



TRANSFORMing Research for Patients with Heart Failure

Robert J. Mentz, MD

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



Duke Clinical Research Institute



@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



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.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov

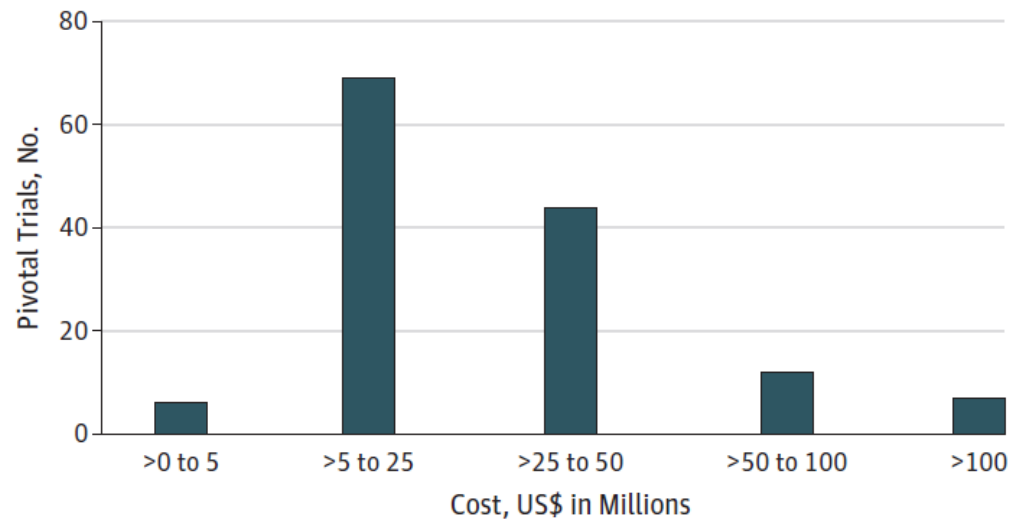
- Mostly small
- Mostly surrogate endpoints
- Huge budgets
- Setting
 - Research enterprise – “parallel universe”
 - Failure to leverage existing resources
 - “...heterogeneity in methodological approaches, including the use of randomization, blinding, and DMCs.”



Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016

- IQVIA cost tool
- 138 trials / 59 agents
- Median \$19m
- Placebo/active=\$35m

Figure. Pivotal Trial Cost Estimates of Novel Therapeutic Agents Approved by the US Food and Drug Administration From 2015 to 2016



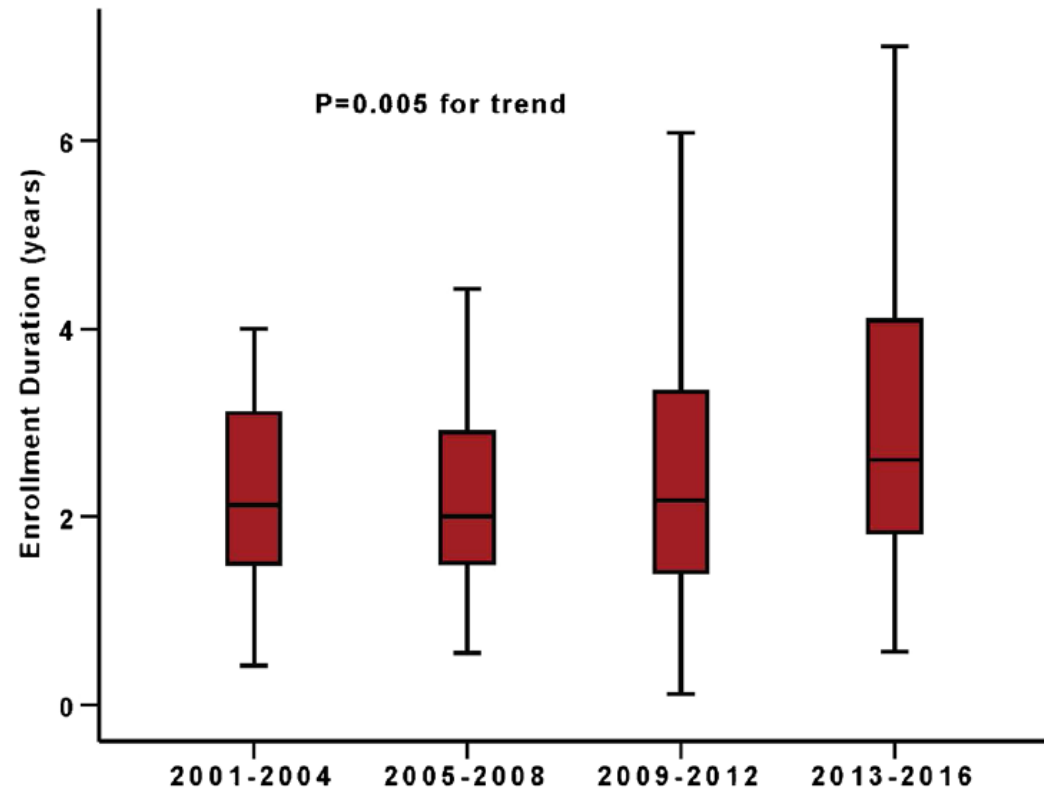
- Varies by size, randomization, control, outcomes
- Highest: PARADIGM (sacubitril/valsartan) = \$347m
- Modest portion of Drug Dev't = \$650m - \$2.8b

