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Behind the Scenes of Clinical Trials in Addiction: Confessions of a Clinical Trialist

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Disclosures

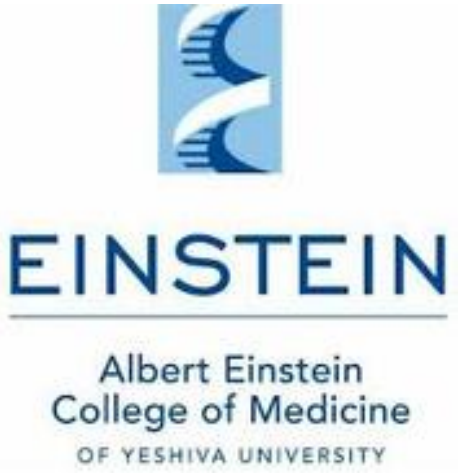
Ethan Cowan has disclosed the following financial relationships: Indivior, LLC: Advisory Board, Gilead: Grant support, Tonix Pharmaceuticals: Data and Safety Monitoring Board

Outline

- Introductions
- Clinical problems to clinical trials
- Clinical trials education
- The nuts and bolts

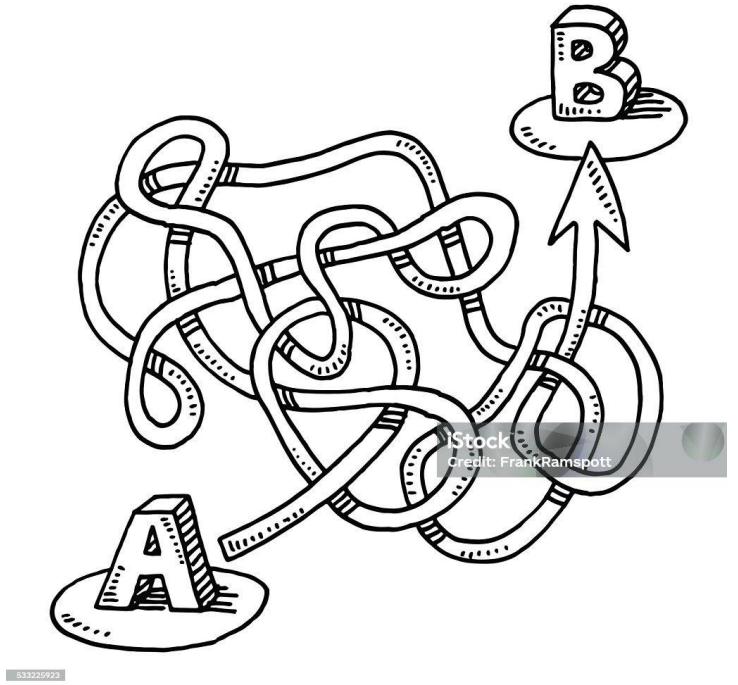
How I ended up here without planning to

Undergraduate → Medical School → Residency → Fellowship /Faculty → Faculty



How I ended up here without planning to

- F32 – Video consent for IV contrast administration
- K23 – Ethics of opt-out HIV testing
- Mapplethorpe Foundation - Pre-Exposure Prophylaxis Provision in the Emergency Department (PrEPPED)-Trial
- R34 - PrEP Services in the Emergency Department for Hard-to-Reach Populations
- CTN Trials 0069 & 0099
- UG3 - Safety and Efficacy of High Dose Buprenorphine Induction in Fentanyl Positive Emergency Department Patients



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From Clinical Problems to Clinical Trials

The dilemma

https://ar.inspiredpencil.com/pictures-2023/unhappy-patient

The guidelines made sense. The ED did not

- The guidelines
  - ASAM, SAMSHA, ACEP
- The real world
  - Time pressure
  - Uncertain thresholds
  - Clinician uncertainty/fear
  - System constraints

