Q: Who to include in pragmatic trials?
A: It depends.

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Outline

- What does it depend on? (Greg)
- Example: SPOT trial of suicide prevention (Greg)
- Example: TIME trial of longer dialysis duration (Laura)
- Summary (Greg)

Explanatory (Traditional) trials: Inclusion criteria focused on patients

- Aim to maximize signal detection (reduce heterogeneity)

- Often require specialized assessment

Pragmatic trials: Inclusion criteria at multiple levels

- Healthcare facilities or systems
- Healthcare providers
- Patients/consumers

What does scripture say? (PRECIS)

- All participants who have the condition of interest are enrolled, regardless of their anticipated risk, responsiveness, co-morbidities, or past compliance.
- The intervention is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to dose setting and side effects.

Thorpe et al, J Clin Epidemiol, 2009.

What does scripture say? (PRECIS-2)

- To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
- How different are the resources, provider expertise, and the organisation of care delivery in the intervention arm of the trial from those available in usual care?

Loudon et al, BMJ, 2015

It depends on what?

- Practical considerations:
  - Technical capability
  - Operational efficiency
- Ethical or regulatory requirements
- Scientific considerations
  - Relevance
  - Generalizability

Two views of generalizability

- Resemblance: How do patients/providers/health systems in this trial resemble the average or most common?
- Prediction: How well will findings of this trial predict what will occur if/when this treatment or program is implemented?

Which view of generalizability?

- We really want prediction.
- We often use resemblance as a proxy.
- But we shouldn't confuse what we really want from what we currently have.

Pragmatic trials are really prediction

- Our questions are about the future (What will happen if we do A or B?)
- So our trials attempt to create those alternative futures – and then compare them.
- Another view of explanatory vs. pragmatic trials:
  - Explanatory: What is true?
  - Pragmatic: What will happen?

It depends on what…we think will happen

- Practical considerations:
  - Technical capability
  - Operational efficiency
- Ethical or regulatory requirements
- Scientific considerations
  - Relevance
  - Generalizability

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Suicide Prevention Outreach Trial (SPOT)

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Supported by NIMH cooperative agreement UH3 MH007755

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SPOT Trial Summary

- Pragmatic randomized trial of two outreach programs (vs. usual care) to reduce risk of suicide attempt in high-risk outpatients
- Participants automatically identified by responses to PHQ9 depression questionnaires
- Expect significant variability in intervention uptake and adherence
- Analyze by original assignment, regardless of intervention uptake and adherence

SPOT Trial Interventions

- Systematic outreach and care management to prompt and maintain engagement in outpatient mental health care
- Online training in Dialectical Behavior Therapy skills, supported by brief coaching messages
- Both delivered primarily via online messaging
- Both intended as supplements to usual care

SPOT Trial Question

- What will happen to the rate of suicide attempt among high risk out patients if we:
  - Implement an outreach and care management program?
  - Routinely offer online DBT skills training?
  - Keep doing what we do now?

SPOT Trial: Which health systems?

- Necessary capabilities
  - Routine use of PHQ9 questionnaires
  - Rapid access to data to assess eligibility
  - High uptake of patient portal online communication
  - Capacity for EHR-based population management
  - Accurate ascertainment of suicide attempts
- Necessary organizational support
  - Prioritizing implementation of EHR tools
  - Improving access for high-risk patients
- Economies of scale/scope
  - Fixed costs of training staff, implementing EHR tools
  - Improved quality with dedicated staff
- Willingness to allow waiver of consent

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SPOT Trial: These health systems

- Four large integrated health systems (HealthPartners, KP Colorado, KP Northwest, KP Washington)
  - KPNW added later when data showed more routine use of PHQ9 questionnaires
- Generalizability to the future depends on:
  - Increasing use of PHQ9 questionnaires
  - Increasing use of online patient portal messaging
  - Improved EHR capabilities for population management
  - Adequate access to outpatient mental health services
  - Accurate ascertainment of suicide attempts (already true)

(If we're being honest, these systems are "the one percent")

SPOT Trial: Which providers?

- No selection of providers within health systems
- BUT, selecting health systems automatically selects some provider characteristics:
  - Familiar with team-based care and centralized outreach programs
  - Familiar with suicide risk assessment tools and standard care pathways
  - Familiar with Dialectical Behavior Therapy skills

SPOT Trial: These providers

- All mental health specialty and primary care providers in practicing in health system facilities
- Generalizability to the future depends on:
  - Increasing familiarity with Zero Suicide principles (risk assessment, care pathways)
  - Increasing acceptability of team-based or integrated mental health care

SPOT Trial: Which patients?