US Enrollment: HF as an Example



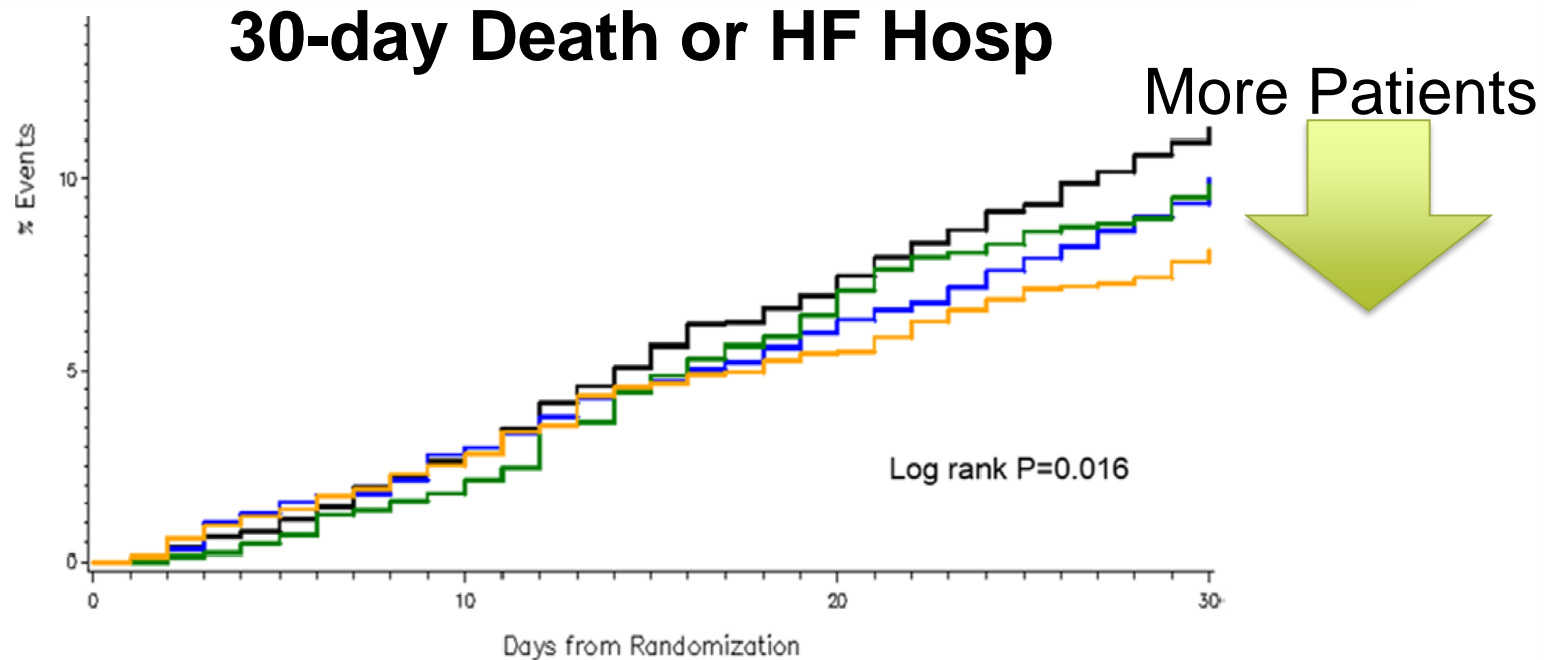
Evolving Landscape of Clinical Trials in Heart Failure: Patient Populations, Endpoint Selection, and Regions of Enrollment

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





Influence of Clinical Trial Site Enrollment on Patient Characteristics, Protocol Completion, and End Points



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



Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

Elliott M. Antman, MD

Robert A. Harrington, MD

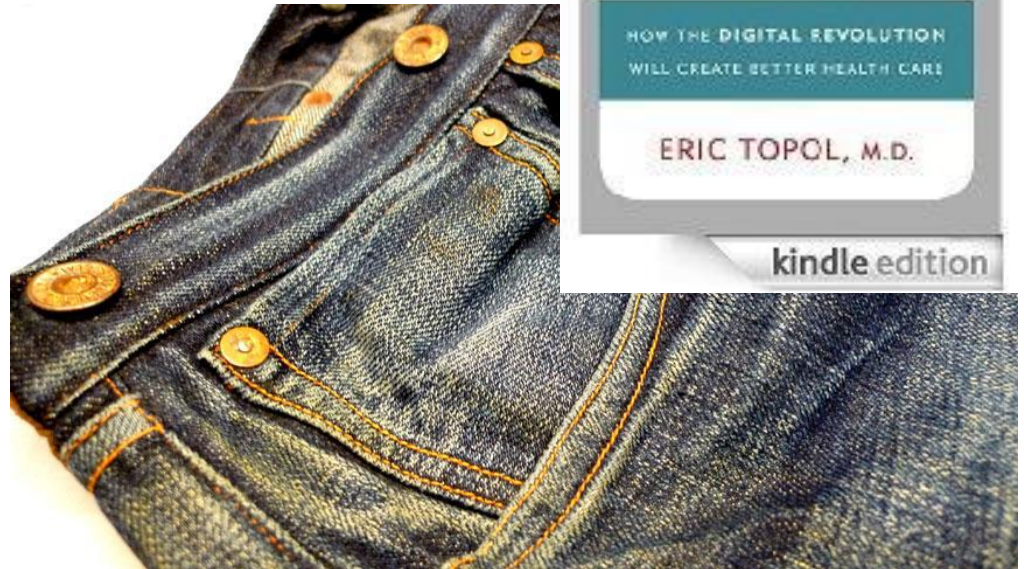
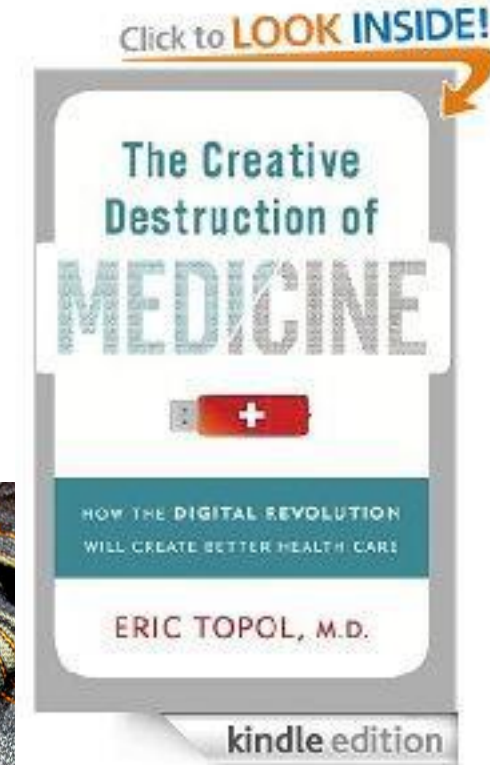
Perhaps the most exciting opportunity for CV
ers is to capitalize on the advances in systems an
tional biology that can inform first-in-human

- “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
- Valuable
- I'
 - Inexpensive
 - Innovative
- S
 - Sound Science



What are Pragmatic Trials?




Dictionary

pragmatic



prag·mat·ic

/prag'madik/ 

adjective

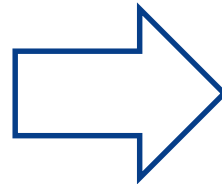
dealing with things sensibly and realistically in a way that is based on practical rather than theoretical considerations.



Making Decisions: Where do you fall on the pragmatism index?

