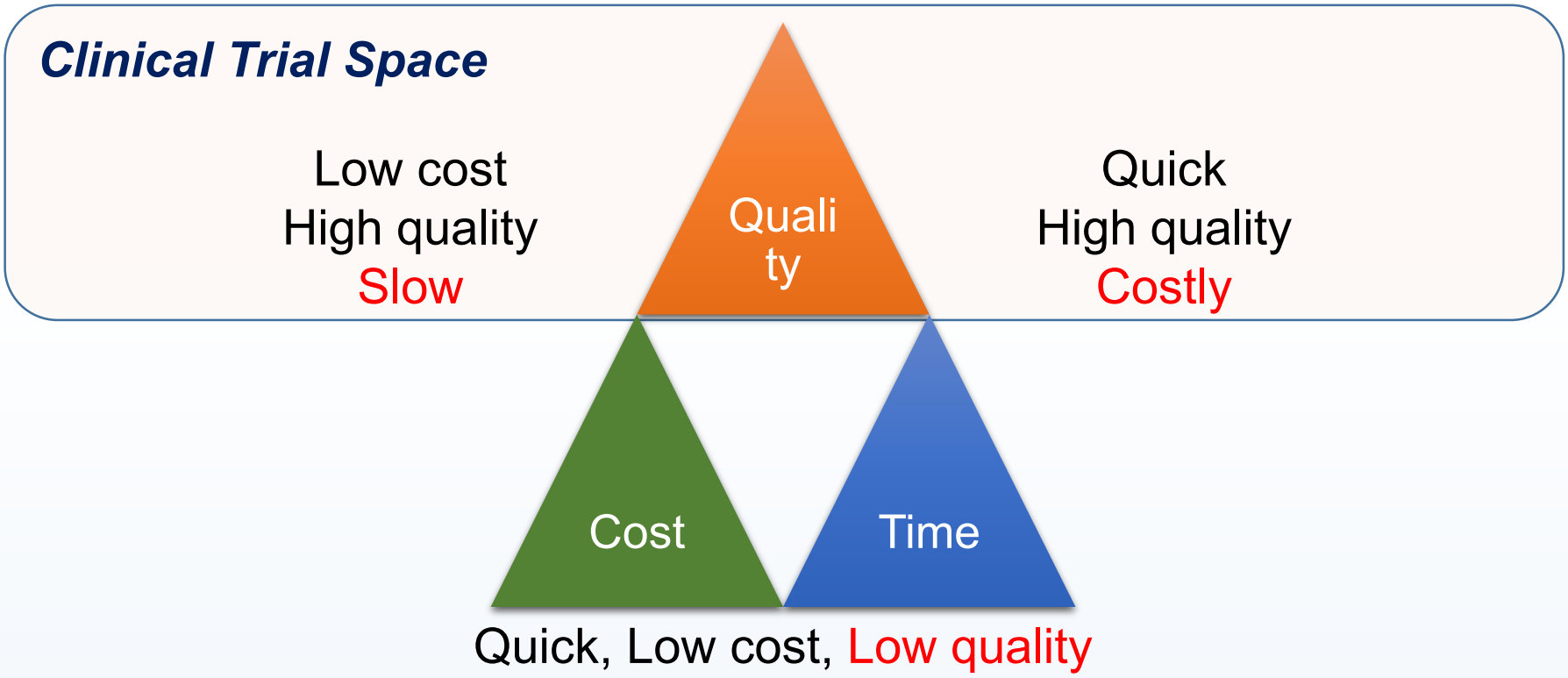
Quick
High quality
Costly

Project management constraints



Quick, Low cost, Low quality

Project management constraints



Quality is federally mandated and highly regulated

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NIH clinical trials

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

FDA investigations

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

