

# Pragmatic Trials in Dialysis: What's Next after the TiME Trial?

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NIH HCS Collaboratory Grand Rounds

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# Outline

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- Design and progress of the TiME Trial
- Implications of TiME Trial experience for future pragmatic trials in dialysis
- Examples of potential future pragmatic trials
  - what is feasible?
  - what are the barriers?

# Dialysis-Dependent ESRD

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- Life-long dependence on dialysis unless transplanted
- High comorbidity burden
- Extremely high mortality rate
  - 21% in first year
  - 50% at 3 years
- Very costly
  - \$50 billion per year
  - 6.3% of Medicare expenditures for 1.2% of beneficiaries

# Dialysis is Well-Suited for Pragmatic Trials

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- Highly accessible study population with frequent, regular clinical encounters
- Highly granular and uniform data collection as part of routine clinical care
- Infrastructure of dialysis provider organizations that allows for
  - Highly centralized trial implementation
  - Inclusion of large number of facilities with broad geographic distribution
- Event rates are high

# Many Unanswered Questions about Fundamental Aspects of Care

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- Duration of hemodialysis sessions?
- Dialysis solution potassium concentration? (or bicarbonate concentration, or sodium concentration)?
- Blood pressure target?
- Phosphorus target?
- Type of phosphate binder?
- Hemoglobin target?
- Anticoagulation for atrial fibrillation?

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

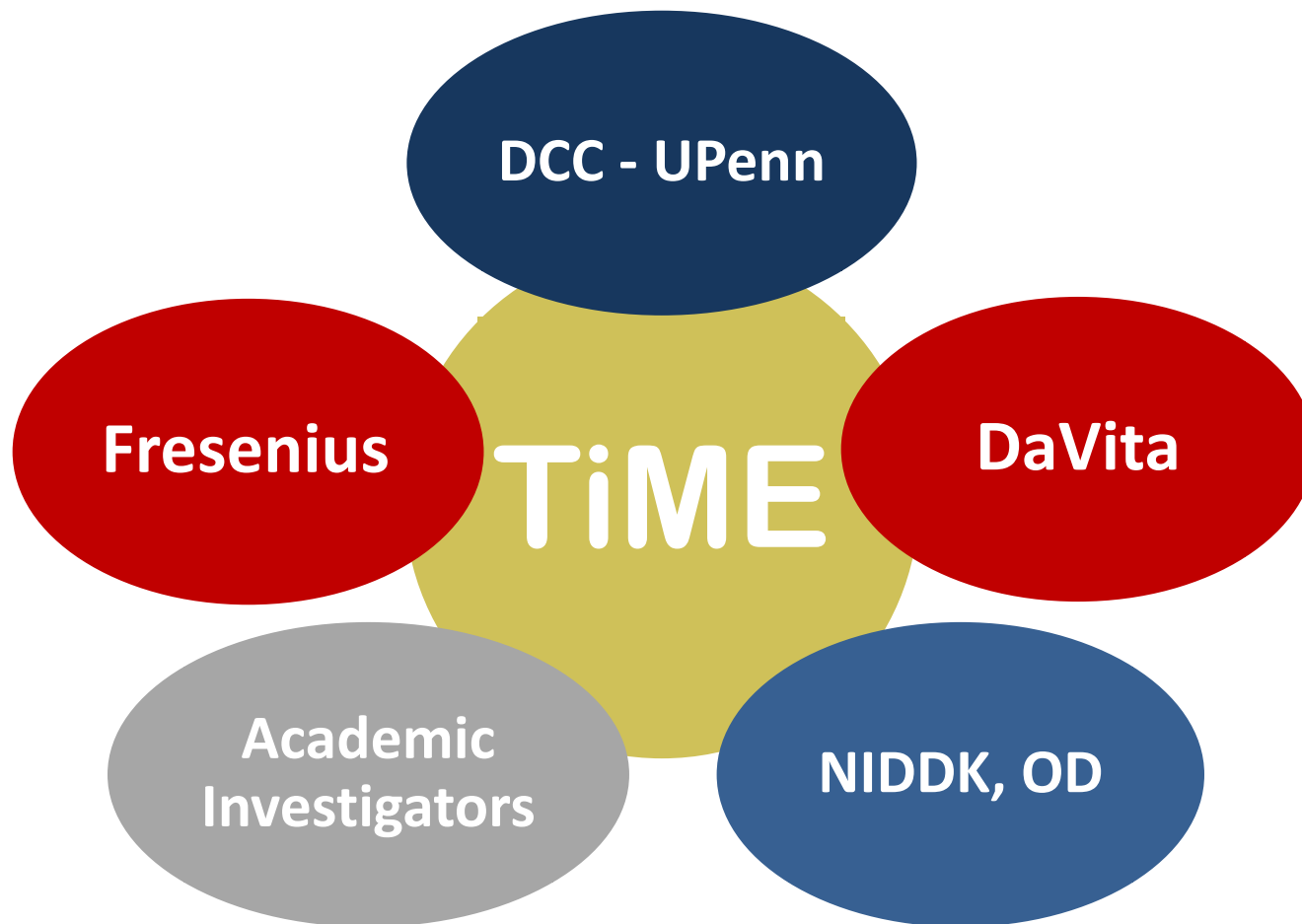
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## Hypothesis