Explanatory

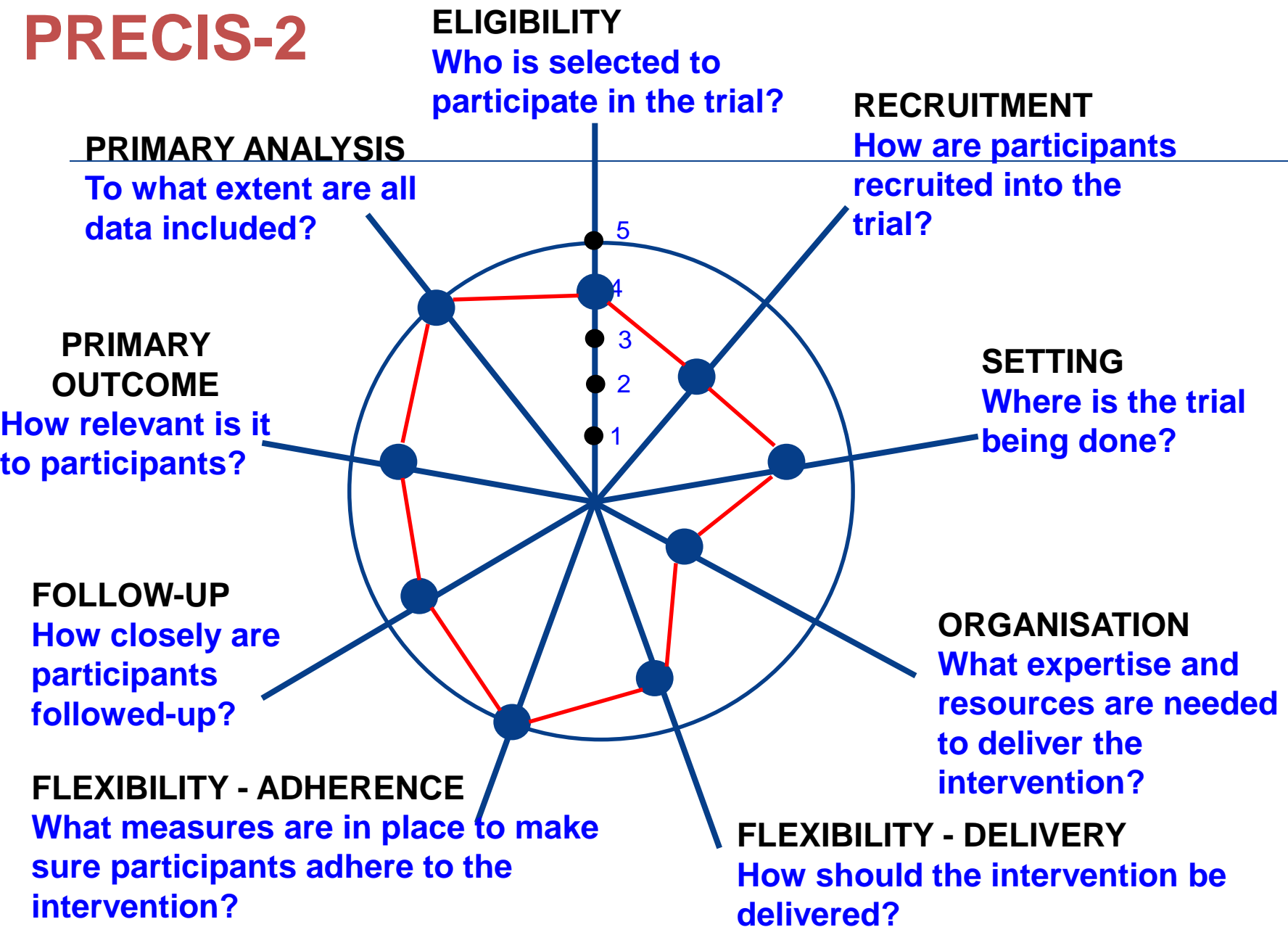
- Ideal Population
- Ideal/Perfect Care
- Blinding
- Placebo
- Coordinator Data Collection



Pragmatic

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

PRECIS-2



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 → IV furosemide → 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

	Furosemide	Torsemide	Bumetanide
Relative potency	1	2 x	40 x
Bioavailability, %	10-100 (avg 50)	80-100	80-100
Affected by food	Yes	No	Yes
Half-life, h			
Normal	1.5-2	3-4	1
Heart Failure	2.7	6	1.3
Renal Dysfunction	2.8	4-5	1.6

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

Loop Diuretic Use

CORRESPONDENCE

Research Correspondence

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 Toremide: 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**

