TRANSFORMing Research for Patients with Heart Failure

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On behalf of the TRANSFORM-HF Investigators, Sites and Participants

@robmentz
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- The content of this presentation is solely the responsibility of the presenters and does not necessarily reflect the views of the National Institutes of Health
Outline

• Current landscape in US clinical trials
• Overview of Pragmatic Trials
• Case Study: TRANSFORM-HF
Current Clinical Trial Model

- Mostly small
- Mostly surrogate endpoints
- Huge budgets

Setting
- Research enterprise – “parallel universe”
- Failure to leverage existing resources
- “…heterogeneity in methodological approaches, including the use of randomization, blinding, and DMCs.”

Califf RM et al. JAMA 2012;307:1838-47
IQVIA cost tool
- 138 trials / 59 agents
- Median $19m
- Placebo/active=$35m

- Varies by size, randomization, control, outcomes
- Highest: PARADIGM (sacubitril/valsartan) = $347m
- Modest portion of Drug Dev’t = $650m - $2.8b

Moore TJ, et al. JAMA Intern Med 2018
US Enrollment: HF as an Example

Evolving Landscape of Clinical Trials in Heart Failure: Patient Populations, Endpoint Selection, and Regions of Enrollment

- Taking longer
- Low enrollment rates
  - Median 0.5 pt/site/mth
- Even worse in US
  - 0.22 pt/site/mth in 2013-2016

Samman Tahhan A...Butler J. Curr Heart Fail Rep 2018
Influence of Clinical Trial Site Enrollment on Patient Characteristics, Protocol Completion, and End Points

30-day Death or HF Hosp

Recruitment Rate associated with patient characteristics, background therapies, protocol completion and clinical outcomes!

Site Principal Investigators in Multicenter Clinical Trials
Appropriately Recognizing Key Contributors

Traditional Site PI Responsibilities

- Supervise conduct including those delegated
- Conduct study in accordance with protocol
- Satisfy and maintain adherence to reg requirements
- Ensure adequate enrollment and financial solvency
- Maintain adequate training of site personnel
- Ensure integrity of study data
- Protect the rights, safety, and welfare of patients
- Permit and participate in FDA inspections
- Submit study documents

Strategies for Improved Engagement

- Involvement on study manuscripts (as appropriate)
- Manuscripts Promotion Process
- CME / MOC
- Scientific Sessions
- Discounted CME
- Trial activities constituting CME and/or MOC

Mentz RJ and Peterson ED. Circulation 2017
• “As large trials became popular…the original simplicity was lost…leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuing costs. An ideal opportunity would be to embed randomization in the EMR...”

The “LEVI’S” Approach to Simple Trials

- L
  - Large
  - Leveraged
- E
  - Embedded
- V
  - Valuable
- I’
  - Inexpensive
  - Innovative
- S
  - Sound Science

Lauer MS. AHA 2013
What are Pragmatic Trials?

Dictionary

pragmatic

prag·mat·ic
/prəgˈmætɪk/

adjective

dealing with things sensibly and realistically in a way that is based on practical rather than theoretical considerations.
Making Decisions: Where do you fall on the pragmatism index?

**Explanatory**
- Ideal Population
- Ideal/Perfect Care
- Blinding
- Placebo
- Coordinator Data Collection

**Pragmatic**
- Routine Population
- Usual Care
- Un-blinded
- Active control
- Centralized data collection (E.M.R, claims, direct to patient)

**ELIGIBILITY**
Who is selected to participate in the trial?

**RECRUITMENT**
How are participants recruited into the trial?

**SETTING**
Where is the trial being done?

**PRIMARY OUTCOME**
How relevant is it to participants?

**FOLLOW-UP**
How closely are participants followed-up?

**FLEXIBILITY - ADHERENCE**
What measures are in place to make sure participants adhere to the intervention?

**FLEXIBILITY - DELIVERY**
How should the intervention be delivered?

**PRIMARY ANALYSIS**
To what extent are all data included?

**ORGANISATION**
What expertise and resources are needed to deliver the intervention?

Case Example:

**ADAPTABLE Study Design**

 Patients with known ASCVD + ≥ 1 “enrichment factor”*

Identified through EHR (computable phenotype) by CDRNs

Patients contacted with trial information and link to e-consent;†
Treatment assignment will be provided directly to patient

ASA 81 mg QD  ASA 325 mg QD

Electronic follow-up: Every 3 or 6 months
Supplemented with EHR/CDM/claims data

**Duration:** Enrollment over 24 months;
maximum follow-up of 30 months

**Primary endpoint:**
Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

**Primary safety endpoint:**
Hospitalization for major bleeding

† Participants without internet access will be consented and followed via a parallel system.
Case Presentation

- 68 yo man with advanced ischemic cardiomyopathy
- Worsening dyspnea and volume overload
- Multiple recent hospitalizations for acute HF
  - Home furosemide $\rightarrow$ IV furosemide $\rightarrow$ Oral furosemide
- Evidence-based HF medications and device therapy
- “Isn’t there something else you can do to help with all of this fluid?”
Next Step at Discharge?