Uncertainty was driving practice more than evidence

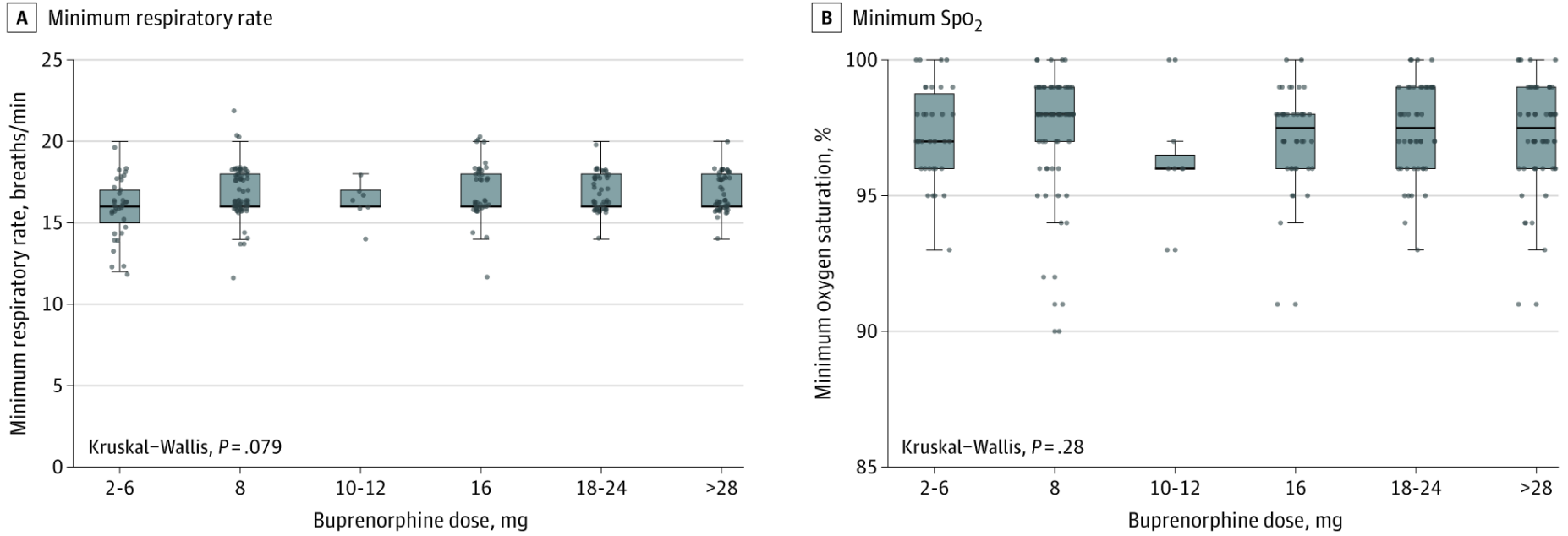
- Failed prior BUP initiation
- Fear of precipitated withdrawal
- Practice variability (Guo, et als.)

ED BUP Administration	% of protocols *(n=31)*
Variable initial BUP dose based on COWS	45%
BUP dose based on COWS 8-12, 13+	39%
Time frame between BUP dose 1 and 2 for continuing withdrawal symptoms	94%
30-60 minutes	87%
<30 or >60 minutes	6%
Maximum total BUP dose in ED	94%
8mg	16%
12mg	16%
16mg	35%
24mg	6%
32mg	19%
Precipitated withdrawal guidelines	35%
Ancillary medications for symptoms of:	29%
Muscle aches and pains	26%
Nausea	29%
Abdominal cramps and diarrhea	26%
Other*	23%

Guo CZ, D'Onofrio G, Fiellin DA, Edelman EJ, Hawk K, Herring A, McCormack R, Perrone J, Cowan E. Emergency department-initiated buprenorphine protocols: a national evaluation. JACEP Open. 2021 Dec 1;2(6):e12606.

From Practice to Clinical Trial Question

- How this problem became my UG3



Herring AA, Vosooghi AA, Luftig J, Anderson ES, Zhao X, Dziura J, Hawk KF, McCormack RP, Saxon A, D'Onofrio G. High-dose buprenorphine induction in the emergency department for treatment of opioid use disorder. JAMA network open. 2021 Jul 1;4(7):e2117128-.

