Time to Reduce Mortality in End-Stage Renal Disease (TiME)

A Large, Pragmatic Cluster Randomized Trial in Maintenance Hemodialysis

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on behalf of the TiME Trial Study Group

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TiME Trial Team

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Outline

• Dialysis care in the United States
• Dialysis as a learning health system
• Rationale and design of the TiME Trial
• Efficiencies and challenges for implementing a pragmatic trial within large dialysis organizations
• Relevance of the dialysis setting to pragmatic trials in other health care delivery systems
Health Care Settings in the HCS Research Collaboratory

• Academic medical centers
• Health plans
• For-profit hospital chain
• Safety net community health centers
• Large for-profit dialysis organizations (LDOs)
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End-Stage Renal Disease in the U.S.

- 600,000 prevalent patients
  - Hemodialysis: 390,000 (65%)
  - Peritoneal dialysis: 30,000 (5%)
  - Functioning allograft: 180,000 (30%)

- 117,000 incident patients per year
  - 91% are treated with hemodialysis as initial renal replacement modality
  - 17,000 kidney transplants / year
Growth of the ESRD Program

USRDS Annual Data Report 2012
ESRD Healthcare Utilization

• Entitlement program of 1972 ensures Medicare coverage for ESRD regardless of age

• Medicare spending for ESRD patient care (total costs) is $47.5 billion / year

• ESRD costs are disproportionate: 7.5% of Medicare expenditures for 1.3% of beneficiaries

USRDS Annual Data Report 2012
Dialysis-Dependent ESRD

• Life-long dependence on dialysis unless transplanted
• High comorbidity burden and poor quality of life
• Exceedingly high mortality
  – 21% in first year
  – 50% at 3 years
Delivery of In-Center Dialysis Care

Dialysis facilities can be:
Delivery of In-Center Dialysis Care

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- Free-standing or hospital-based
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Dialysis Provider Organizations

• Dialysis Providers
  – Large dialysis organizations (LDOs): 4160 units
  – Small dialysis organizations: 500 units
  – Hospital-based or independent: 1600 units

• TiME Trial LDOs
  – DaVita 1850 units
  – Fresenius Medical Care 2100 units

\[ \text{Total} = 280,000 \text{ pts} \]
Dialysis Facility is the Principal Source of Health Care for Many Patients with ESRD

• Patients have frequent contact with multi-disciplinary team members

• Dialysis facilities perform/provide laboratory studies, blood pressure measurements, QOL assessments, vaccinations, nutritional supplements, pharmacy services

• Burdensome for patients to go elsewhere for care

• Primary care providers often relinquish care to nephrologists and dialysis unit personnel

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Dialysis is Already a Learning Health System

• United States Renal Data System (USRDS)
• Dialysis Outcomes and Practice Patterns Study (DOPPS)
• Dialysis provider organization data
• Quality improvement initiatives

But very little data from randomized clinical trials!

Many Unanswered Questions in Dialysis about Fundamental Aspects of Care

• Duration of hemodialysis sessions?
• Dialysis solution potassium concentration?
• Blood pressure target?
• Phosphorus target?
• Hemoglobin target?
• Preventive health care?
• Anticoagulation for atrial fibrillation?
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Determination of “Adequate” Hemodialysis

• Focus has been on clearance of small solutes (urea)
• Session duration decreased markedly with the development about 20 years ago of more efficient dialyzers that provide “adequate” urea clearance in 3-4 hours rather than 5-6 hours.
• But small solute clearance is not the full story
  – Fluid removal
  – Hemodynamic stability
  – Removal of sequestered solutes
# Observational Studies of Time

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Longer Treatment Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tentori et al NDT 2012</td>
<td>DOPPS</td>
<td>Lower mortality</td>
</tr>
<tr>
<td>Flythe et al Kidney Int 2012</td>
<td>Fresenius Medical Care</td>
<td>Lower mortality</td>
</tr>
<tr>
<td>Ramirez et al CJASN 2012</td>
<td>CMS ESRD CPM Project</td>
<td>Higher mortality (not statistically significant)</td>
</tr>
<tr>
<td>Brunelli et al Kidney Int 2010</td>
<td>Fresenius Medical Care</td>
<td>Lower mortality</td>
</tr>
<tr>
<td>Saran et al Kidney Int 2006</td>
<td>DOPPS</td>
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TiME Trial Hypothesis

