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Opportunities for LSTs

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The NEW ENGLAND JOURNAL of MEDICINE

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

Karl Swedberg, M.D., Ph.D., James B. Young, M.D., Inder S. Anand, M.D., Sunfa Cheng, M.D., Akshay S. Desai, M.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Christopher O'Connor, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., Yan Sun, M.S., Michal Tendera, M.D., and Dirk J. van Veldhuisen, M.D., Ph.D., for the RED-HF Committees and Investigators*

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PEPSI
Coca-Cola

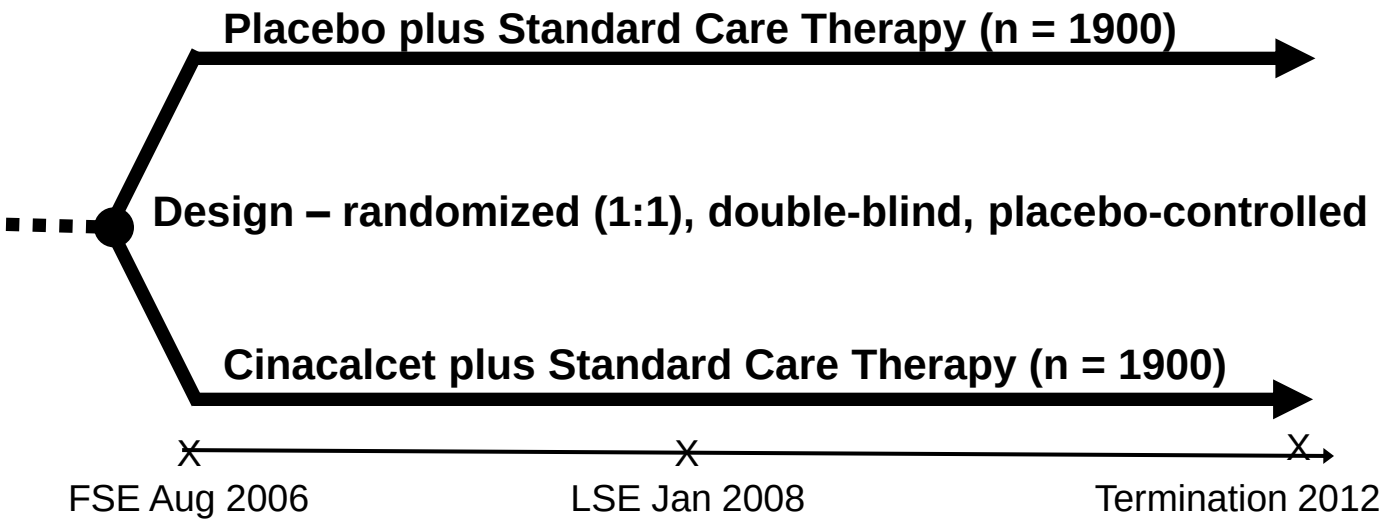
Topics to Address Today

- Why do we design trials the way we do
- EVOLVE as an example of *not* an LST
- REVOLVE as a hypothetical LST
- Areas of opportunity

EVOLVE™

Study Population

- Adult
- Hemodialysis
- iPTH ≥ 300 pg/mL
- Ca ≥ 8.4 mg/dL
- Ca x P ≥ 45 mg^2/dL^2



Primary Endpoint

Time to composite event:
- All-cause mortality
- Myocardial infarction
- Hospitalization for unstable angina
- Heart failure
- Peripheral vascular event

Secondary Endpoints

- Clinical bone fracture
- Parathyroidectomy
- Cardiovascular mortality
- Stroke
- Individual components of primary endpoint

Standard Care Therapy:

- Vitamin D sterols
- Phosphate binders

FSE = first subject enrolled; LSE = last subject enrolled.

Chertow GM, et al. *Clin J Am Soc Nephrol.* 2007;2:898-905.

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EVOLVE™ Study Objectives

- Primary: To determine the efficacy of a secondary HPT treatment regimen including cinacalcet compared to a treatment regimen not including cinacalcet (placebo) on the composite of time to all-cause mortality or first non-fatal cardiovascular event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event)

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EVOLVE™ Study Objectives (continued)

- Secondary: To assess the effects of a secondary HPT treatment regimen including cinacalcet versus a treatment regimen not including cinacalcet, by determining:
  - All-cause mortality
  - Cardiovascular mortality
  - Fatal and non-fatal MI
  - Fatal and non-fatal hospitalization for unstable angina
  - Fatal and non-fatal HF event
  - Fatal and non-fatal peripheral vascular event
  - Fatal and non-fatal stroke
  - Bone fracture
  - Parathyroidectomy
  - The safety and tolerability of cinacalcet

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EVOLVE™ Study Objectives (continued)