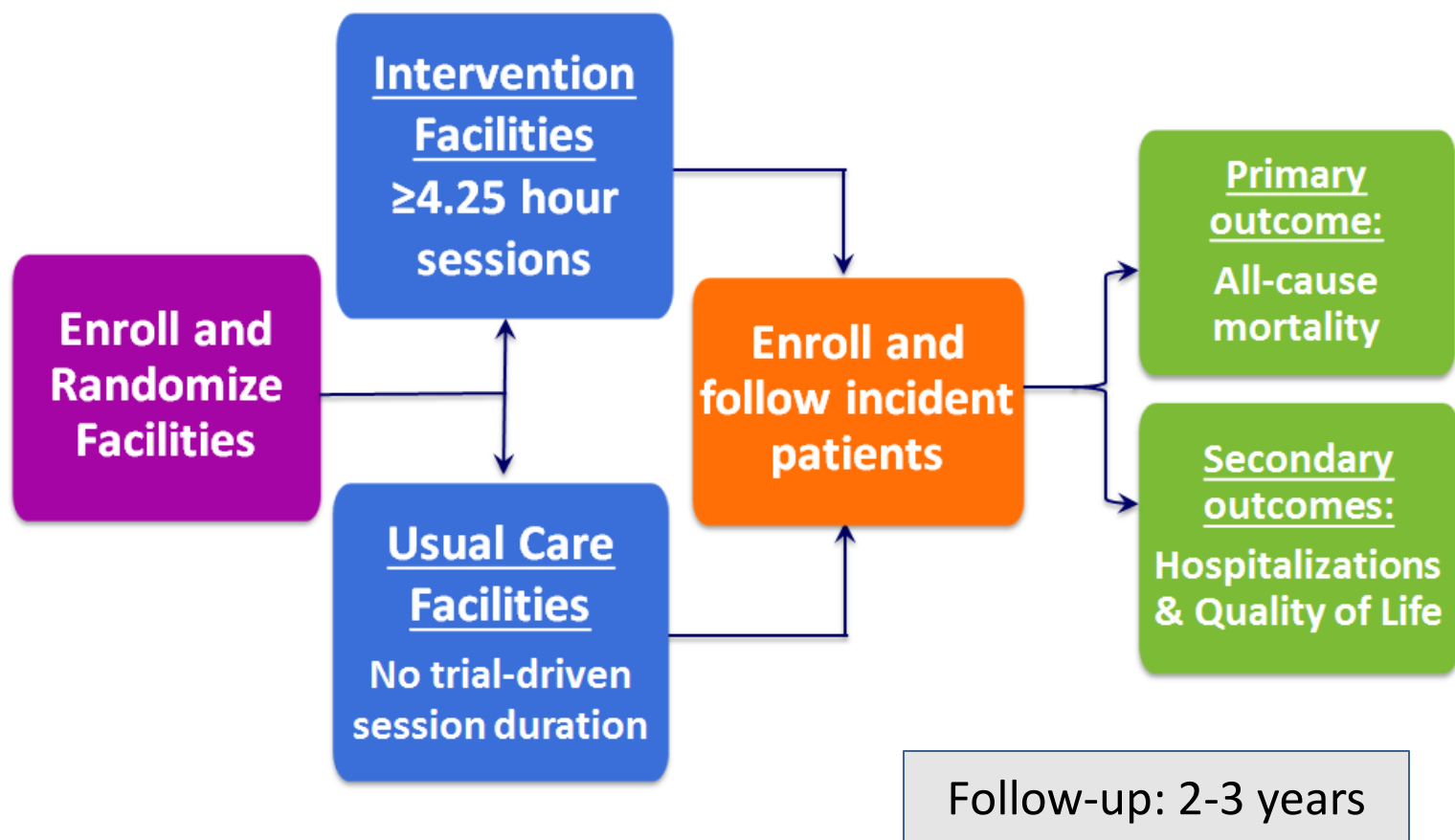
Thrice weekly hemodialysis with session durations of at least 4.25 hours improves outcomes compared with usual care.

