

# The TiME Trial: From Planning to Implementation

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February 6, 2015

# TiME Trial Collaborators

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Eduardo Lacson, Jr – Fresenius  
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## Penn Data Coordinating Center

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# Outline

- Dialysis care in the U.S.
- TiME Trial design
- Challenges during the planning phase
- Challenge during implementation

# End-Stage Renal Disease in the U.S.

636,905 prevalent patients

- Hemodialysis: 408,711 (64%)
- Peritoneal dialysis: 40,631 (6%)
- Functioning allograft: 186,303 (29%)

114,813 incident patients

- 90% are treated with hemodialysis as initial renal replacement modality

17,305 kidney transplants / year

# ESRD Healthcare Utilization

- Entitlement program of 1972 ensures Medicare coverage for ESRD regardless of age
- Total healthcare cost for patients with ESRD: \$50 billion per year
- Costs are disproportionate: 6% of Medicare expenditures for <1% of beneficiaries

# Dialysis-Dependent ESRD

- Life-long dependence on dialysis unless transplanted
- High comorbidity burden
- Exceedingly high mortality rate
  - 21% in first year
  - 50% at 3 years

# Dialysis Provider Organizations

- Dialysis Providers

- Large dialysis organizations: 4600 units
- Small dialysis organizations: 500 units
- Hospital-based or independent: 1600 units

- TiME Trial Providers

- DaVita ~2000 units
  - Fresenius Medical Care ~2150 units
- } 285,000 pts

# Dialysis Provider Organizations as Health Care Systems

- For many patients dialysis facility is the principal source of health care
  - Frequent contact
  - PCPs often relinquish care
- Large dialysis organizations have central laboratories, electronic data systems and, increasingly, pharmacy services
- A small number of providers serve a large proportion of all patients with a specific condition



# 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?

# Many Unanswered Questions in Dialysis about Fundamental Aspects of Care

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# Determination of “Adequate” Hemodialysis

- Focus has been on clearance of small solutes (urea)
- Session duration decreased markedly with development 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

