Opportunities for Embedded Pragmatic Trials in Nephrology

Laura M. Dember, M.D.
Perelman School of Medicine
University of Pennsylvania

American Society of Nephrology Kidney Week
November 8, 2019
• What are pragmatic trials and why is there interest?
• Challenges for conducting pragmatic trials embedded in clinical care delivery
• Examples of pragmatic trials in nephrology
Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD
Deborah A. Zarin, MD
Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BSPH
Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

40,970 intervention trials
66% single-center
62% <100 participants
4% >1000 participants
What about Nephrology?

The Landscape of Clinical Trials in Nephrology: A Systematic Review of ClinicalTrials.gov

Jula K. Inrig, MD,1,2 Robert M. Califf, MD,1 Asba Tasneem, PhD,1 Radha K. Vegunta, MD,3 Christopher Molina, BS,4 John W. Stanifer, MD,1 Karen Chiswell, PhD,1 and Uptal D. Patel, MD1

1054 nephrology intervention trials

66% single-center

65% <100 participants

1.7% >1000 participants
Our Current Approach to Clinical Trials is Remarkably Inefficient

- Highly selected participants
- Many study procedures, complex protocol
- Many outcomes: primary, secondary, efficacy, safety, mechanistic...
- Adjudication of outcomes
- Conducted in a “parallel universe”

Trials are very slow, very expensive, and have limited generalizability
Pragmatic Trials

- Pragmatic trials - use real-world conditions to inform choices between treatment options (assess effectiveness)

- Explanatory trials – use ideal experimental conditions to test a causal hypothesis (assess efficacy)

- Tradeoff between achieving high generalizability (pragmatic) and high internal validity (explanatory)
Characteristics of Pragmatic Trials

- Non-restrictive eligibility criteria – all individuals with the condition of interest
- Intervention implemented in clinical care setting by clinical care providers
- Ascertainment of outcomes relies on data acquired through routine clinical care
- Outcomes – hard clinical outcomes, patient-important outcomes
- Analysis – intention to treat, noise is expected (embraced?)

- Generalizable findings
- Sustainable intervention
- Efficient trial conduct
# PRECIS Criteria

**(Pragmatic-Explanatory Continuum Indicator Summary)**

<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
<th>Explanatory</th>
<th>Pragmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• <strong>Restrictive</strong>: highest risk for</td>
<td>• <strong>All individuals</strong> with condition of</td>
</tr>
<tr>
<td></td>
<td>outcome, most likely to respond,</td>
<td>interest <strong>regardless of risk</strong>,</td>
</tr>
<tr>
<td></td>
<td>most likely to comply</td>
<td>comorbidities, adherence, language</td>
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| Intervention Implementation | • **Strict delivery**                    | • **Flexible delivery**                   |
|                            | • Expert practitioners                   | • **No expertise** needed                 |
|                            | • **Close monitoring** of dose, adverse  | • Full range of clinical settings         |
|                            |   effects with adjustment or treatment,  | • **Comparator is often usual practice**  |
|                            |   respectively                          |                                           |

| Follow-up                | • High intensity                        | • **Low intensity**                       |
|                         | • **More f/u than usual care**          | • **No study visits**                     |
|                         | • Data collection for trial             | • **Administrative databases**            |

*Thorpe KE J Clin Epidemiol 2009*
# PRECIS Criteria
*(Pragmatic-Explanatory Continuum Indicator Summary)*

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<thead>
<tr>
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<th>Explanatory</th>
<th>Pragmatic</th>
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<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td>• Direct and immediate consequence of intervention</td>
<td>• Clinically meaningful</td>
</tr>
<tr>
<td></td>
<td>• May be surrogate</td>
<td>• Objectively measured</td>
</tr>
<tr>
<td></td>
<td>• Specialized <strong>training for ascertainment</strong></td>
<td>• No adjudication</td>
</tr>
<tr>
<td></td>
<td>• May require <strong>adjudication</strong></td>
<td>• Assessed under usual conditions</td>
</tr>
<tr>
<td><strong>Intervention adherence</strong></td>
<td>• Close monitoring</td>
<td>• <strong>Unobtrusive</strong> or no measurement</td>
</tr>
<tr>
<td></td>
<td>• Adherence may be requirement for participation</td>
<td>• No strategies to improve adherence outside of those used in clinical care</td>
</tr>
<tr>
<td></td>
<td>• Strategies employed to increase adherence</td>
<td></td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>• Attempt to answer <strong>narrowest, mechanistic question</strong></td>
<td>• Pure intention to treat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Noise is accepted</strong></td>
</tr>
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</table>
SPRINT: A Trial with Both Pragmatic and Explanatory Features

- Systolic bp target of <120 vs <140 mm Hg
- >9000 participants – included older individuals, included CKD
- Lower bp target group did better
  - Composite of CV events and CV mortality
  - All-cause mortality
- VERY important trial that is changing clinical practice

But... what should the target be outside of the trial setting?