Is High Dose Buprenorphine Initiation Safe and Effective?

What Are Some Potential Clinical Trial Designs to Answer this Question?

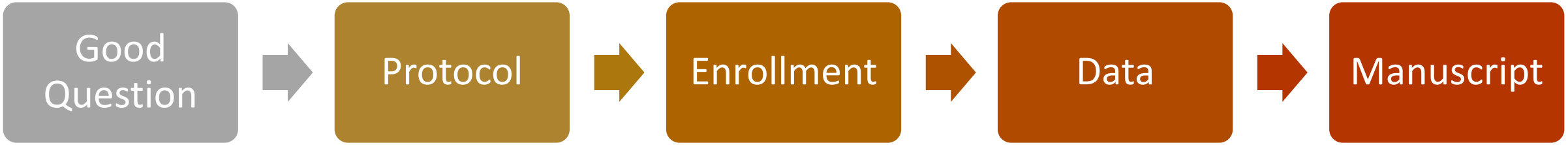
Why EDs (and other non-traditional clinical sites) Force Trials to be Pragmatic

- Uncontrolled environment
- Intervention delivered by clinicians
- Inclusion/Exclusion criteria impact care
- Feasibility is an equally valuable outcome
- Complexity has costs

How are clinical trials in addiction different?

- Complex, unstable patient populations
- High rates of loss to follow up
- Nontraditional and high acuity settings
- Ethical and consent considerations
- Stigma and institutional barriers
- Feasibility as a core design concern