Thrice weekly hemodialysis with session durations of at least 4.25 hours improves outcomes compared with usual care.
TiME Trial Design

• Cluster Randomization by dialysis facility

• Intervention
  Facility adopts approach of recommending minimum dialysis session duration of 4.25 hours for patients new to dialysis

• Usual Care
  No trial-driven facility approach for dialysis session length

• Patient Eligibility
  All patients initiating treatment with maintenance hemodialysis at participating facilities

• Outcomes:
  Mortality, hospitalization rate, HRQOL
Primary Treatment Analysis Population

• Comprised of subset for which separation in session duration between treatment groups is likely
  – Exclude large patients (V >42.5L)

• Expect 63% of participants to be in primary treatment analysis population
Sample Size

• 402 facilities, 6437 patients (4023 primary analysis population)

• Average cluster size: 16 (10 in primary analysis population)

• Power 80% for HR 0.85

• Assumptions
  – Mortality rate 18% per year
  – Intra-class correlation 0.03
  – 5% loss to f/u per year
Data Acquisition

• Clinical and administrative data are transmitted electronically from individual facilities and centralized laboratory to LDO data warehouses

• De-identified data elements are transmitted from LDO data warehouses to Penn DCC
Pragmatic Features

• All patients starting dialysis are eligible
• Intervention is delivered by clinical providers
• Outcomes:
  – ascertained from routine clinical data
  – derived from data elements common to all sites
• Adherence to intervention at the patient level will be promoted using systems already in use
• Highly centralized implementation approach
• Testing effectiveness rather than efficacy
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Dialysis Environment for Pragmatic Trials

• Dialysis organizations have the features of large, highly structured businesses
Dialysis Environment for Pragmatic Trials

• Dialysis organizations have the features of large, highly structured businesses
  – Multiple administrative levels, regional divisions, and governance levels
  – Operate under business rules and conventions
  – Operate in a highly regulated environment which necessitates a level of uniformity and rigidity
Dialysis Environment for Pragmatic Trials

• But at the dialysis facility level there is always some degree of variability in practices and conventions
  – Small team of care providers
  – Local culture and “neighborhood flavor”
Dialysis Environment for Pragmatic Trials

- But at the dialysis facility level there is always some degree of variability in practices and conventions
  - Small team of care providers
  - Local culture and “neighborhood flavor”

We are accommodating and leveraging aspects of both the centralized business structure and the local operations
Example: Facility Selection

Facility Eligibility

1. Willingness to adopt minimum session duration approach
2. Current median treatment time $\leq 3.5$ hours
3. Capacity to increase times (14 – 18 patients)

Both centralized systems and local activities will be used to determine facility eligibility.
Example: Facility Selection

• Central level:
  – Screen for facilities with treatment time $\leq 3.5$ hours
  – Use centrally-developed tools for determining operational capacity for increased time

• Local level:
  – Supplement centralized assessment of operational capacity with local determination
  – Willingness to participate is a local decision and implementing the intervention requires formal approval by facility’s governing body
Example: Adherence to Intervention

• Central level:
  – Use provider organization’s electronic system to “label” patients as trial participants
  – Use centralized data systems for monitoring prescribed and delivered treatment times by participating facilities

• Local level:
  – Use direct communication and trouble shooting with individual facilities
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Relevance of Dialysis Setting to Other Health Care Settings for Pragmatic Trials

• Model for trials involving:
  – Patients with large burden of illness and complex disorders
  – Interventions implemented at the health care delivery site
  – Large number of centers, broad geographic distribution
  – Research alliances between academic institutions and business organizations
Relevance of Dialysis Setting to Other Health Care Settings for Pragmatic Trials

• Other “chains”
  – Nursing homes
  – Rehabilitation facilities
  – Chemotherapy centers
  – Free-standing surgical centers
  – Pharmacies
  – IVF centers