# TiME Trial Team

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# TiME Trial Design





# Pragmatic Features of TiME

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- Non-restrictive eligibility criteria
- Delivery of intervention by clinicians; flexible implementation
- Reliance on data acquired through routine clinical care
- Highly centralized implementation approach with no on-site research staff
- Testing effectiveness rather than efficacy

## Information about the TIME Trial

- This dialysis facility is participating in a national research study called the TIME Trial, sponsored by the National Institutes of Health (NIH). This facility is participating in this clinical trial along with many other dialysis units throughout the country.
- The purpose of this research is to compare how patients feel, how often they are hospitalized, and how long they live based on the length of their dialysis sessions.
- Because this facility is participating in the TIME Trial, the standard approach at this facility is to prescribe a dialysis session length of at least 4 hours and 15 minutes for new patients starting hemodialysis treatment. Your nephrologist will consider the appropriateness of this treatment time for you, taking into account your individual health characteristics. If your nephrologist feels that this treatment time is not appropriate for you, he/she will prescribe a different session time. As always, you should talk with your doctor about treatment options.
- Your dialysis facility will send information about your dialysis treatments and results of laboratory tests that are done as part of your routine dialysis care to the TIME Trial study team at the University of Pennsylvania and to the NIH. **There will be no extra tests done for the TIME Trial.** Even if your treatment times are shorter than 4 hours and 15 minutes your treatment data and lab results will provide information that is important for this research. To protect your confidentiality, the information sent to the University of Pennsylvania and NIH will be identified by a scrambled code number. The research team will not be able to identify you from this code. **Your confidential information (such as name, address, or date of birth) will not be distributed.**
- Thank you for reading this information about the TIME Trial. On the other side of this paper are answers to frequently asked questions that might be helpful to you. If you would like more information about the TIME Trial or if you do not want your anonymous data reported to the study team, please call this **toll-free telephone number** and a representative from DaVita will call you back to answer your questions: **1-855-557-5813.**



## Frequently Asked Questions About Research and About the TIME Trial

### *What is a clinical trial?*

A clinical trial is a research study in which treatments are evaluated to determine what is best for patients. In order to best compare treatments, clinical trials often involve assignment of patients or treatment centers to a specific treatment approach. Clinical trials help doctors answer a variety of questions about diseases and their treatments.

### *Why is this clinical trial being conducted?*

This trial is being done to determine if longer dialysis sessions are better for patients in terms of how patients feel, how often they are hospitalized, and how long they live.

### *Why am I being included in this clinical trial?*

You are being included in this trial because your dialysis unit has agreed to participate. Like all other patients in this facility who are new to dialysis, you will be included in this trial unless you choose not to participate.

### *How will this clinical trial affect my care?*

Because of this trial, the standard dialysis time for new patients at this facility is at least 4 hours and 15 minutes. This means that that your treatment time might be longer than it otherwise would have been. However, your nephrologist will decide whether you should receive the research-assigned treatment time or a different treatment time for your dialysis sessions.

### *What if I object to having a dialysis session of at least 4 hours and 15 minutes?*

As always, you should discuss your care and treatment options with your doctor and let your doctor know if you have concerns.

### *How long will my participation in this clinical trial last?*

Your participation will be for approximately 2-3 years.

### *What if I move and have dialysis treatments in a unit that is not part of the clinical trial?*

If you move to another DaVita unit, information about your dialysis treatments and results of lab tests that are done as part of your medical care will continue to be included as trial data even if the dialysis unit is not part of the trial. Your dialysis session length will be prescribed by your nephrologist in the new unit and may stay the same or may change. You should call the toll-free telephone number shown below if you do not want your information included as trial data after you move to a new facility.

### *Are there risks related to this clinical trial?*

Dialysis sessions of 4 hours and 15 minutes are used routinely in dialysis and do not have risks compared with shorter dialysis treatments as far as we know. There is a very low risk that your dialysis treatment information could be seen by people other than the researchers. The confidentiality of your data is very important to us and we will make every effort to keep all information collected in this trial strictly confidential.

### *Are there benefits to taking part in this clinical trial?*

There is no direct benefit from participating in this research. It is possible that findings from this trial could help patients in the future.

### *Whom can I contact if I have questions about this clinical trial?*

If at any time you have questions or concerns about this trial, please contact the research team at DaVita using this toll free telephone number: **1-855-557-5813.**

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**Required Elements of Consent Forms**

**All Consent Forms**

- A statement that the study involves research
- Purpose of research
- Duration of participation
- Description of experimental procedures
- Risks or discomforts
- Benefits
- Available alternatives
- Confidentiality protection

**Greater than Minimal Risk Studies**

- Compensation for injury
- Research participant rights
- Voluntary participation



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**Greater than Minimal Risk Studies**

