Opportunities for Embedded Pragmatic Trials in Nephrology

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Outline

- 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

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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.

JAMA 2012;307: 1838-1847

40,970 intervention trials

66% single-center

62% <100 participants

4% >1000 participants

What about Nephrology?

Am J Kidney Dis 2014 65:771-780

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

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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 stud
- Many outc ety, mechanisti
- Adjudicatio
- Conducted in a "parallel universe"

Parallel Universe

Investigators

Research coordinators

Study Visits

Data Collection

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
- Interventi tting by clinical care provi
- Ascertainr cquired through routine cli
- 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)

	Explanatory	Pragmatic
Eligibility Criteria	• **Restrictive:** highest risk for outcome, most likely to respond, most likely to comply	• **All individuals** with condition of interest **regardless of risk, comorbidities, adherence, language**
Intervention Implementation	• **Strict delivery** • Expert practitioners • **Close monitoring** of dose, adverse effects with adjustment or treatment, respectively	• **Flexible delivery** • **No expertise** needed • Full range of clinical settings • **Comparator is often usual practice**
Follow-up	• High intensity • **More f/u than usual care** • **Data collection for trial**	• **Low intensity** • **No study visits** • **Administrative databases**

Thorpe KE J Clin Epidemiol 2009

PRECIS Criteria
(Pragmatic-Explanatory Continuum Indicator Summary)

	Explanatory	Pragmatic
Outcomes	• **Direct and immediate consequence of intervention** • May be surrogate • Specialized **training for ascertainment** • May require **adjudication**	• **Clinically meaningful** • Objectively measured • No adjudication • **Assessed under usual conditions**
Intervention adherence	• Close monitoring • Adherence may be requirement for participation • Strategies employed to increase adherence	• **Unobtrusive** or no measurement • No strategies to improve adherence outside of those used in clinical care
Analysis	• Attempt to answer **narrowest, mechanistic question**	• Pure intention to treat • **Noise is accepted**

Thorpe KE et al J Clin Epidemiol 2009

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

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N Engl J Med 2018; 378:819-828

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
- Pri
- Ta
- Ce
  - 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?

Lederle F et al, Ann Intern Med. 2016;165:663-664

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

TiME Trial

NIH Collaboratory Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

NIH National Institute of Diabetes and Digestive and Kidney Diseases

- Trial question: D estly longer than many patients i mes?
- Cluster-random hours vs Usual Care
- Partnership wit
- No on-site researchers, no primary data collection
- >7000 incident patie nt approach
- Primary outcome: m

	TiME	USRDS
Age, years	64.1	63.7
% Male	57.8	57.8
% Black	24.7	26.2
% Diabetes	44.0	43.9

	HEMO	EVOLVE
Age	55.8	54.5

Dember LM et al, J Am Soc Nephrol 2016; 27:2955-2963

TiME Trial

NIH Collaboratory Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

NIH National Institute of Diabetes and Digestive and Kidney Diseases

- 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

NIH Collaboratory Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

NIH National Institute of Diabetes and Digestive and Kidney Diseases

- Trial Question: Is there a difference in outcomes with a liberal (<6.5 mg/dl) versus usual (<5.5 mg/dl) serum phosphate target
- [redacted]
- [redacted] hospitalization rate
- Informed consent (electronic)
- Dietitians will implement intervention and be champions

- eConsent to move beyond minimal risk research
- Engagement: dietitian champions

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

Pragmatic Trials: Opportunities in Nephrology

- 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)