Infrastructure maturity in clinical research

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

Funding types and research pathways

Funding types and research pathways

Responsibilities of sponsors and investi

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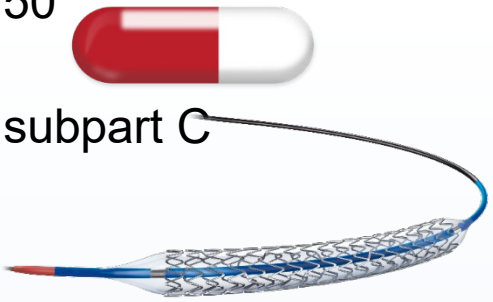
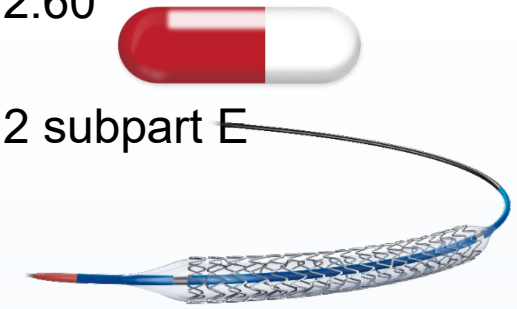
Sponsor

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



Investigator

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



FDA-regulated clinical trial start-up

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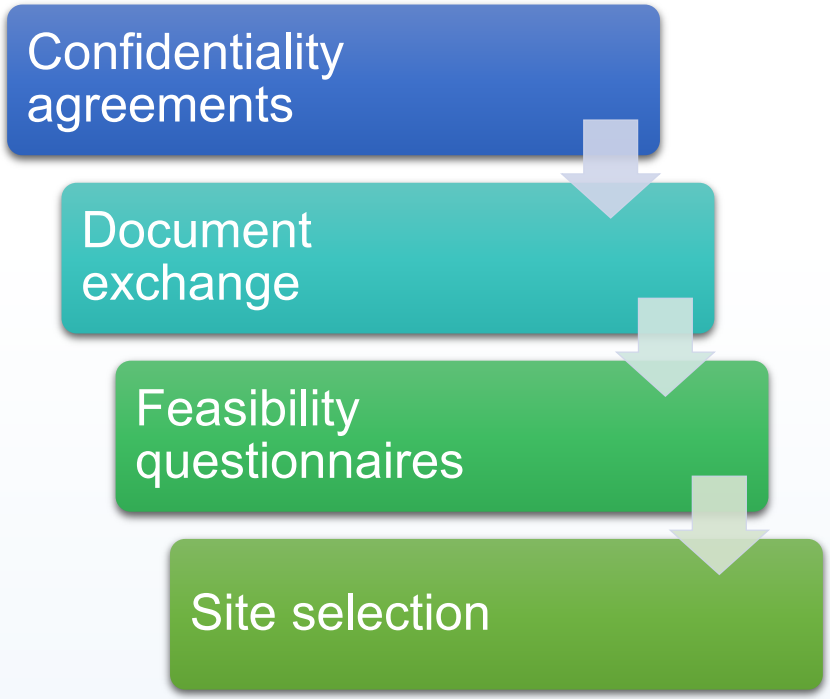
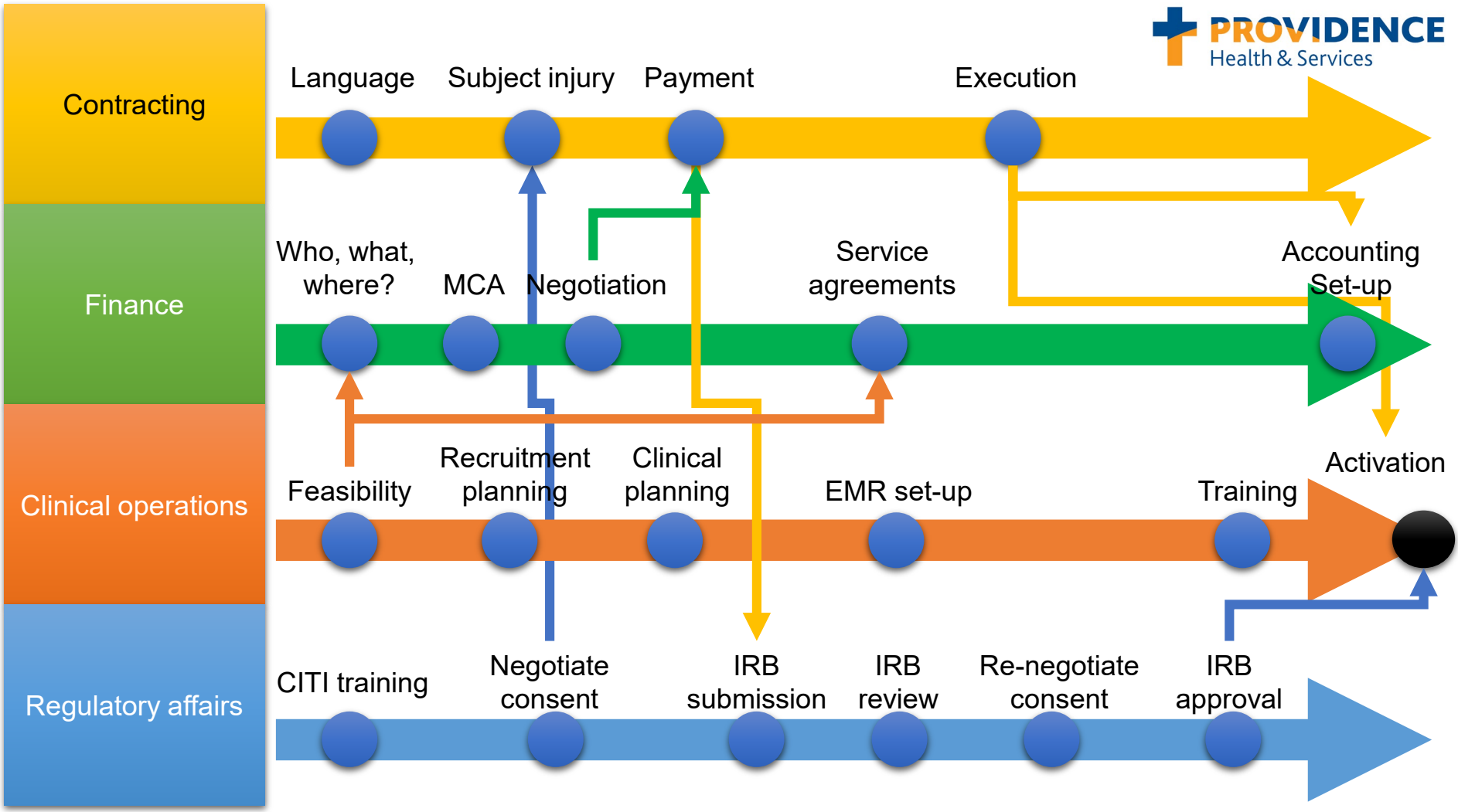
- Study start-up is a mutual evaluation between the sponsor and the site
- Feasibility is crucial