Buggey J, et al. *Am Heart J* 2015

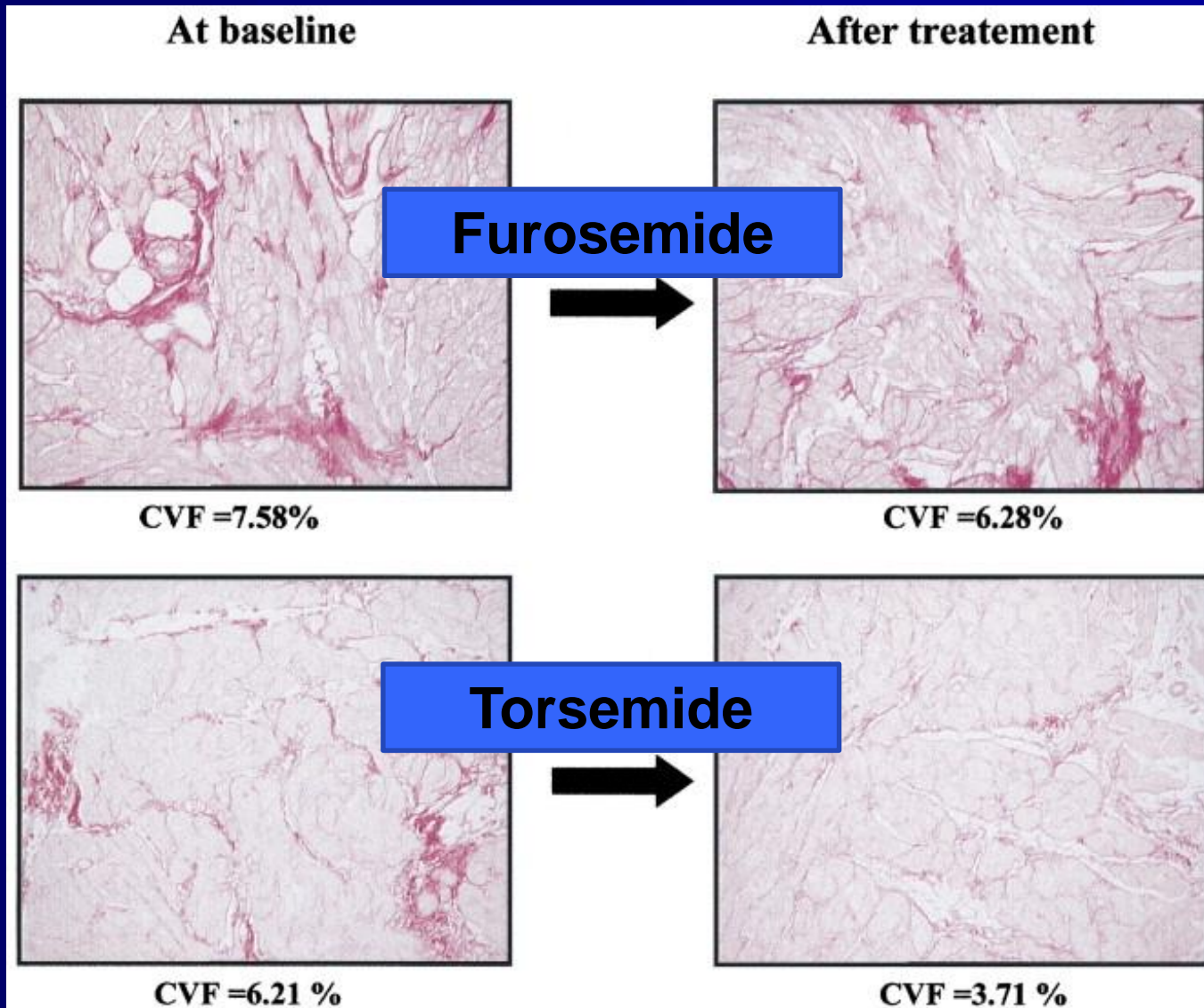
Kasama S, et al. *Heart* 2006

Murray MD, et al. *Am J Med* 2001

Cosin J, et al. *EJHF* 2002



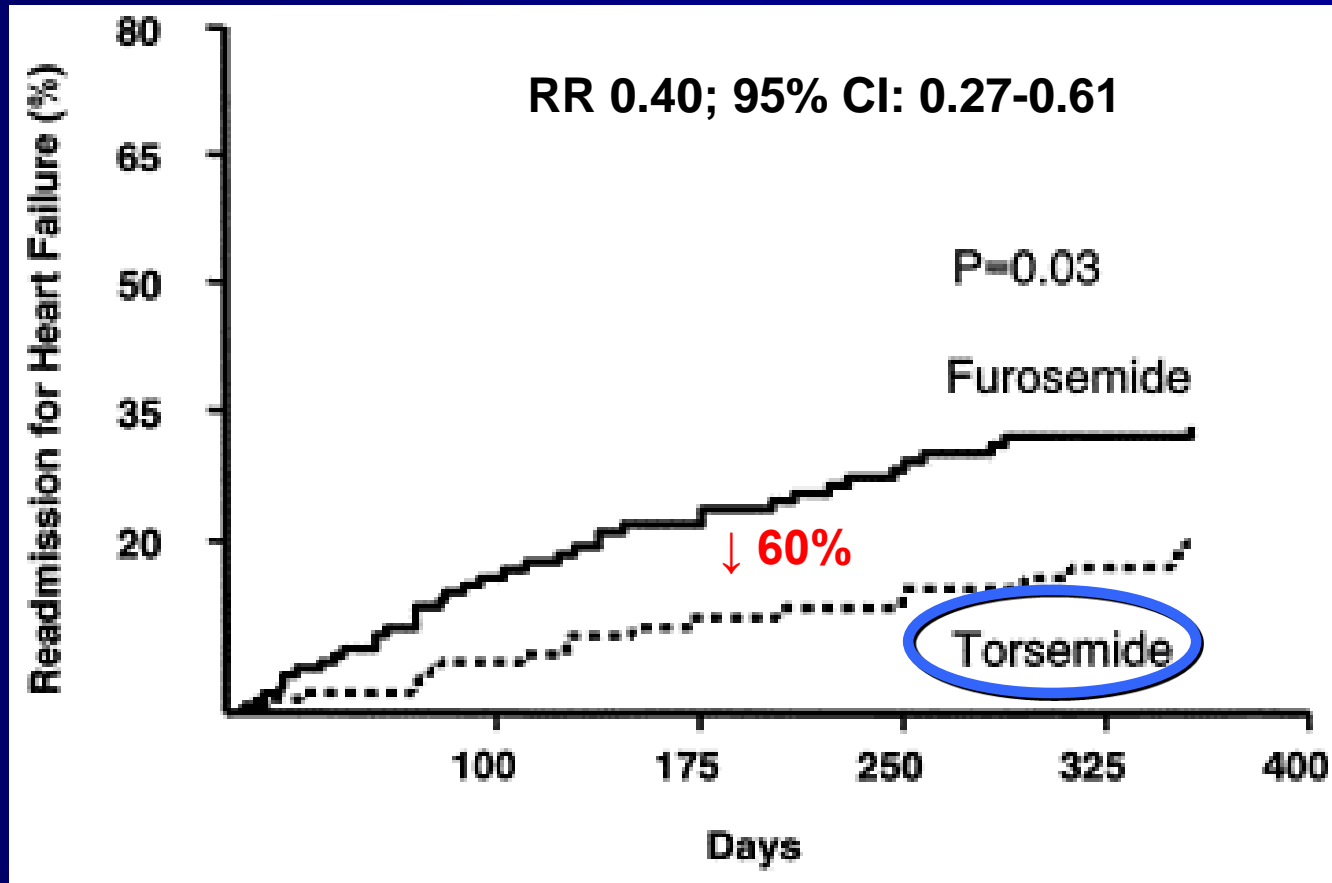
Reduced Myocardial Fibrosis



Rehospitalization Benefit

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

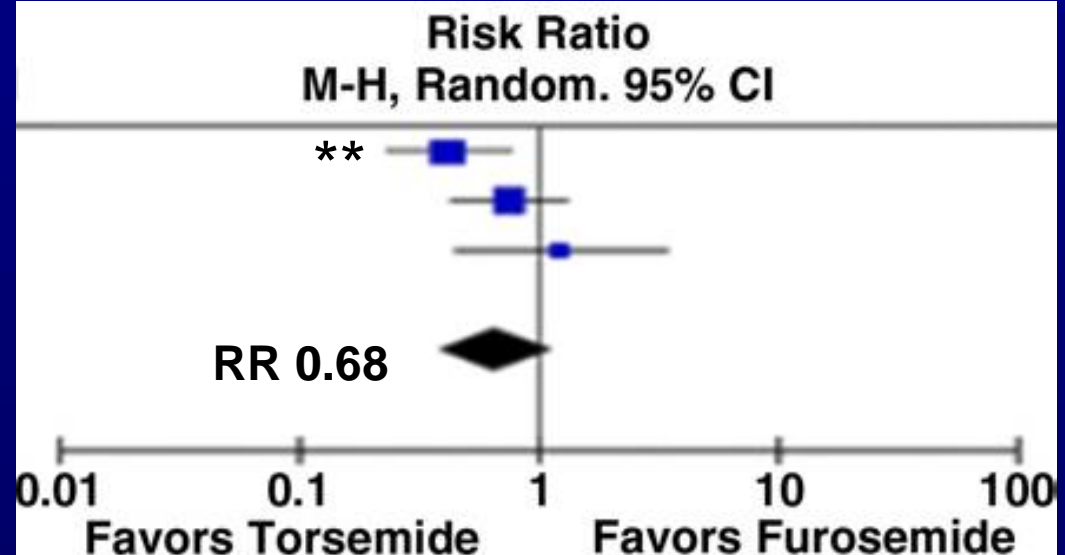
HF Hospitalization



Meta-Analysis: Mortality

Study or Subgroup	Torsemide		Furosemide		Weight	Risk Ratio M-H, Random. 95% CI
	Events	Total	Events	Total		
Cosin 2002	17	778	27	527	38.4%	0.43 [0.23, 0.77]
Murray 2001	18	113	25	121	41.2%	0.77 [0.45, 1.33]
Müller 2003	8	122	6	115	20.4%	1.26 [0.45, 3.51]
Total (95% CI)		1013		763	100.0%	0.68 [0.39, 1.18]
Total events	43		58			
Heterogeneity: Tau² = 0.11; Chi² = 3.87, df = 4 (P = 0.14); I² = 48%						
Test for overall effect: Z = 1.38 (P = 0.17)						