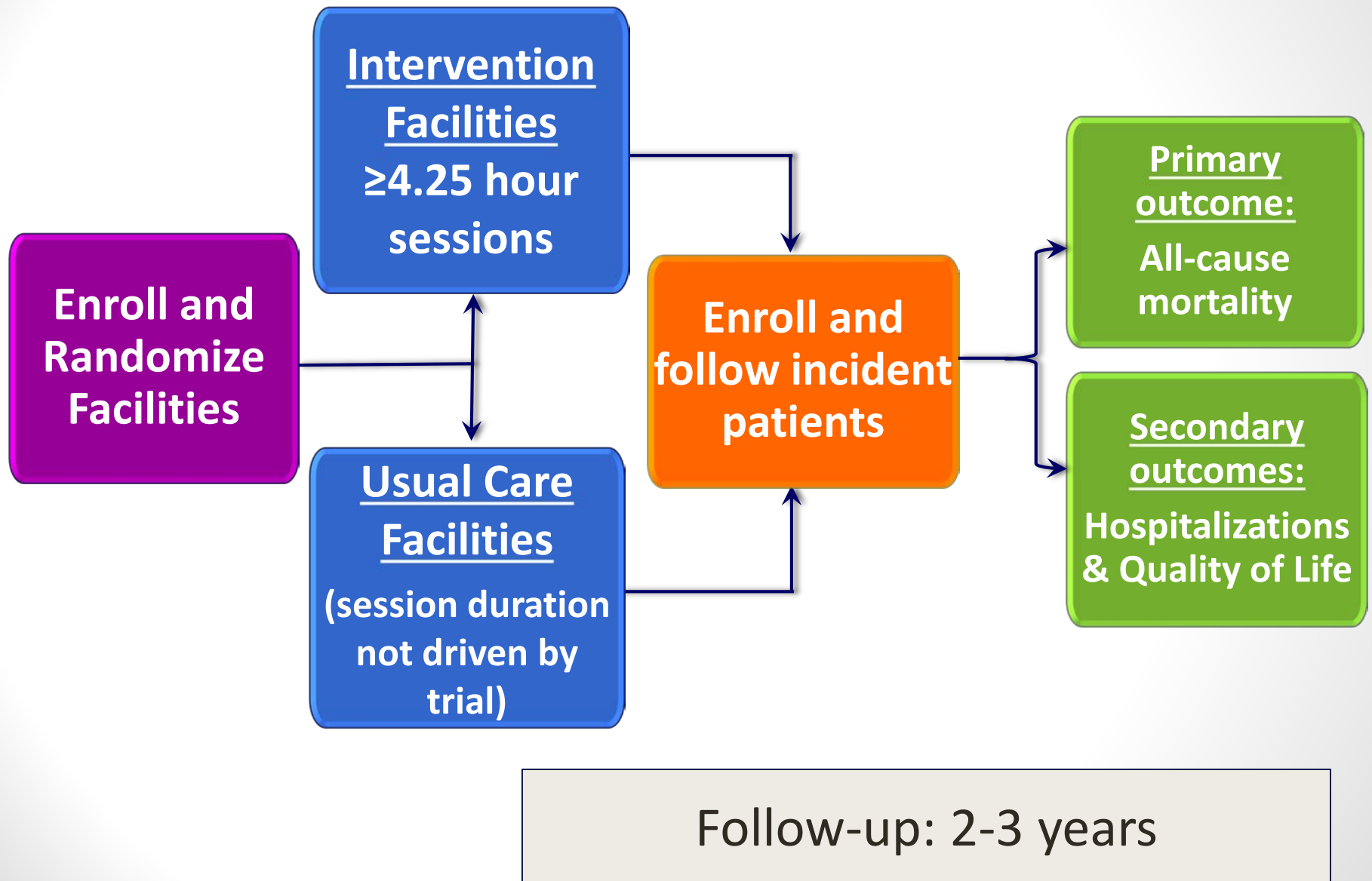
# Observational Studies of Time

Reference	Source	Longer Treatment Time
Tentori et al NDT 2012	DOPPS	Lower mortality
Flythe et al Kidney Int 2012	Fresenius Medical Care	Lower mortality
Ramirez et al CJASN 2012	CMS ESRD CPM Project	Higher mortality (trend)
Brunelli et al Kidney Int 2010	Fresenius Medical Care	Lower mortality or not depending on analytical approach
Miller et al, AJKD 2010	DaVita	Lower mortality but no difference beyond 3.5 hours
Saran et al Kidney Int 2006	DOPPS	Lower mortality
Marshall et al Kidney Int 2006	ANZDTA	Lower mortality

# **TiME Trial Hypothesis**

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

# Trial Design



# Eligibility Criteria

## Facility

- Capacity to accommodate 4 hr, 15 minute treatments for incident patients
- Agreement by nephrologists and facility leadership to implement the intervention

## Patient

- Age >18 years
- Initiation of maintenance dialysis within past 120 days
- Ability to provide consent for dialysis care

# Primary Analysis Population

- Subset for which separation in session duration between treatment groups is likely
  - Exclude large patients ( $V > 42.5L$ )
- Expect 63% of patients to be in primary treatment analysis population



# Sample Size

- 402 facilities, 6432 patients  
(4020 in 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

# Pragmatic Features of TiME

- (Nearly) all patients starting dialysis are eligible
- Intervention is delivered by clinicians
- Outcomes
  - ascertained from routine clinical data
  - derived from data elements common to all sites
- Highly centralized implementation approach
- Single IRB of record
- Testing effectiveness rather than efficacy

# **Challenges During Planning Phase**

# 1. Opt-Out Approach to Consent

## What we are doing:

- Patients are given a brief information document that includes
  - purpose of the trial
  - how session duration will be affected by the trial
  - toll-free telephone number to obtain additional information and to opt-out of data sharing
- Informational posters in dialysis facilities throughout duration of the trial

# 1. Opt-Out Approach to Consent

Why we can do it:

- IRB: open to the approach because although “default” session duration in intervention facilities is trial-driven, both treating physicians and patients maintain autonomy with respect to session duration

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- FDA determination: dialysis machines are being used in accordance with device label so exempt from requirement for IDE

# 1. Opt-Out Approach to Consent

How is it working in implementation phase?