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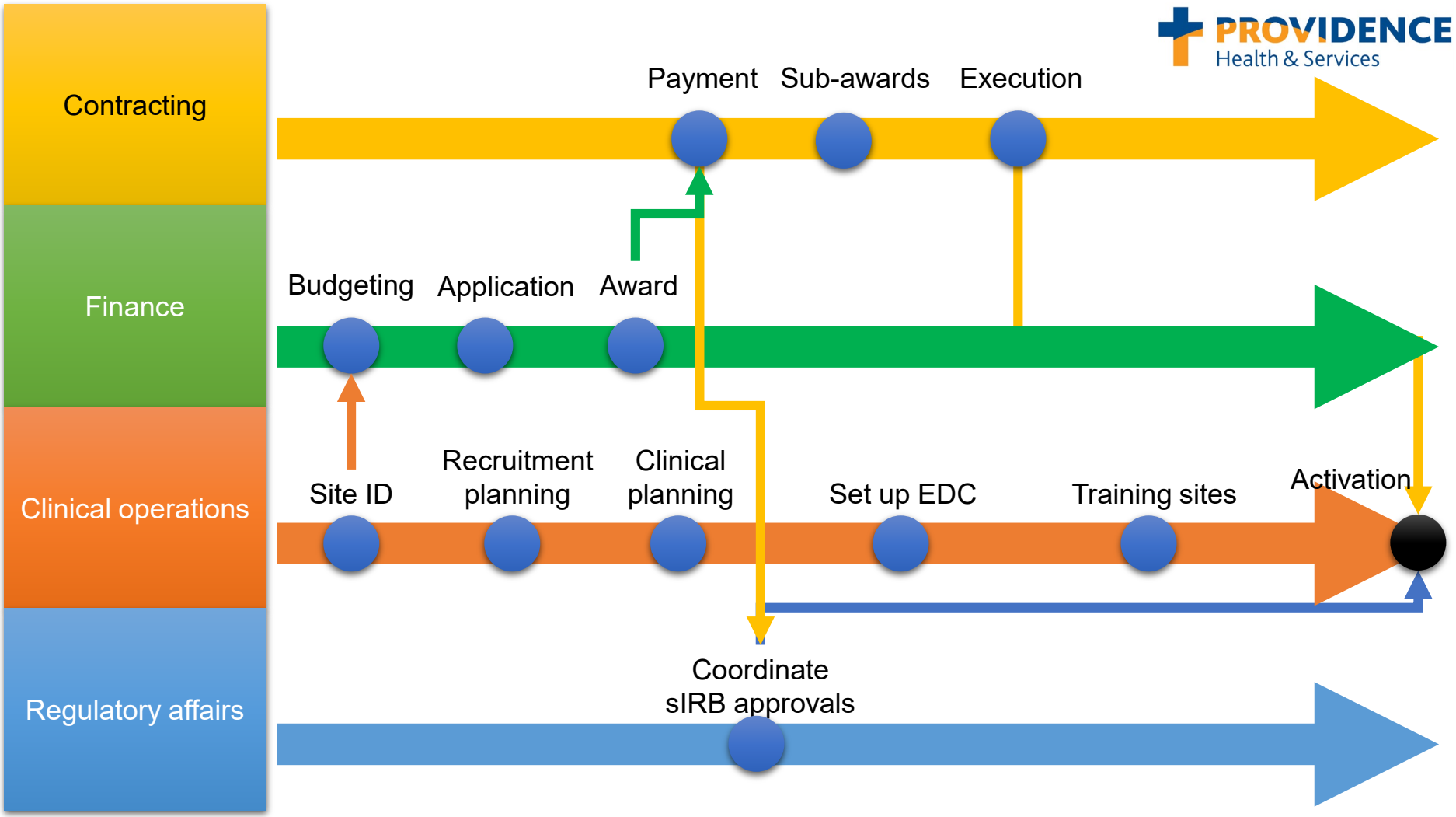
Health & Services
Language
Subject injury
Payment
Execution
Who, what, where?
MCA
Negotiation
Service agreements
Accounting Set-up
Feasibility
Recruitment planning
Clinical planning
EMR set-up
Training
Activation
CITI training
Negotiate consent
IRB submission
IRB review
Re-negotiate consent
IRB approval