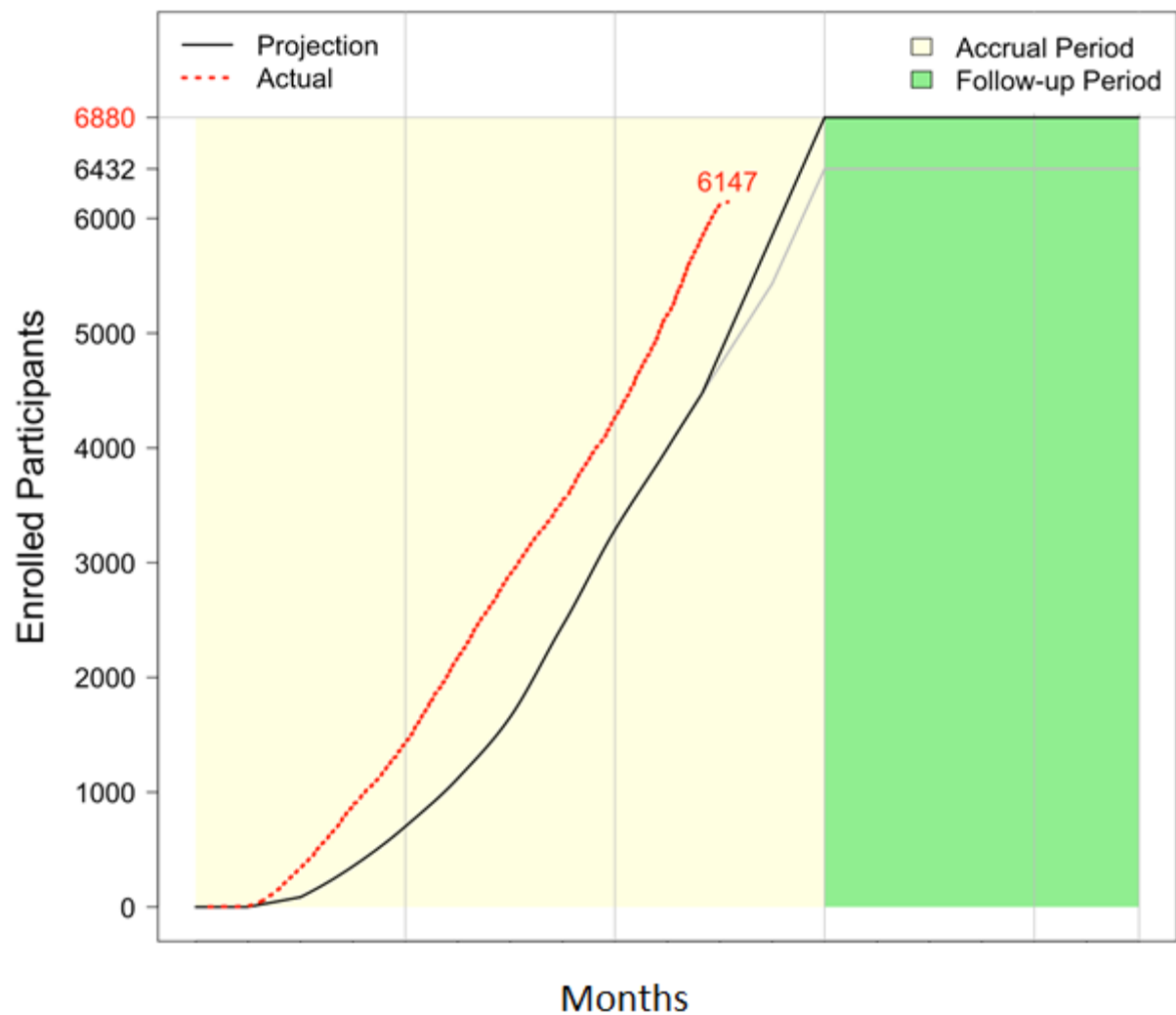
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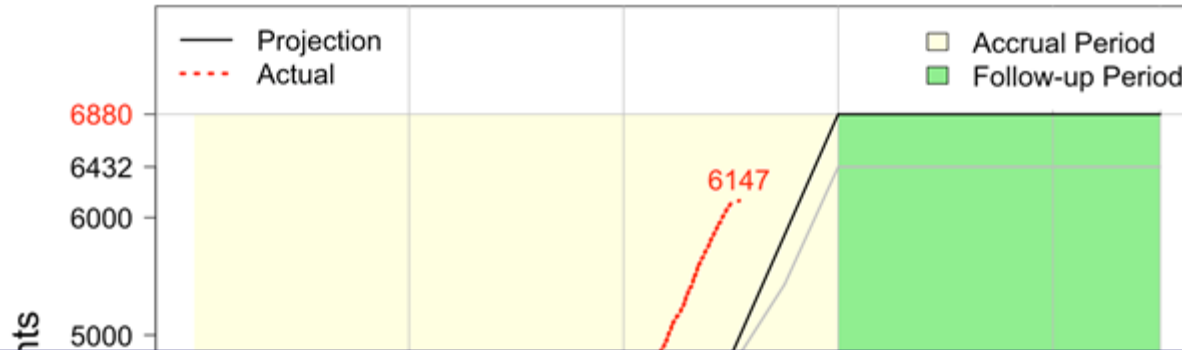
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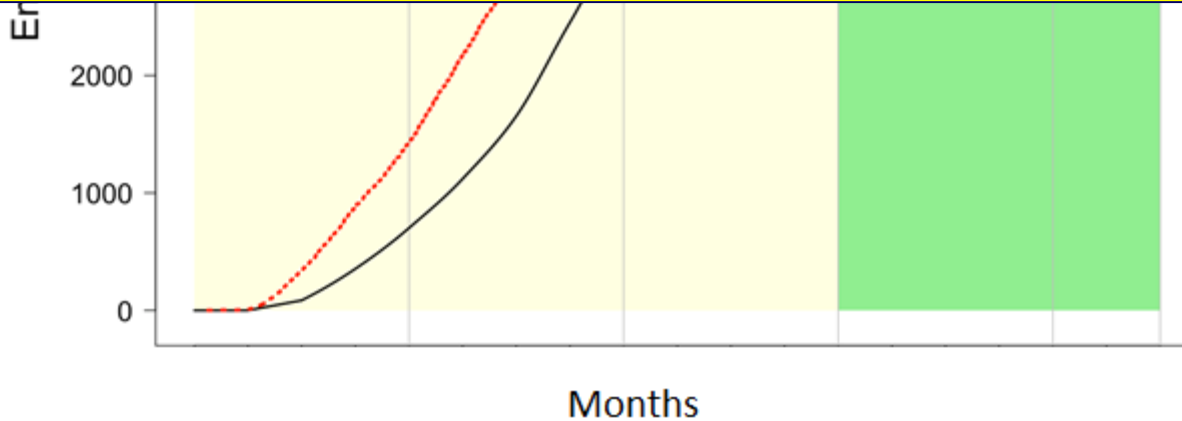
# Patient Enrollment