<120? <130?

N Engl J Med 2015;373:2103-16
Important Points

• Pragmatic does not mean EASY
• Most trials are neither fully pragmatic nor fully explanatory
• A trial should not be pragmatic just to be pragmatic
Examples of Pragmatic Trials in Nephrology

1. AKI
2. Hypertension
3. Dialysis
4. CKD — Miguel Vazquez
Challenges for Embedded Pragmatic Trials

- Stakeholder engagement and health system buy-in
- Intervention implementation
- Informed consent: when can it be waived and how can it be obtained
- Data acquisition
- Analytical issues
- Post-trial implementation
Acute Kidney Injury: SMART

The NEW ENGLAND JOURNAL of MEDICINE

Balanced Crystalloids versus Saline in Critically Ill Adults

SMART

• Trial question: Is there less AKI with balanced crystalloid solutions (lactated Ringer’s or Plasmalyte) compared with 0.9% saline
• Cluster-randomized, multiple cross-over trial of all patients in 5 ICUs at Vanderbilt
• Primary outcome: major renal event within 30 days (creatinine doubling, renal replacement therapy or death)
• Enrolled >15,000 patients under waiver of consent
• Balanced solution was beneficial: 14.3% vs 15.4% had major renal event; OR 0.91 (95% CI 0.84 – 0.99; p=0.04)
Questions about SMART

- Are the findings generalizable to other settings?
- Could this be done as a multicenter trial?
SMART

• Implemented by the health system and clinicians
• Short-term trial
• Trial cost: <$300,000 (data extraction, statistical analyses)

Health System Buy-In:
SMART could not have been successful without true commitment/buy-in by the health system
Hypertension: VA Point of Care Diuretic Trial

• Trial question: Is there a difference in outcomes with hydrochlorothiazide or chlorthalidone?

• Patients > 65 yrs receiving HCTZ

• Primary outcome: major adverse cardiac events (MACE)

• Target enrollment: 13,000

• Centralized activities
  – identification of patients at time of HCTZ prescription
  – obtaining permission from MDs and consent from patients
  – placement of notes and orders into local record
  – ascertainment of outcomes

A national integrated health system (EMR, pharmacy, outcomes) is a huge plus

Informed Consent: is it necessary?

Maintenance Hemodialysis as a Setting for Pragmatic Trials

• Highly accessible study population with frequent, regular clinical encounters
• Granular and uniform data collection as part of routine clinical care
• Infrastructure of dialysis provider organizations that allows for centralized implementation approach
• Many unanswered questions about fundamental aspects of care
• High event rates
• Trial question: Does use of dialysis sessions that are modestly longer than many patients in the US currently receive improve outcomes?
• Cluster-randomized trial of hemodialysis sessions $\geq 4.25$ hours vs Usual Care
• Partnership with DaVita and Fresenius Medical Care
• No on-site researchers, no primary data collection
• >7000 incident patients enrolled using opt-out consent approach
• Primary outcome: mortality

**HEMO**

- Age: 55.8

**EVOLVE**

- Age: 54.5

**TiME Trial**

<table>
<thead>
<tr>
<th></th>
<th>TiME</th>
<th>USRDS</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>64.1</td>
<td>63.7</td>
</tr>
<tr>
<td>% Male</td>
<td>57.8</td>
<td>57.8</td>
</tr>
<tr>
<td>% Black</td>
<td>24.7</td>
<td>26.2</td>
</tr>
<tr>
<td>% Diabetes</td>
<td>44.0</td>
<td>43.9</td>
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TiME Trial

• Trial question: Do dialysis sessions that are modestly longer than many patients in the US currently receive improve outcomes?

• Stakeholder engagement:
  Engagement of patients and treating clinicians critical for implementing an intervention that is “palpable”

• No on-site researchers, no primary data collection

• >7000 incident patients enrolled using opt-out consent approach

• Primary outcome: mortality

• Uptake of the intervention was not adequate to answer primary question
Other Large Pragmatic Trials in Hemodialysis

- MyTemp – dialysate cooling
- HELPS-HD – oral protein supplements
- RESOLVE – dialysate sodium concentration
- HiLo – less restrictive vs usual phosphate target
HiLo: A Pragmatic Trial of Phosphate Targets

• Trial Question: Is there a difference in outcomes with a liberal (<6.5 mg/dl) versus usual (<5.5 mg/dl) serum phosphate target
• eConsent to move beyond minimal risk research
• Engagement: dietitian champions
• Informed consent (electronic)
• Dietitians will implement intervention and be champions
Pragmatic clinical trials have many appealing features
   - Results are more generalizable to non-research setting
   - Intervention is more readily implementable after trial ends
   - More affordable, so more questions can be answered

But they also have limitations
   - Less control over the experiment
   - Variable quality and completeness of clinical data
   - Not all interventions can be studied (regulatory barriers, implementation barriers)