- No selection based on motivation or likelihood of accepting outreach interventions
- BUT, exclude those clearly unable to use or benefit:
  - Not registered for online portal messaging
  - Diagnosis indicating cognitive impairment or significant developmental delay
  - Limited English proficiency (“needs interpreter”)
- All eligible participants included in analyses (but IRBs did require abbreviated consent prior to interventions)

SPOT Trial: These patients

- Enroll and randomize all comers, except:
  - Exclude those unable to use interventions
  - Somewhat artificial “consent” process to receive intervention services
- Generalizability to the future depends on:
  - Increasing use of online portal messaging
  - Assuming that intervention “consent” procedures do not affect uptake or benefit

TiME Trial Question:
Does dialysis that is longer than many US patients currently receive improve outcomes?

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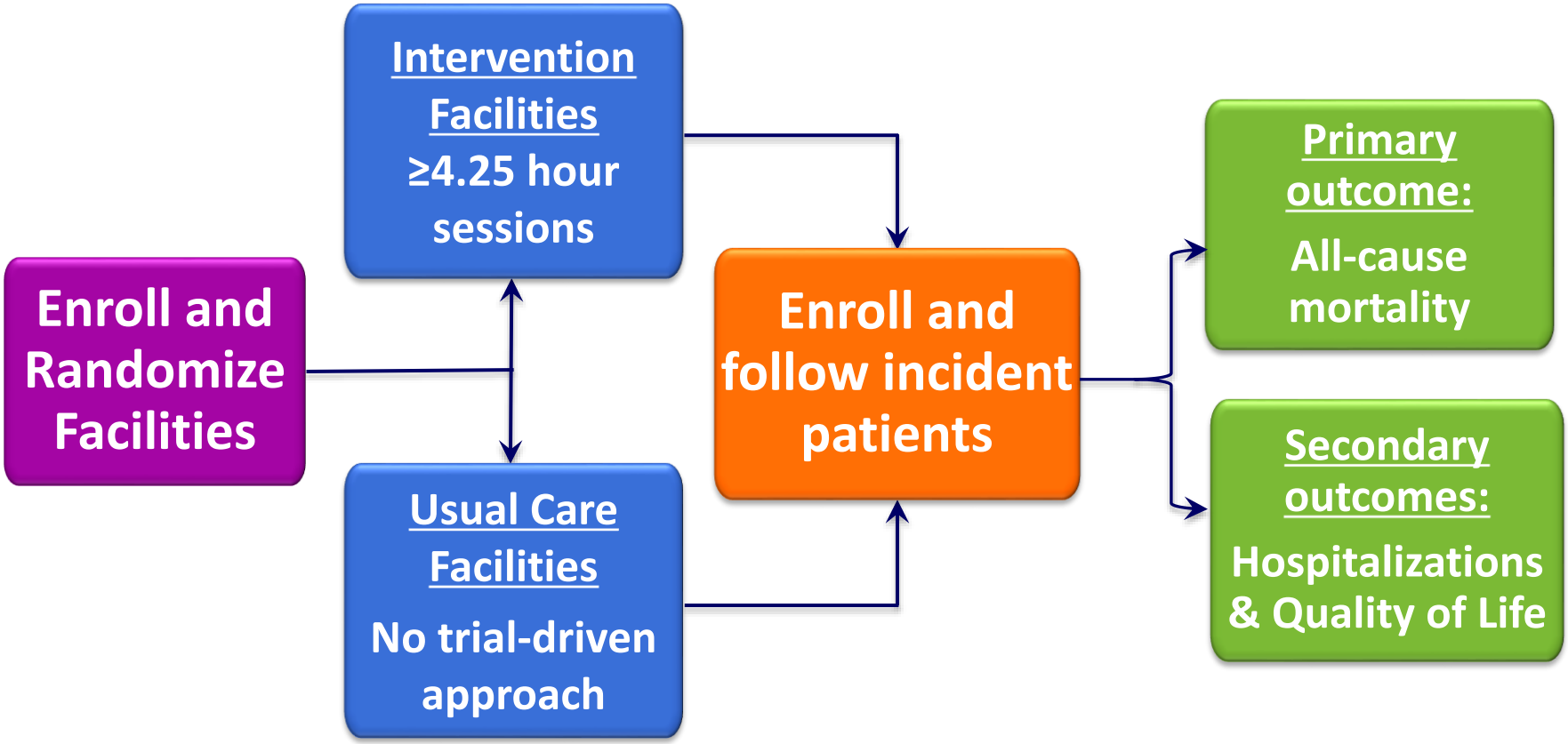
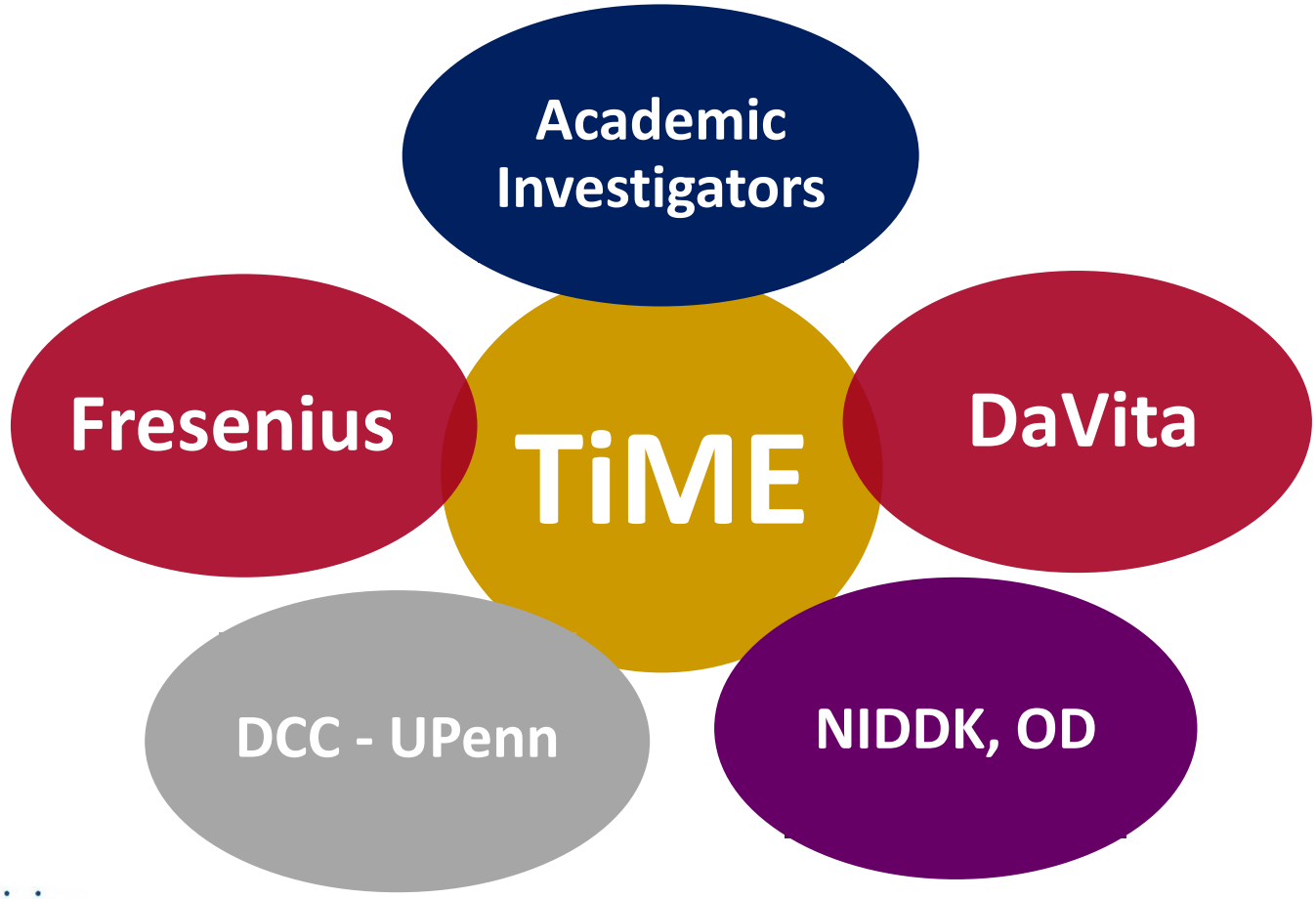


Who to Include?