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

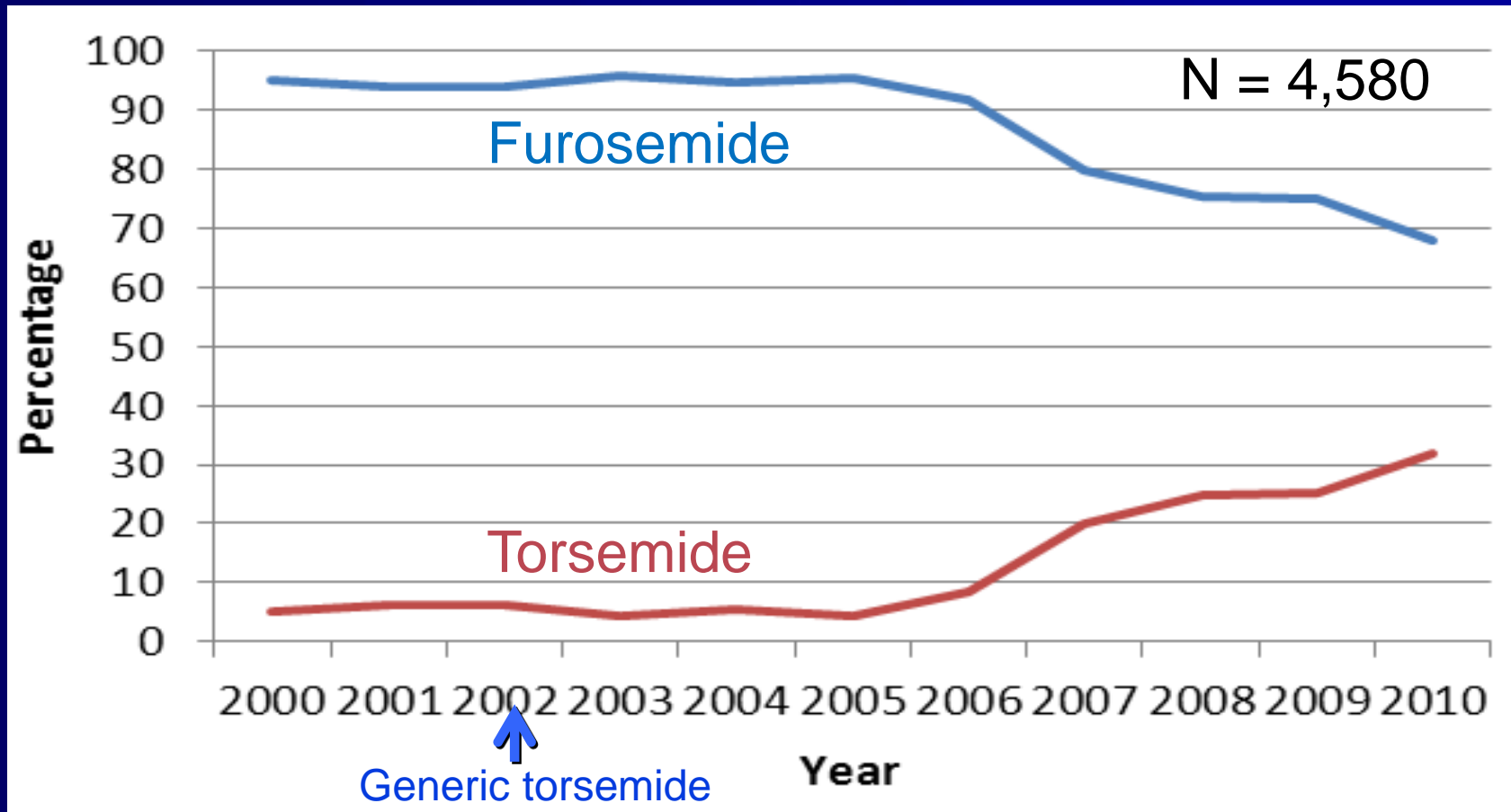


Guidelines: Loop Diuretics

- 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



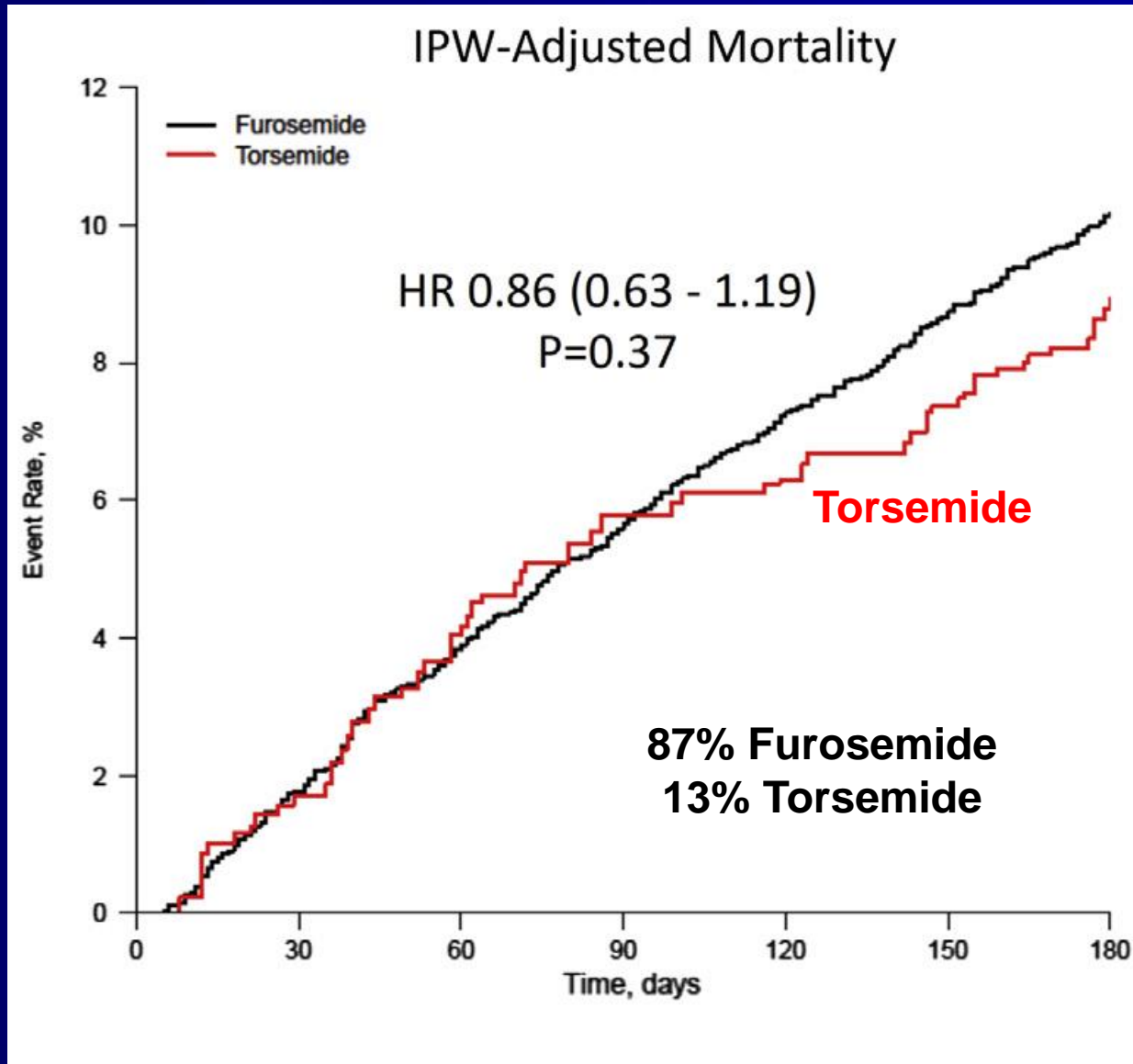
- Furosemide: 86% (n=3,955)
- Torsemide: 14% (n=625)

Baseline Characteristics: Duke

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

Presented as median (IQR) or %.

ASCEND-HF: Torsemide Use



A reappraisal of loop diuretic choice in heart failure patients

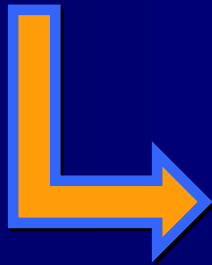