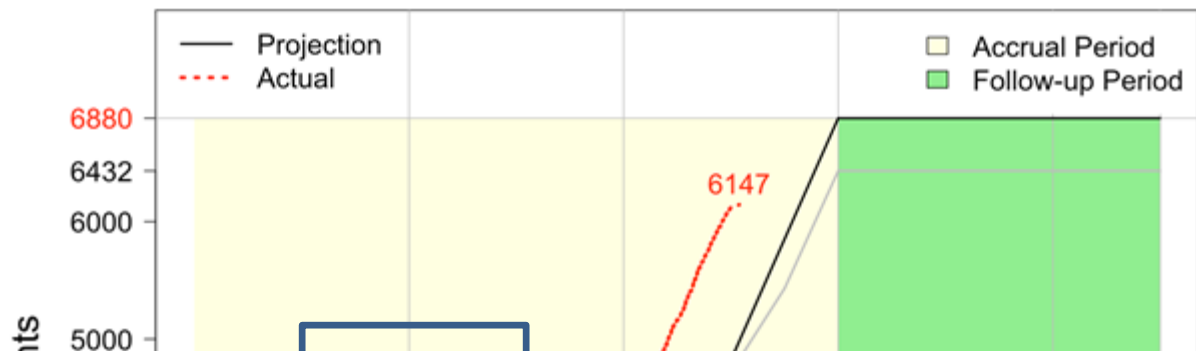
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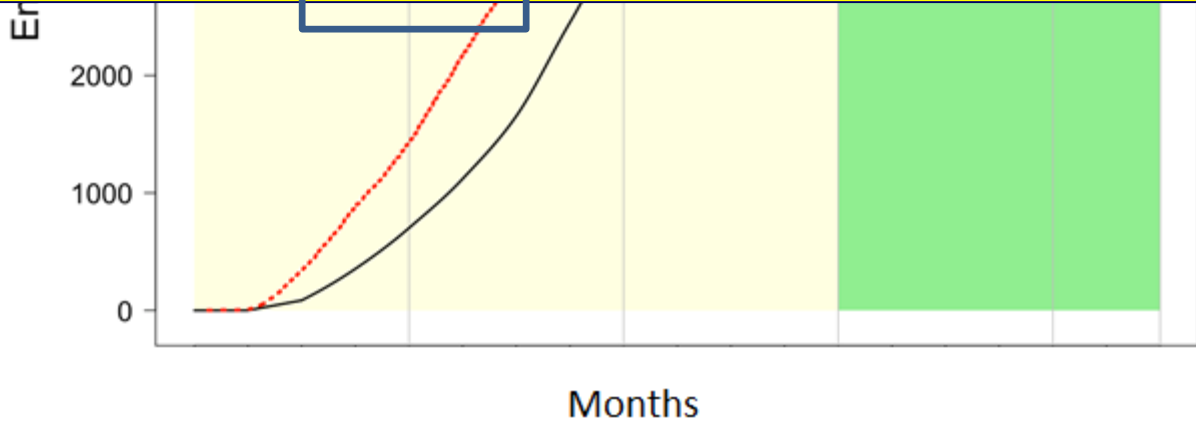
	<u>TiME</u>	<u>USRDS</u>	<u>HEMO</u>	<u>EVOLVE</u>
<b>Mean Age, yr</b>	<b>64.0</b>	<b>63.7</b>	<b>55.8</b>	<b>54.5</b>