My Mental Model of Clinical Trials



On Paper, This Design Looked Clean

Trial 1

Figure 2: UG3 Specific Aim 1 Dose Cohorts

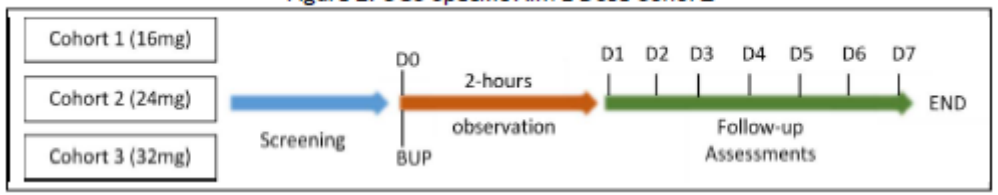
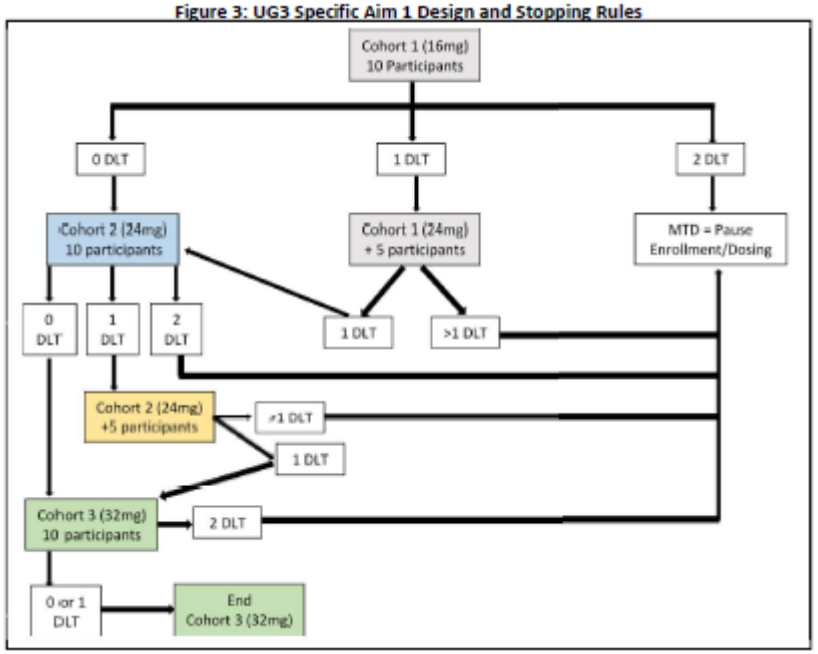
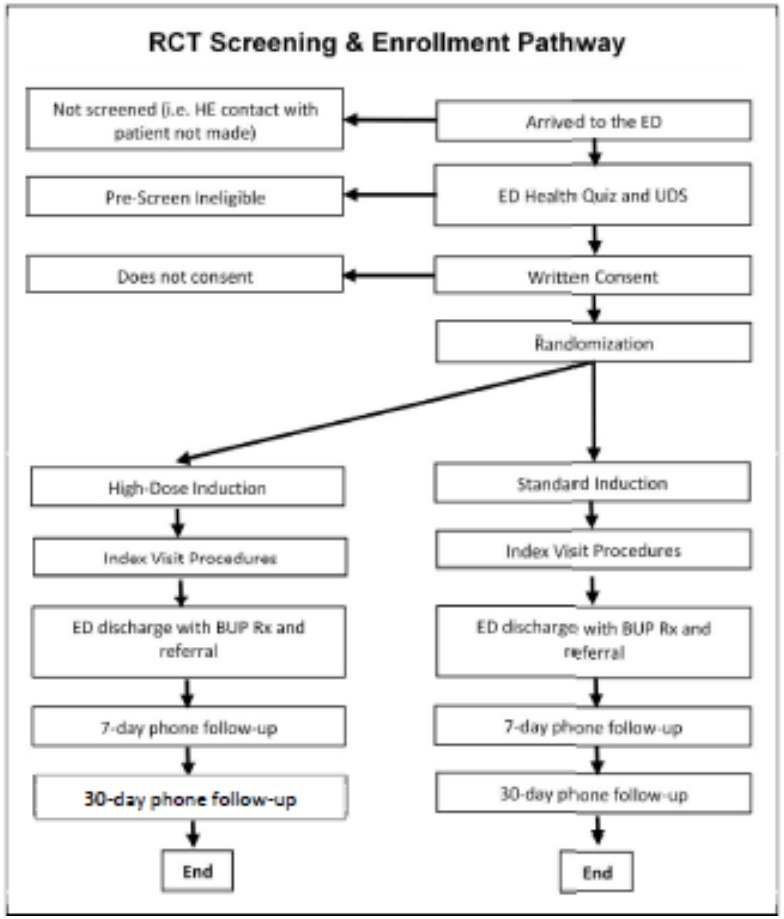


Figure 3: UG3 Specific Aim 1 Design and Stopping Rules



Trial 2

Figure 4. UG3 Randomized Controlled Trial Design



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Clinical Trial Learning Experiences

What CTN Trials Taught Me

- CTN0069 (Site PI) and CTN0099 (Core-Co-I)
  - Working with CROs
  - The complexity of multi-site clinical trials
  - The infrastructure required to answer “simple” questions
  - Rigor
  - The need for help (lots of it)
  - Monitoring, Monitoring, Monitoring

National Drug Abuse Treatment
Clinical Trials Network

Industry Trials: A Different Education

- Budgeting
- Contracting
- Site readiness
- Speed

Participating vs Owning a Trial

Participating

- Contributes to protocol design
- Enrolls and treats participants
- Implements study procedures
- Interprets results
- Buffered from regulatory responsibility

Owning

- Defines the question and its constraints
- Holds regulatory and ethical responsibility
- Owns safety reporting and deviations
- Designs for feasibility and failure
- Accountable for what happens next

What Running a Trial Actually Means

- Population & Environment
- What type of clinical trial am I doing
- Grant mechanism matters
- Regulatory
- Site selection
- Data harmonization

Am I doing a clinical trial?