- Requests by dialysis units for information sheet in 13 languages other than English
- Documentation of information sheet distribution matches with provider organization census reports
- Very few patients have opted out: 9 of ~2000



## 2. Data Harmonization, Transmission, and Completeness

During planning phase:

- Developed standardized data file formats and protocols for data transfer
- Defined data extraction and exportation methods to ensure accuracy and de-identification
- Developed database at DCC to accommodate differences in data structure between dialysis provider organizations
- Reviewed sample data files, tested data transfer processes

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- Monthly data transfers from both providers are happening according to schedule
- DCC compiles transferred data and reviews for outliers and completeness
- Selectively query providers for missing data
- Thus far for 2,016 patients:
  - 119,116 dialysis sessions
  - ~476,000 blood pressures
  - 198,532 laboratory values
  - 23,563 comorbidities

# Baseline Characteristics (December, 2014)

		Intervention N=819	Usual Care N=972	Total
<b>Age</b>	Missing	1	0	1
	Mean (SD)	63.5 (14.6)	63.9 (14.8)	63.7 (14.7)
<b>Sex</b>	Male	480 (58.6%)	554 (57.0%)	1,034 (57.7%)
<b>Race</b>	Missing	49 (6.0%)	68 (7.0%)	117 (6.5%)
	Native Amer/Alaskan	6 (0.7%)	5 (0.5%)	11 (0.6%)
	Asian	19 (2.3%)	32 (3.3%)	51 (2.8%)
	Black or African American	203 (24.8%)	190 (19.5%)	393 (21.9%)
	Native Hawaiian/Other Pacific Islander	1 (0.1%)	2 (0.2%)	3 (0.2%)
	White	538 (65.7%)	664 (68.3%)	1,202 (67.1%)
	Other	3 (0.4%)	11 (1.1%)	14 (0.8%)
<b>Ethnicity</b>	Missing	3 (0.4%)	4 (0.4%)	7 (0.4%)
	Hispanic	105 (12.8%)	72 (7.4%)	177 (9.9%)
	Non-Hispanic	711 (86.8%)	896 (92.2%)	1,607 (89.7%)
<b>Weight</b>	Mean (SD)	85.5 (25.4)	85.3 (25.9)	85.4 (25.7)
<b>Watson V</b>	Missing	1 (0.1%)	0(0%)	1 (0.1%)
	≤42.5	499 (60.9%)	614 (63.2%)	1,113 (62.1%)
	>42.5	319 (38.9%)	358 (36.8%)	677 (37.8%)

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# **Challenges During Implementation Phase**

# 1. Achieving Adequate Separation between Treatment Groups

Requires that:

- Intervention facilities implement 4.25 hour sessions
- Usual Care facilities have session durations consistent with what we expect based on previous experience

# Implementation of Intervention

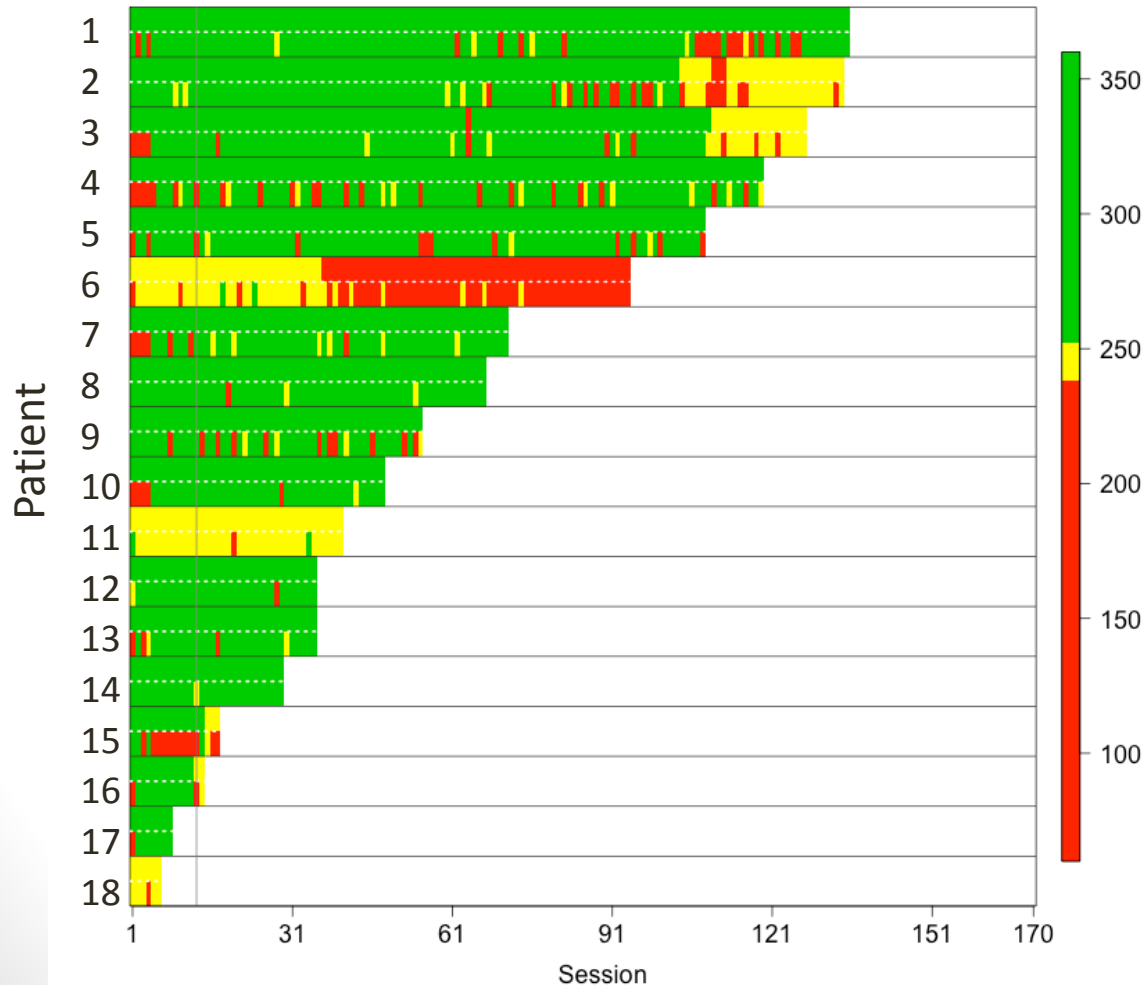
What are we finding?