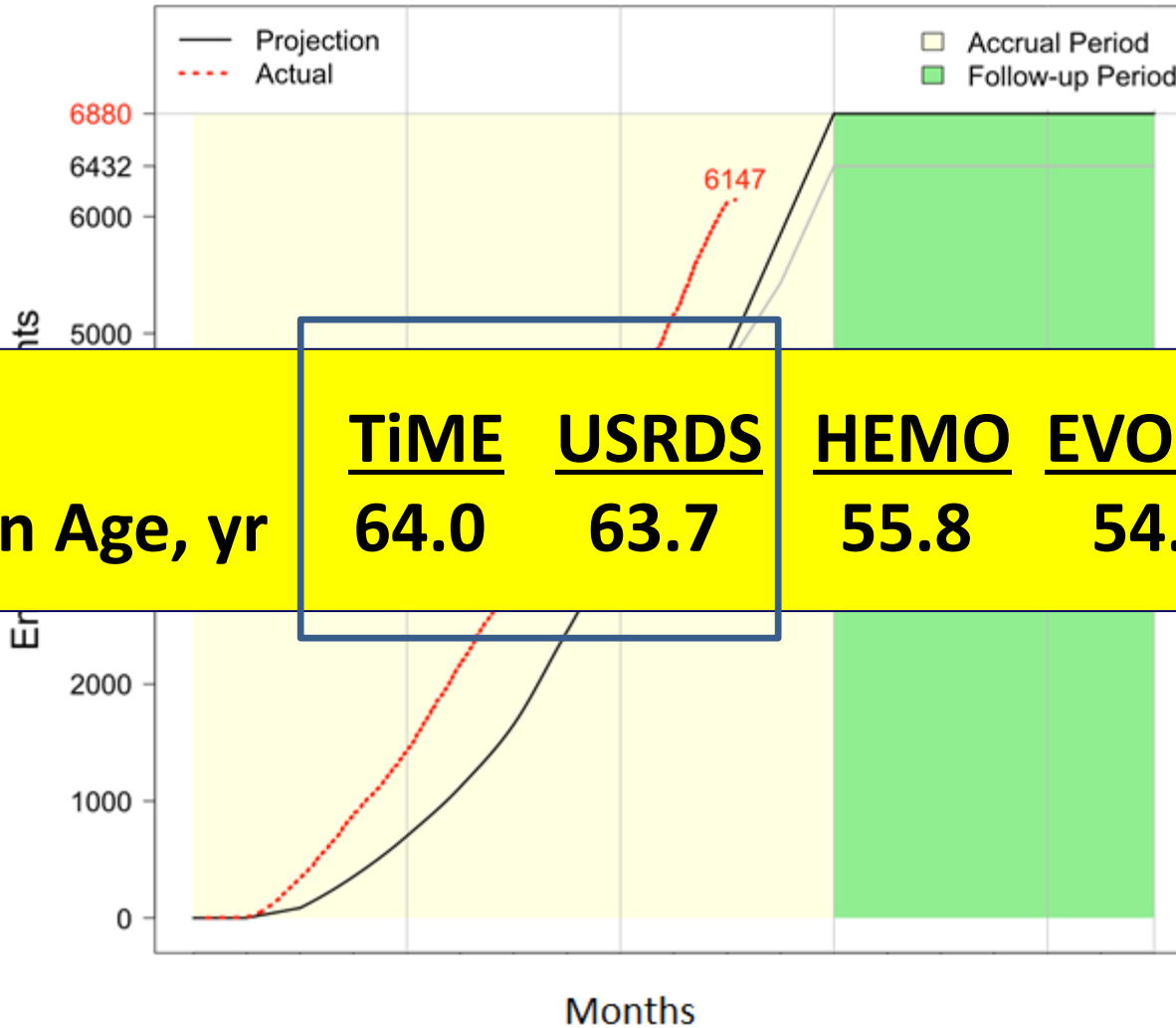
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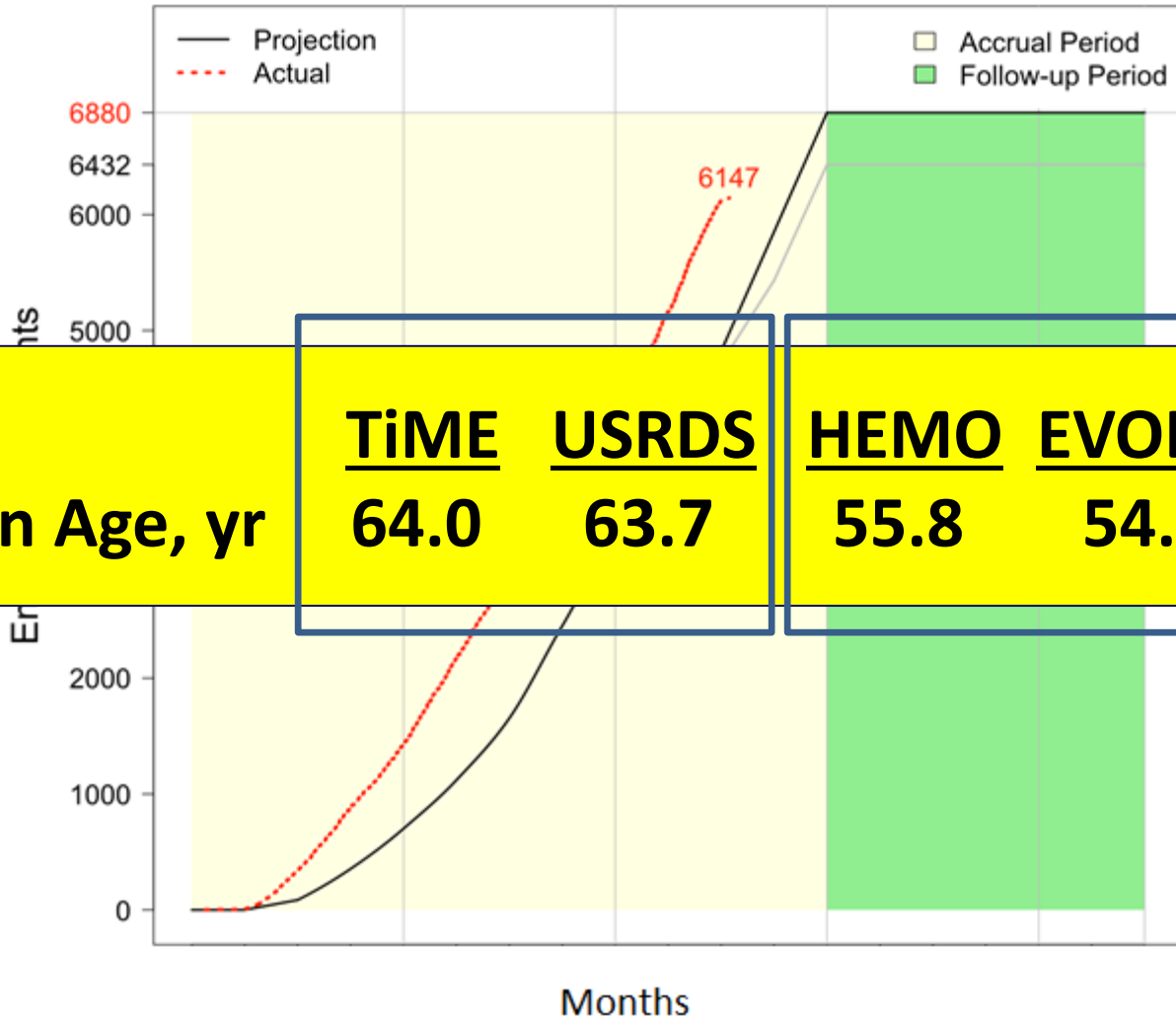
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# Patient Enrollment