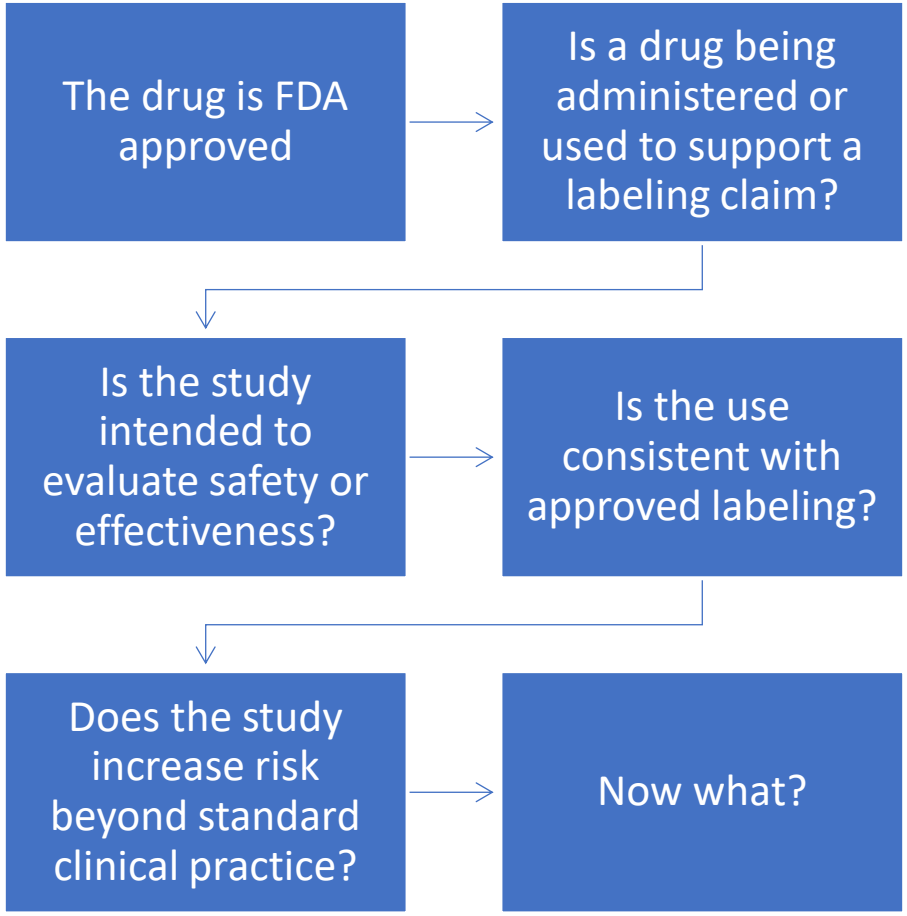
- NIH
  - Human subjects research
  - Prospectively assigned
  - Testing an intervention
  - Evaluate the effect on health or behavior
- FDA
  - Any experiment involving a drug or device used in humans
  - Evaluate safety and/or effectiveness

Grant Mechanism Matters

NIH Funding Mechanisms

- F = Fellowships (pre- & post-doc)
- K = Career Development Awards
- T = Training Grants
- R = Research Projects
- P = Program Project/Center Grants
- U = Cooperative Agreements Grants

Do I Need and IND?



FORMAT OF IND

A. Cover sheet (Form FDA-1571)
   - Name, address, telephone of sponsor
   - Identification of phases
   - Commitment not to begin CT until IND approval
   - Commitment by IRB- Form 56
   - Commitment for conducting CT- accordance with regulations
   - Name, title – Monitor
   - Name, title – person(s) for reviewing
   - Name, Address of CRO, if any
   - Signature of sponsor