1. Healthcare systems
2. Healthcare providers
3. Patients/consumers

1. Which Health Systems?



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- Need lots of dialysis units
- Need infrastructure for centralized implementation and data acquisition

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For generalizability

1. Which Health Systems?

- Need lots of dialysis units ✓
  - DaVita: 2,445 units, 194,600 patients
  - Fresenius: 2,200, 190,000 patients
- Need infrastructure for centralized implementation and data acquisition ✓
- Want more than one health system ✓
- Want broad geographic distribution ✓

1. Which Health Systems?

- Need lots of dialysis units ✓
  - DaVita: 2,445 units, 194,600 patients
  - Fresenius: 2,200, 190,000 patients

  ~70% of US patients
- Need infrastructure for centralized implementation and data acquisition ✓
- Want more than one health system ✓
- Want broad geographic distribution ✓

These systems are the ninety-nine percent

2. Which Health Providers (which dialysis units)?

Facility Eligibility Criteria

- Willingness of nephrologists and facility leadership to adopt the 4.25 hour session duration for incident patients
- Capacity to accommodate 4.25 hour treatments

2. Which Health Providers (which dialysis units)?

- Need willingness to accommodate and prescribe longer treatments
  - Administrators
  - Nephrologists
- Need capacity for longer treatments

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For implementation of the intervention

Eligibility criteria increase the likelihood of answering trial question but reduce generalizability (no longer quite the 99%)

3. Which Patients?

Patient Eligibility Criteria

- Age >18 years
- Initiated dialysis within past 120 days
- Provided consent for dialysis care (clinical care)

Analysis

All enrolled patients regardless of adherence to the intervention

3. Which Patients?

- Why incident patients only?
  - Allows for gradual increase in session duration at facility level
  - Increases acceptability to patients – not changing an established session duration
- But…this decreases generalizability

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- But…this decreases generalizability

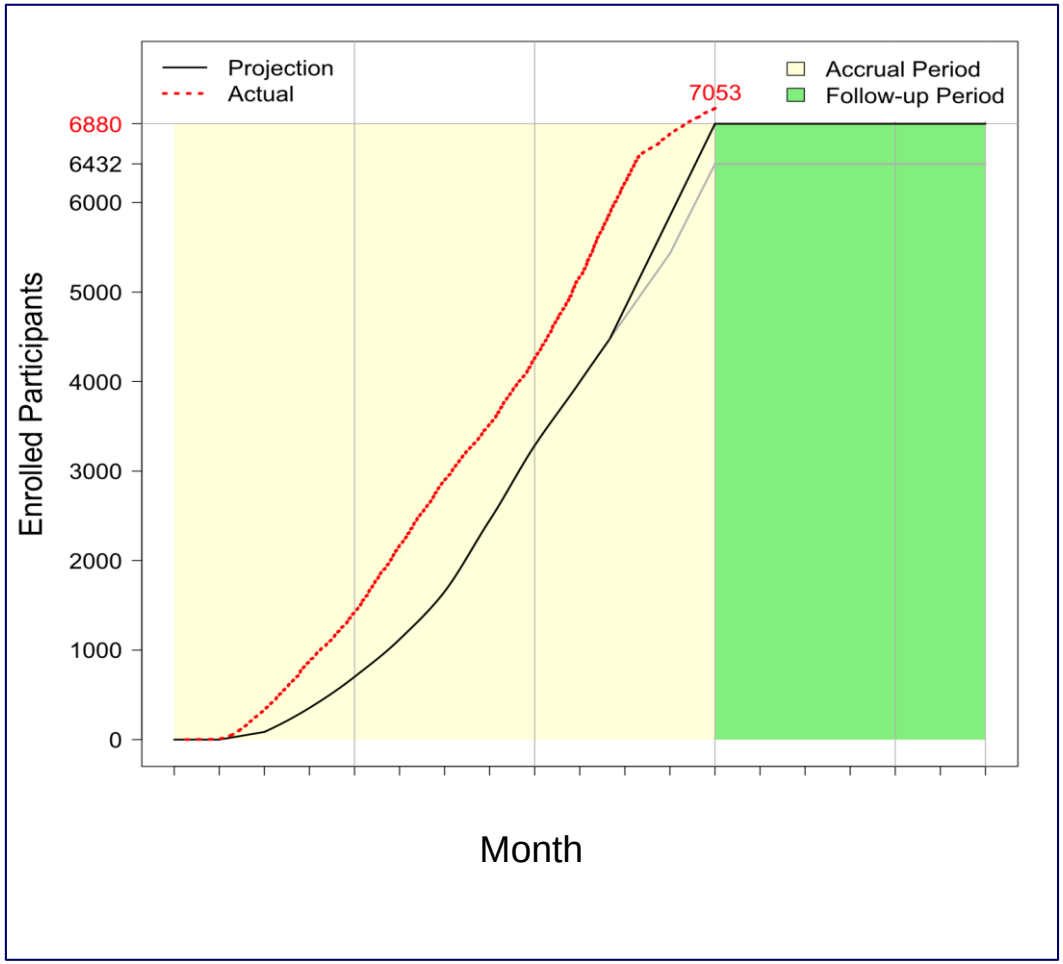
Sometimes it is pragmatic to be less pragmatic