- Performance varies across facilities

# A “Good” Intervention Facility

## Ordered/Actual Treatment Duration

Ordered: 80%  $\geq$  255 | Avg. = 264 | 104% of 255  
Actual: 67%  $\geq$  255 | Avg. = 257 | 101% of 255



- 18 patients ordered by duration as trial participant
- Green  $\geq$ 4.25 hour or more
- Red  $<$ 4 hours
- 1st row in each pair is ordered session duration
- 2<sup>nd</sup> row for each pairs is delivered duration
- Individual sessions represented along X axis

# Intervention facility with good initial performance that has not been sustained

## Ordered/Actual Treatment Duration

Ordered: 46%  $\geq$  255 | Avg. = 243 | 96% of 255

Actual: 33%  $\geq$  255 | Avg. = 228 | 90% of 255



# Implementation of Intervention

## What are we doing?

- DCC closely tracks performance and provides facility level feedback
- We have developed facility educational materials, FAQ documents, newsletters....
- Frequent interaction with intervention facilities is needed



# What about Usual Care Facilities?

What are we finding?

# What about Usual Care Facilities?

What are we finding?

- Session duration at one provider organization is about 6 minutes longer than we expected

# What about Usual Care Facilities?

AJKD

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Special Report

**Improving Clinical Outcomes Among Hemodialysis Patients:  
A Proposal for a “Volume First” Approach From the Chief  
Medical Officers of US Dialysis Providers**

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## Improving Clinical Outcomes Among Hemodialysis Patients: A Proposal for a “Volume First” Approach From the Chief Medical Officers of US Dialysis Providers

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“Based on the evidence summarized above, until further data are available, we propose a 4-hour first policy, such that the expected minimum duration of maintenance thrice-weekly hemodialysis is 4 hours....”

# What about Usual Care Facilities?

What are we doing?

# What about Usual Care Facilities?

What are we doing?

- Reassessing eligibility of potential facilities before enrollment using recent session duration data

# The Good News...

- Intervention implementation is improving over time

# Lessons Learned

- A highly developed and centralized health care delivery infrastructure does not obviate the need for activity at the local level
- One health care provider organization = thousands of health care providers (and two organizations = 2X thousands)
- TiME Trial enrollment sites (400!) are made up of individuals with:
  - Different opinions
  - Different concerns
  - Different personalities
  - Different roles
- At facility level we need ongoing interaction with:
  - Administrator
  - Medical Director
  - Every nephrologist
  - And..... the patients!