- A. Increase oral furosemide dose
- B. Metolazone as needed
- C. Switch furosemide to torsemide
## Pharmacology

All available as generic formulations

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Torsemide</th>
<th>Bumetanide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative potency</strong></td>
<td>1</td>
<td>2 x</td>
<td>40 x</td>
</tr>
<tr>
<td><strong>Bioavailability, %</strong></td>
<td>10-100 (avg 50)</td>
<td>80-100</td>
<td>80-100</td>
</tr>
<tr>
<td><strong>Affected by food</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Half-life, h</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.5-2</td>
<td>3-4</td>
<td>1</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2.7</td>
<td>6</td>
<td>1.3</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>2.8</td>
<td>4–5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Torsemide has more consistent oral bioavailability and a longer duration of action

Felker GM and Mentz RJ. *JACC* 2012
Loop Diuretic Use

**Dominance of Furosemide for Loop Diuretic Therapy in Heart Failure**

Time to Revisit the Alternatives?

Furosemide is the most commonly used loop diuretic
Why preferential use of furosemide?

- Furosemide was first to market
- FDA approval:
  - Furosemide: 1966
  - Torsemide: 1993
- Torsemide became generic in 2002
- Long-time clinical experience with furosemide
Benefits of Torsemide: Preclinical and Clinical Studies

- Anti-Aldosterone Effects
- Anti-Fibrotic Myocardial Effects
- Positive Ventricular Remodeling
- Favorable BNP Effects
- Functional Status Benefits
- Reduced HF Rehospitalization
- Potential Mortality Benefits

Cosin J, et al. EJHF 2002
Reduced Myocardial Fibrosis

At baseline

CVF = 7.58%

After treatment

CVF = 6.28%

Furosemide

CVF = 6.21%

Torsemide

CVF = 3.71%

Rehospitalization Benefit

Open-label study: 234 chronic HF patients treated for 1 yr

HF Hospitalization

RR 0.40; 95% CI: 0.27-0.61

↓ 60%
## Meta-Analysis: Mortality

**TORIC:** Open-label, non-randomized

### Table

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Torsemide</th>
<th>Furosemide</th>
<th>Risk Ratio M-H, Random. 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Cosin 2002</td>
<td>17</td>
<td>778</td>
<td>27</td>
</tr>
<tr>
<td>Murray 2001</td>
<td>18</td>
<td>113</td>
<td>25</td>
</tr>
<tr>
<td>Müller 2003</td>
<td>8</td>
<td>122</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>43</strong></td>
<td><strong>1013</strong></td>
<td><strong>58</strong></td>
</tr>
</tbody>
</table>

Total events: 1013

Heterogeneity: \( \tau^2 = 0.11; \) \( \chi^2 = 3.87, \text{df} = 4 (P = 0.14); \) \( I^2 = 48\% \)

Test for overall effect: \( Z = 1.38 (P = 0.17) \)

### Risk Ratio

**RR 0.68**
Guidelines: Loop Diuretics

- Loop diuretics are recommended in patients with HFrEF and HFpEF who have evidence of fluid retention, unless contraindicated, to improve symptoms (Class I, LOE: C).

- The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (e.g., bumetanide, torsemide) because of their increased oral bioavailability.
Duke: Loop Diuretics over Time

- Furosemide: 86% (n=3,955)
- Torsemide: 14% (n=625)

## Baseline Characteristics: Duke

<table>
<thead>
<tr>
<th></th>
<th>Furosemide n=3,955</th>
<th>Torsemide n=625</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, year</strong></td>
<td>65 (54-76)</td>
<td>64 (53-74)</td>
</tr>
<tr>
<td><strong>LVEF ≥ 55%</strong></td>
<td>47%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>84%</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>48%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Renal dysfunction</strong></td>
<td>19%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>41%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>Mod-Sev TR</strong></td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Creatinine, mg/dL</strong></td>
<td>1.2 (1.0-1.6)</td>
<td>1.4 (1.0-2.0)</td>
</tr>
<tr>
<td><strong>BUN, mg/dL</strong></td>
<td>23 (17-35)</td>
<td>27 (18-45)</td>
</tr>
<tr>
<td><strong>NT-proBNP, pg/mL</strong></td>
<td>3501 (1379-8488)</td>
<td>4214 (1725-9499)</td>
</tr>
</tbody>
</table>

Presented as median (IQR) or %.