Jonathan Buggey, MD,^a Robert J. Mentz, MD,^{a,b} Bertram Pitt, MD,^c Eric L. Eisenstein, DBA,^b Kevin J. Anstrom, PhD,^b Eric J. Velazquez, MD,^{a,b} and Christopher M. O'Connor, MD^{a,b} *Durham, NC and Ann Arbor, MI*

“...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



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FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE

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

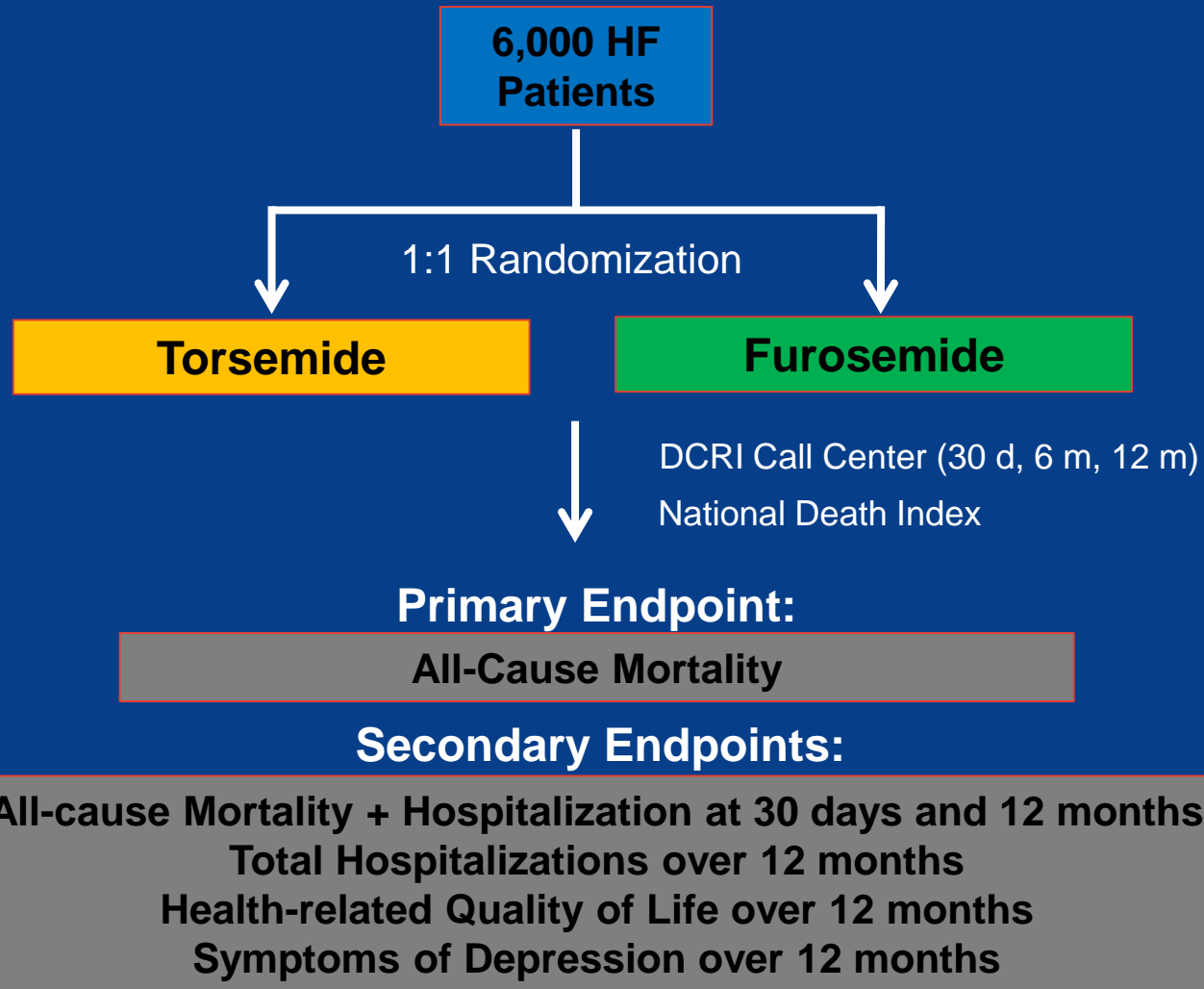
Inclusion Criteria

- **Either** LVEF \leq 40% **or** \uparrow (NT-pro)BNP
- Age \geq 18 years
- Hospitalized HF patient
- Outpatient plans for daily loop
- Signed inform consent