**Mean Age, yr**

**TiME**

**USRDS**

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# Data Granularity and Completeness

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From ~6,000 patients:

- >500,000 dialysis sessions
- >1,000,000 blood pressure values
- >1,200,000 laboratory values
- >95,000 comorbidities
- >6,000 hospitalizations
  
- Missing race: 7%
- Missing ethnicity: 11%

# Summary: TiME Trial Experience

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- Opt-out approach is going smoothly
  - Patients are willing to share data
  - Enrollment is rapid
  - Participants are representative of dialysis patient population
- Data acquisition is going smoothly
  - Data elements are readily harmonized across dialysis providers
  - Frequent transmission of data set allows for ongoing QC
  - Limitation: only have dialysis unit data
- Implementing the intervention has been challenging
  - Inter-facility variability in performance

# Why is the Intervention Challenging?

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- Requires ongoing (not just initial) buy-in and support at many levels
  - Corporate leadership
  - Administrators at all levels
  - Facility staff
  - Facility nephrologists (all of them!)
  - Patients

# What Next after TiME?

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- Duration of hemodialysis sessions?
- Dialysis solution potassium concentration? (or bicarbonate concentration, or sodium concentration)?
- Blood pressure target?
- Phosphorus target?
- Type of phosphate binder?
- Hemoglobin target?
- Anticoagulation for atrial fibrillation?

# What Next after TiME?

- Duration of hemodialysis sessions?
- Dialysis bicarbonate concentration? (Can these questions be addressed with a large pragmatic trial?)
- Blood pressure?
- Phosphate?
- Type of dialysis?
- Hemoglobin target?
- Anticoagulation for atrial fibrillation?