Funding types and research pathways


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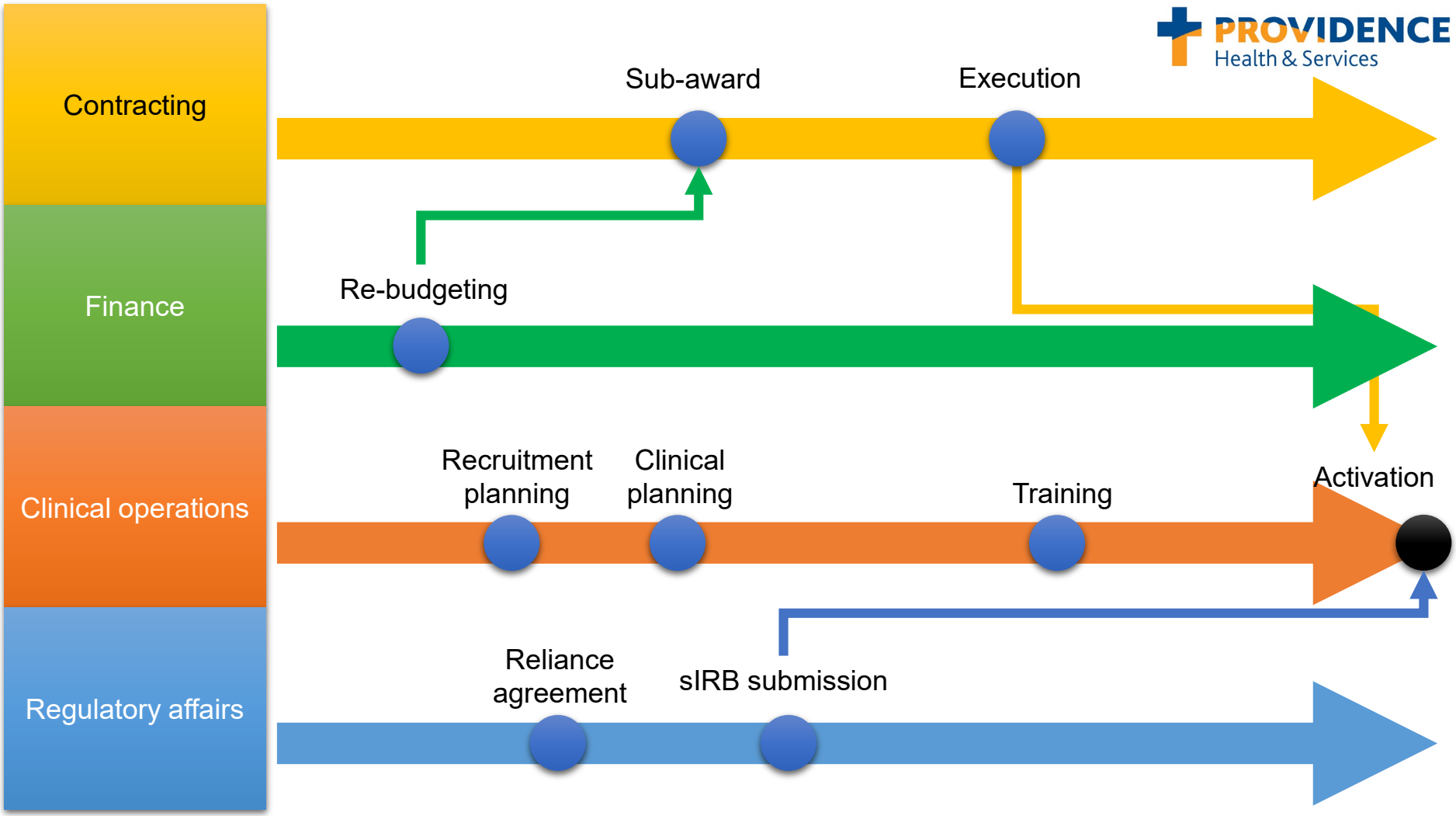
Health & Services
Payment
Sub-awards
Execution
Budgeting
Application
Award
Site ID
Recruitment planning
Clinical planning
Set up EDC
Training sites
Activation
Coordinate sIRB approvals

How will I…

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

Funding types and research pathways


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

Common pitfalls for PIs

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

Changing perspectives on start-up “delays”

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Cost of planning

Cost of mistakes

Continuous process improvement

Scott Adams, Dilbert.com

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The TERRIBLE Trial*

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WHAT WAS SUPPOSED TO HAPPEN

Open in 90 days
Enroll 3 participants in 180 days

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

* Fictional trial.

The TERRIBLE Trial*

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WHAT ACTUALLY HAPPENED

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

* Fictional trial.

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Questions for after-action review

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

Questions for consideration

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

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After Action Review Worksheet

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

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

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

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