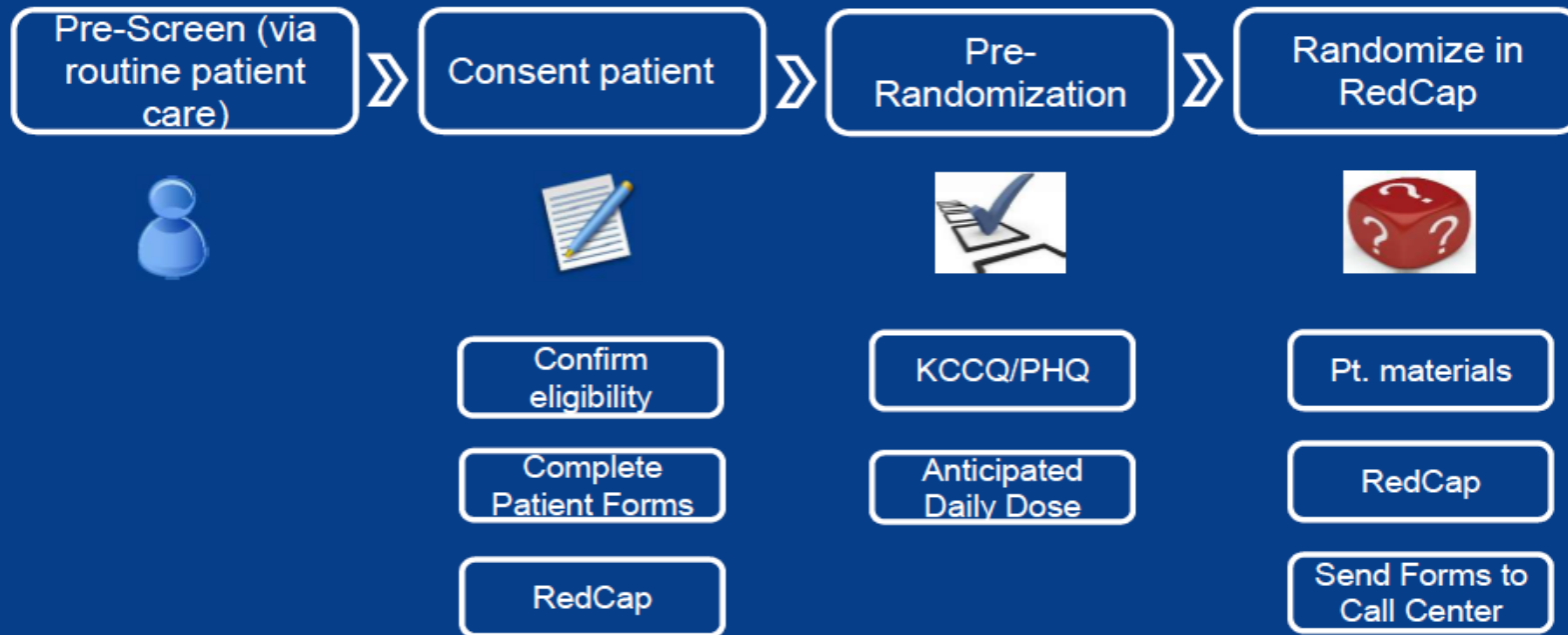
Exclusion Criteria

- 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

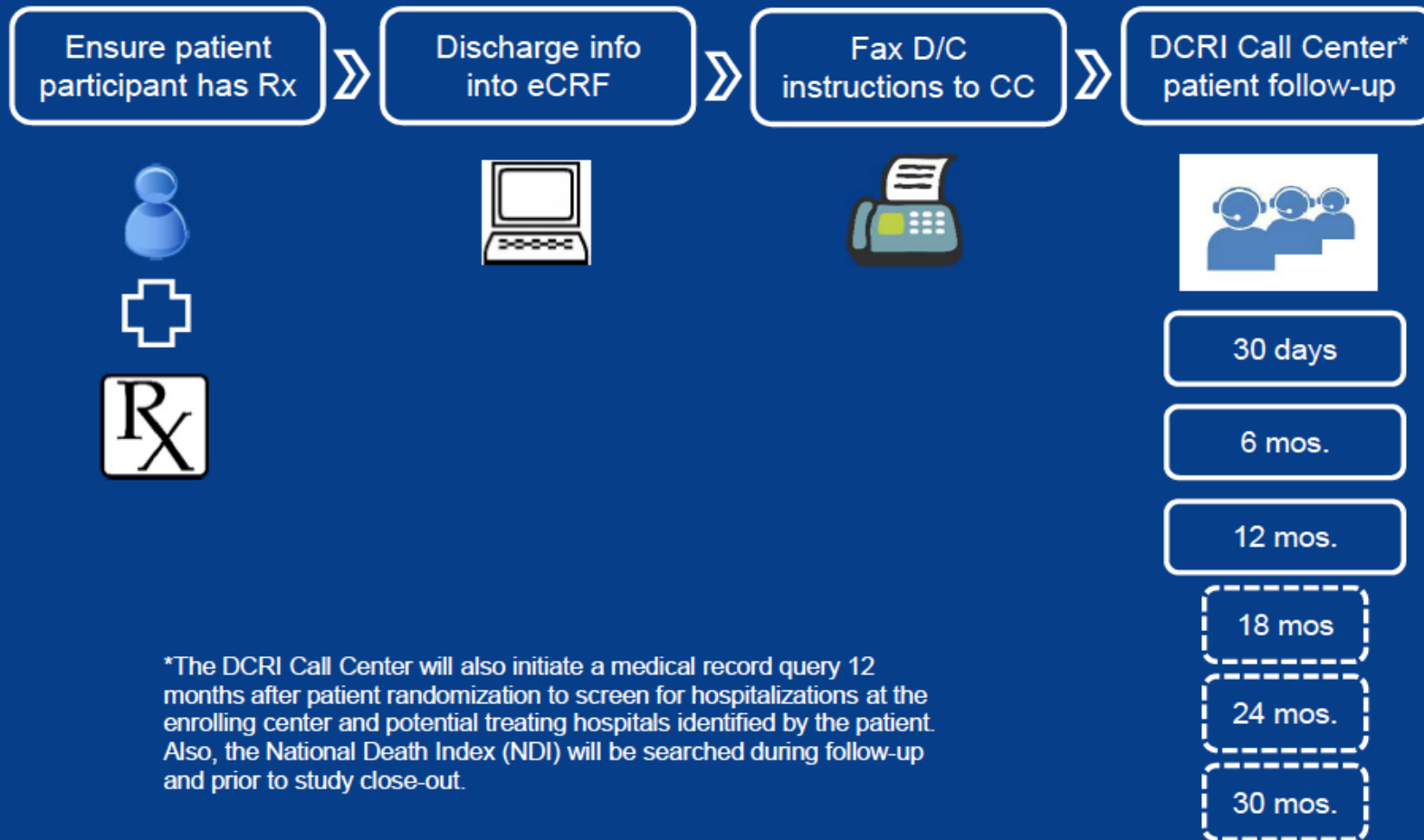
The TRANSFORM-HF Trial



Pre-Screen/Screen/Randomization



Discharge and Call Center



*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

ELIGIBILITY

Who is selected to participate in the trial?