**Can these questions be addressed with a large pragmatic trial?**

**Pragmatic = Incorporated into routine clinical care delivery**

# 1. Dialysis solution potassium concentration (or bicarbonate, or sodium)

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- Sudden death, likely due to arrhythmias, is a leading cause of death in ESRD
- High, low, or rapidly changing blood potassium concentrations are all potential causes
- Emphasis on preventing hyperkalemia might have unintended consequence of causing intra- or post-dialysis hypokalemia
- Hypothesis: Standardized algorithm for dialysis solution  $[K^+]$  with less use of low-K solutions will reduce the occurrence of clinically important arrhythmias
- Pragmatic trial: Algorithm vs Usual Care



# Protocolized K vs Usual Care Pragmatic Trial: Is it doable?

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- Who needs to buy-in?
  - Provider organization leadership
  - Facility leadership
- Is there burden to patients?
  - No
- Randomization at participant or cluster level?
  - Cluster probably necessary to facilitate implementation & minimize contamination
- Consent approach?
  - Can use opt-out for data sharing but difficult to opt-out of K protocol
- Minimal risk?
  - Yes since we do not know which approach is better and experience of patient is not qualitatively different between treatment arms
- FDA purview?
  - Unclear
  - Good opportunity for direct discussion w/FDA

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→ **Easier than the TiME Trial!**

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## Major barriers:

- Uncertainty about minimal risk designation
- Uncertainty about FDA oversight

contamination

of patient is not

## 2. Serum phosphorus target

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- Phosphorus is poorly cleared by dialysis
- High phosphate blood/tissue levels important contributor to vascular disease
- Low-phosphate diet and phosphate binders used to reduce GI absorption
  - very burdensome to patients
  - 3-5 pills with every meal, significant dietary restrictions
- Target for phosphate used clinically has not been evaluated rigorously and is not met by many patients
- Hypothesis: less stringent phosphate target might be okay
- Pragmatic trial: less restrictive target vs current clinical target

# Phosphorus target pragmatic trial: Is it doable?

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- Who needs to buy-in?
  - Provider organization leadership
  - Facility leadership
  - Facility staff, in particular dietitians
  - Patients
- Is there burden to patients?
  - No, intervention reduces burden
- Randomization at participant or cluster level?
  - Participant level possible but cluster preferred to reduce contamination
- Consent approach?
  - If cluster-randomized, opt-out is preferable to reduce imbalances across treatment groups
- Minimal risk?
  - Probably not since more liberal target is not current standard
- FDA purview?
  - No

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## Major barrier:

Inability to use opt-out consent approach if trial is not minimal risk

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# 3. Type of phosphate binder: Calcium-containing vs non-calcium-containing

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- Calcium-containing binders (calcium carbonate, calcium acetate) were the staple for many years
- Non-calcium-containing binders (sevelamer, lanthanum) were developed to reduce calcium load and resulting vascular toxicity
  - Theoretical benefit but no convincing clinical trial data
  - Expensive
  - Widely adopted initially but use is now decreasing with new bundled payments to dialysis providers
- Question: Will this changing practice harm patients?
- Pragmatic trial: Calcium-containing vs non-calcium containing binder as first line treatment

# Phosphorus binder pragmatic trial: Is it doable?

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- Who needs to buy-in?
  - Provider organization leadership
  - Facility leadership
  - Dietitians, nephrologists
  - Patients
- Is there burden to patients?
  - No
- Randomization at participant or cluster level?
  - Either would work if operational issues could be overcome
- Consent approach?
  - Opt-out if cluster randomization used to avoid imbalance across treatment groups
- Minimal risk?
  - Probably is minimal risk but feels a little funny given the motivating question for trial
- FDA purview?
  - Yes – even though IND is not needed, the trials are evaluating medications. FDA might grant waiver of documentation of informed consent??



# Phosphorus binder pragmatic trial: Is it doable?

- Who needs to buy-in?
  - Provider organization leadership
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  - Dietitians
  - Patients
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- Randomization
  - Either
- Consent approach?
  - Opt-out if cluster randomization used to avoid imbalance across treatment groups
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## Major barriers:

- Uncertainty about minimal risk designation
- FDA purview considerations

# Common Barriers Across Example Trials

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- Uncertainty about minimal risk designation
- Inability to use altered consent approach if trial is not minimal risk
- Uncertainty about criteria for FDA oversight
- Uncertainty about altered consent approaches if under FDA oversight

# Summary

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- TiME Trial experience includes important successes and important challenges that should inform future pragmatic trials in dialysis
- There are many questions about fundamental aspects of dialysis care that lend themselves nicely to pragmatic trial approaches especially if we can overcome regulatory uncertainties and barriers
- The challenges presented today should not be viewed as prohibitive
  - TiME Trial would not have gotten off the ground if we'd been daunted by what at times felt like show-stoppers!

## **Steering Committee**

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