Mentz RJ, *et al.* J CV Pharm 2015
ASCEND-HF: Torsemide Use

IPW-Adjusted Mortality

HR 0.86 (0.63 - 1.19)
P = 0.37

87% Furosemide
13% Torsemide

A reappraisal of loop diuretic choice in heart failure patients

Jonathan Buggey, MD, a Robert J. Mentz, MD, a,b Bertram Pitt, MD, c Eric L. Eisenstein, DBA, b Kevin J. Anstrom, PhD, b Eric J. Velazquez, MD, a,b and Christopher M. O'Connor, MD a,b Durham, NC and Ann Arbor, MI

“…need for a well-powered, randomized control trial assessing torsemide versus furosemide use.”
Next Step?

- A. Increase oral furosemide dose
- B. Metolazone as needed
- C. Switch furosemide to torsemide
- D. Not sure

We need an adequately powered clinical trial
The TRANSFORM-HF Trial

ToRsemide compArisoN with furoSemide FOR Management of Heart Failure

ClinicalTrials.gov Identifier: NCT03296813
TRANSFORM: Primary Objective

To compare the treatment strategy of torsemide versus furosemide on long-term clinical outcomes among patients hospitalized for HF

Primary Endpoint: All-cause mortality
Overall Design

- Prospective, multicenter, randomized, unblinded trial of 6,000 hospitalized HF patients at 50 US sites
- 1:1 randomization to oral torsemide or furosemide (dose per clinician)
- Broad eligibility criteria
- Consent and randomization prior to discharge
- Streamlined case report form and data collection
- Continuation of randomized therapy post-discharge
- No study-specific visits
- DCRI Call Center obtained outcomes at 30 days, 6 mos, and 12 mos
- National Death Index reviewed during follow-up
Population and Entry Criteria

Patients hospitalized for HF

- Regardless of LVEF
- Include newly diagnosed HF and worsening chronic HF

Inclusion Criteria
- Either LVEF ≤ 40% or ↑ (NT-pro) BNP
- Age ≥ 18 years
- Hospitalized HF patient
- Outpatient plans for daily loop
- Signed informed consent

Exclusion Criteria
- ESRD requiring RRT
- LVAD or anticipated < 3 mos
- History of OHT or listed
- Non-cardiac condition limiting < 12 mos
- Pregnant/nursing women
- Known hypersensitivity to T or F
The TRANSFORM-HF Trial

6,000 HF Patients

1:1 Randomization

Torsemide

Furosemide

DCRI Call Center (30 d, 6 m, 12 m)
National Death Index

Primary Endpoint:
All-Cause Mortality

Secondary Endpoints:
All-cause Mortality + Hospitalization at 30 days and 12 months
Total Hospitalizations over 12 months
Health-related Quality of Life over 12 months
Symptoms of Depression over 12 months
Pre-Screen/Screen/Randomization

Pre-Screen (via routine patient care) → Consent patient → Pre-Randomization → Randomize in RedCap

- Confirm eligibility
- Complete Patient Forms
- RedCap

- KCCQ/PHQ
- Anticipated Daily Dose

- Pt. materials
- RedCap
- Send Forms to Call Center
Discharge and Call Center

Ensure patient participant has Rx ➔ Discharge info into eCRF ➔ Fax D/C instructions to CC ➔ DCRI Call Center* patient follow-up

*The DCRI Call Center will also initiate a medical record query 12 months after patient randomization to screen for hospitalizations at the enrolling center and potential treating hospitals identified by the patient. Also, the National Death Index (NDI) will be searched during follow-up and prior to study close-out.
TRANSFORM

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Challenges (& Opportunities) with TRANSFORM

- Randomization rate targets (3-5 pt/site/mth)
- Recruitment volume to offset lower per-patient site payment
- Cross-over
  - Intentional
  - Unintentional: Transitions of care
- Patient and Clinician Engagement
- Getting over equipoise concerns
- Right balance of pragmatism?
  - Call Center Outcomes: Answer phone?
  - National Death Index delays
  - No adjudication of cause of death or hospitalization
  - Relationship with routine care providers
The Positives of Pragmatic Trials like TRANSFORM

- Real-world effectiveness
- Broad patient and provider groups
- More generalizable results
- Reduction in number and complexity of visits
- Streamline data collection
- Potentially faster and cheaper

Ford I and Norrie J. *NEJM* 2016
Limitations / Cons

• Ethical and regulatory challenges
  – Informed consent vs. waiver
• Investigator buy-in
• Competition with other studies
• Streamlining site/pt burden may not be enough to support recruitment
• Concerns around data quality: Monitoring, data acquisition, completeness and cleaning
• Bias in unblinded trials

Ford I and Norrie J. *NEJM* 2016
TRANSFORM Status

- 33/50 sites activated
- Considering additional high quality sites
- As of Dec 31st: 316 patients randomized
- Many sites enrolling >3 pt / mth
- Leading sites enrolling 8-10 pt / mth
- Median age 64 yo, 36% black, 41% women
Conclusion

• Current clinical trial approach is unsustainable in many respects

• Elements of pragmatism may improve clinical trial efficiencies and conduct

• TRANSFORM-HF is investigating a foundational question for HF patients through a trial incorporating pragmatic design features