RECRUITMENT

How are participants recruited into the trial?

PRIMARY ANALYSIS

To what extent are all data included?

PRIMARY OUTCOME

How relevant is it to participants?

SETTING

Where is the trial being done?

FOLLOW-UP

How closely are participants followed-up?

ORGANISATION

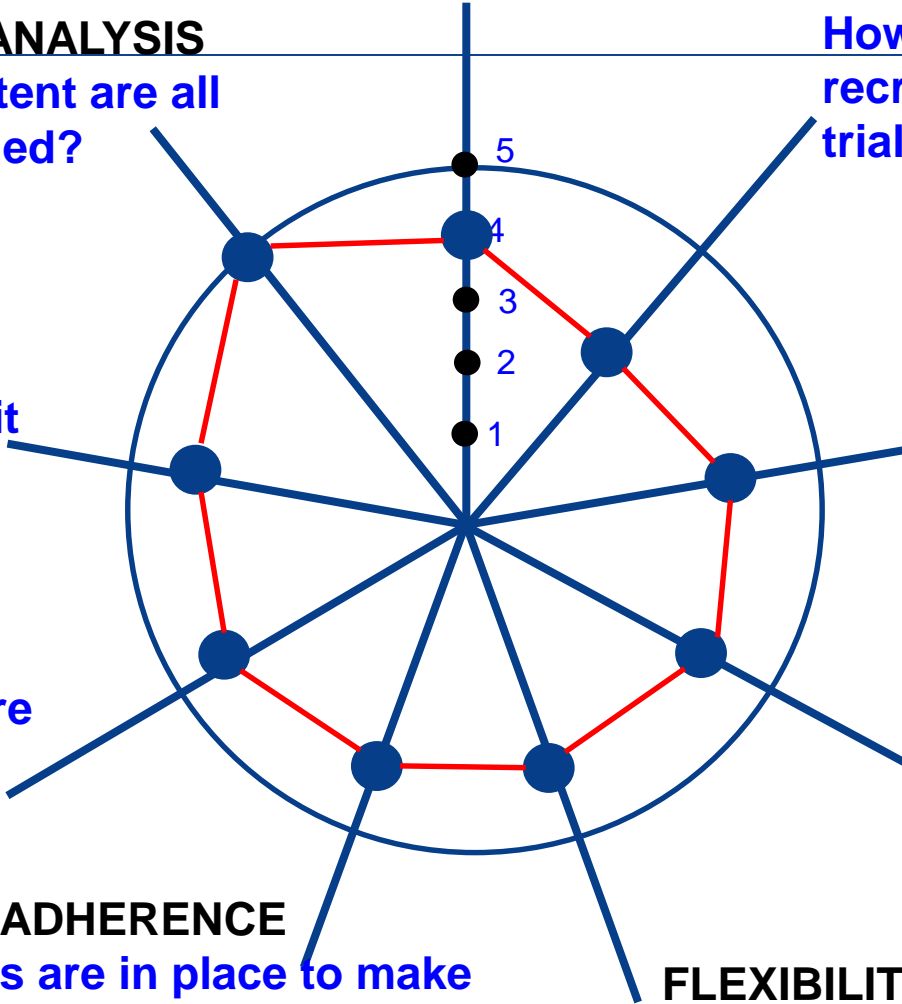
What expertise and resources are needed to deliver the intervention?

FLEXIBILITY - ADHERENCE

What measures are in place to make sure participants adhere to the intervention?

FLEXIBILITY - DELIVERY

How should the intervention be delivered?



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



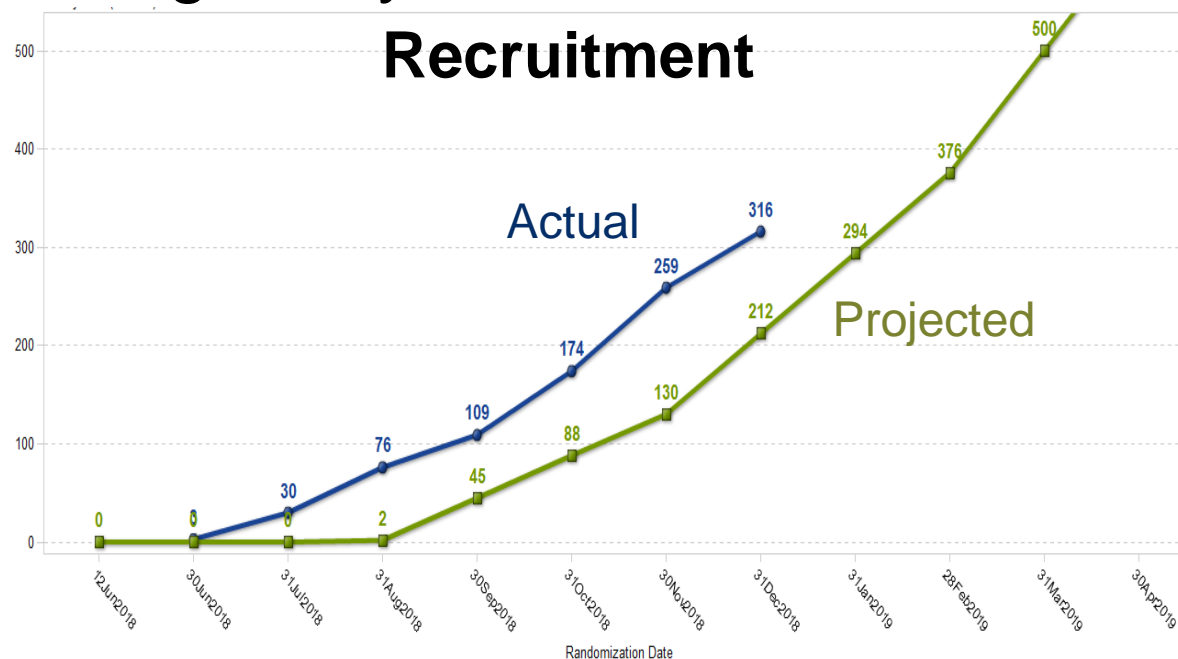
Limitations / Cons

- 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

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