Opt-Out Consent Approach

- Opt out is extremely helpful if we want to:

  Enroll “all participants who have the condition of interest…regardless of their anticipated risk, responsiveness, co-morbidities, or past compliance..” (PRECIS)

Opt-Out Consent Approach



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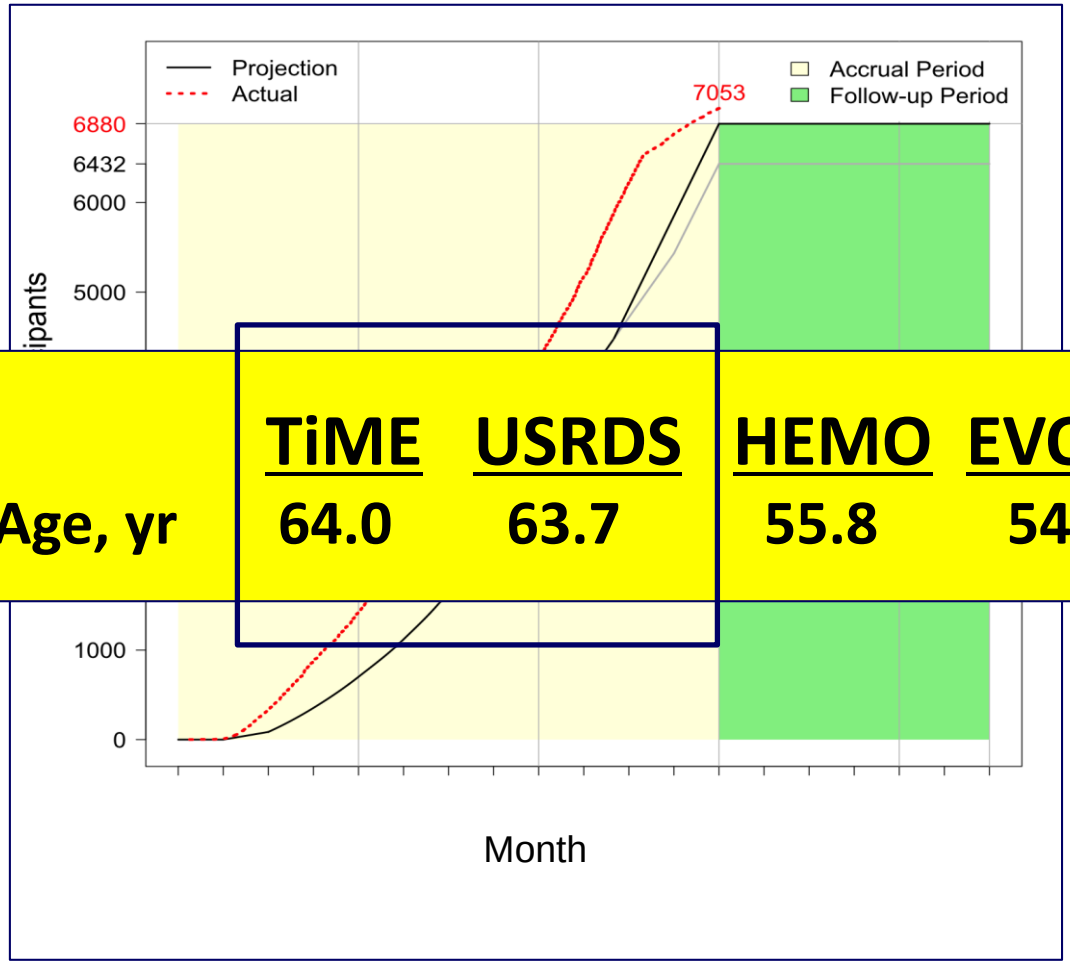

	TiME	USRDS	HEMO	EVOLVE
Mean Age, yr	64.0	63.7	55.8	54.5

Opt-Out Consent Approach

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  Enroll “all participants who have the condition of interest…regardless of their anticipated risk, responsiveness, co-morbidities, or past compliance..” (PRECIS)

- But it can bring protocol infidelity, competing risks, insufficient follow-up…..

Be careful what you wish for?

Summary

- Consider inclusion criteria at multiple levels (patients, providers, and health systems).
- Generalizability is more about the future than the present.
- Accept that you will be wrong; just try to be less wrong.

Friendly amendments to PRECIS-2

- To what extent are the participants in the trial similar to those who ~~would~~ will receive this intervention if it ~~was~~ becomes part of usual care?
- How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those that will be available ~~in usual care~~ when and where the intervention will be implemented?

“It’s tough to make predictions, especially about the future.”

Yogi Berra