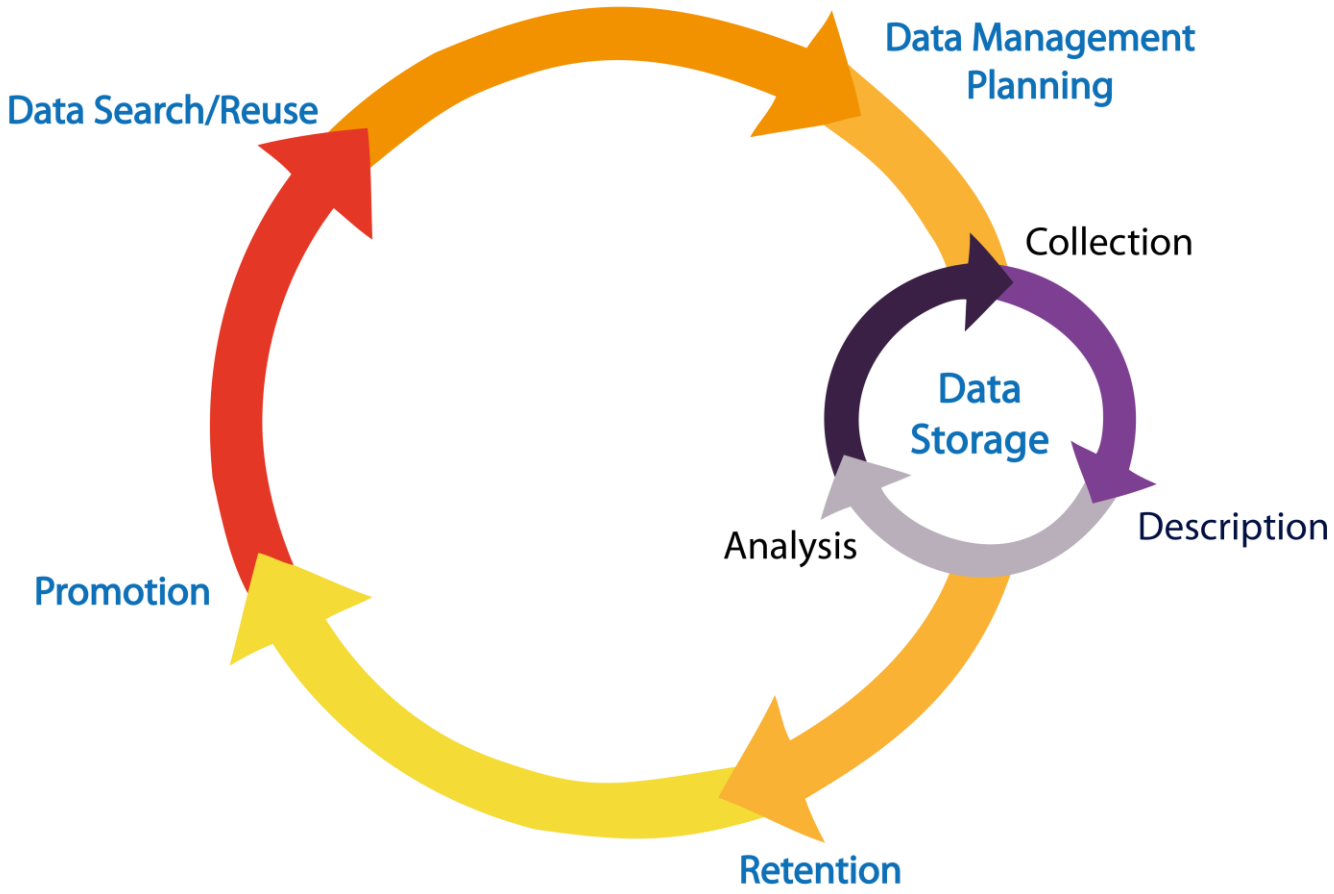
B. Table of contents
C. Introductory statement & general investigational plan
D. Investigators brochure
E. Study protocol
F. Investigator facilities & IRB data
G. Chemistry manufacturing & control data
H. Pharmacology & toxicology data
I. Previous human experience

Regulatory Gravity

- FDA oversight, IND responsibility & California
- Protocols, MOPs, SOP
- DSMP, DSMB and external safety review
- Medical Monitoring
- Site Monitoring
- AE/SAE/PD reporting
- Training/Retraining/Documentation

Site Selection and Coordination

Data Management



Publications

- A-priori planning
  - Manuscripts
  - Authors
  - Hypothesis
  - Data
  - Journals
- Allow for flexibility
- Continuously update

Key Takeaways

- Good questions are not enough
- Trials succeed or fail based on operations and people
- Feasibility is critical
- Regulation complexity is real
- You will need help
- Context matters

Questions