- Other: The study also assessed the effects of cinacalcet on:
  - The composite event comprising of cardiovascular death, MI, hospitalization for unstable angina, or HF
  - Achievement of NKF-K/DOQI™ Metabolism and Disease recommended targets for intact parathyroid hormone (PTH), serum Ca x P, calcium, and phosphorus levels
  - Percent change from baseline in PTH, Ca x P, serum calcium, and serum phosphorus
  - Health Resource Utilization per subject follow-up time including number and duration of all-cause and cause-specific hospitalizations
  - Assess the patient reported outcomes following a study event using the EQ-5D

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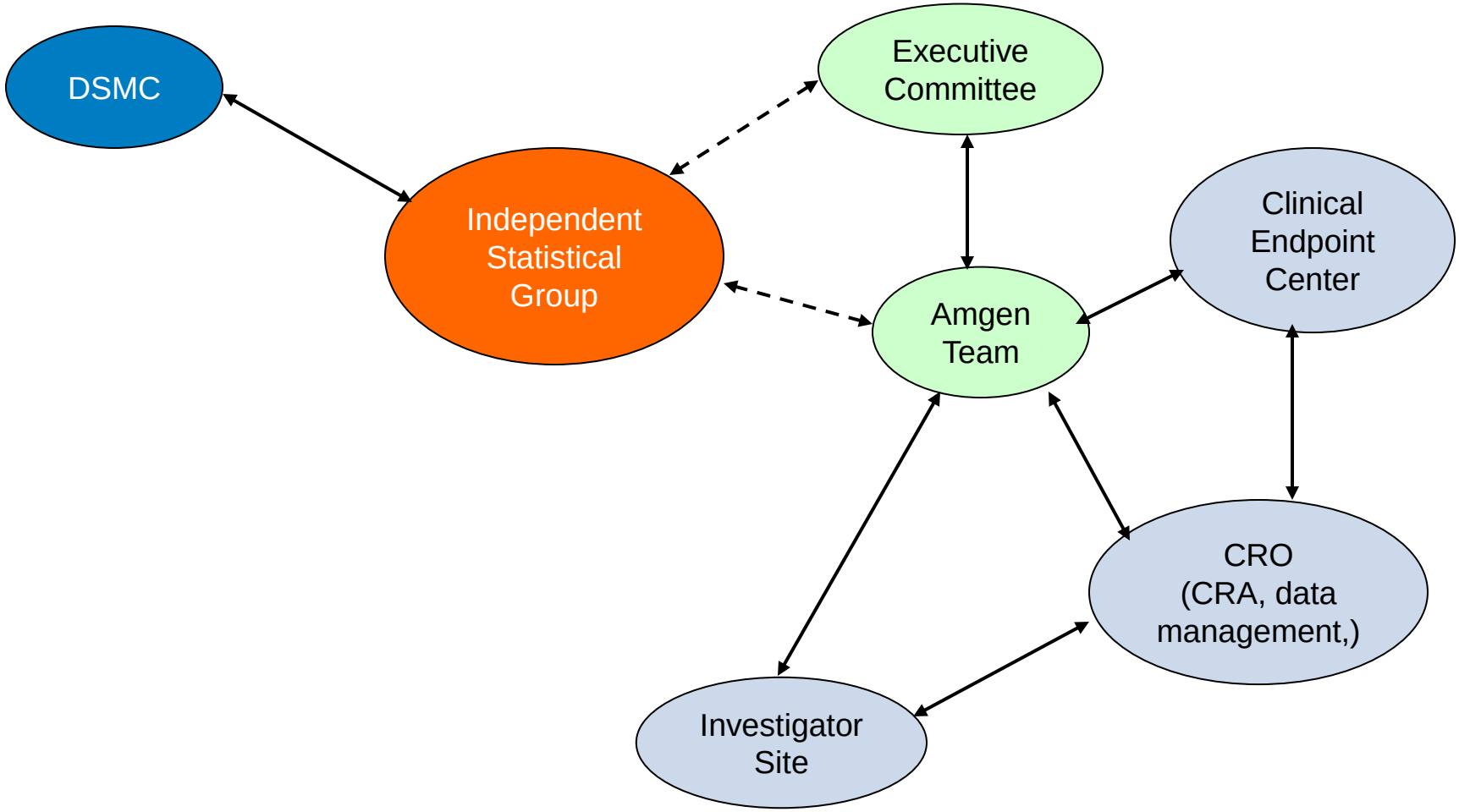
Committees



DSMC – Data Safety Monitoring Committee

List of Potential Baseline Covariates (1)

- Age (years) at randomization
- Gender (male, *female)*
- Race (*white*, black, other*)*
- BMI (kg/m^2)
- Blood pressure - systolic/diastolic (mmHg)
- Geographic region (*US, Canada, Latin America, Europe, Russia, Australia)*
- History of (*yes*/no*):*
  - myocardial infarction
  - heart failure
  - coronary artery disease
  - family history of coronary artery disease
  - cardiac arrhythmia
  - hypertension
  - other cardiac disease (as defined by valvular heart disease and angina)
  - stroke
  - transient ischemic attack
  - peripheral vascular disease
  - revascularization
  - endocrine disorder
    - dyslipidemia
    - diabetes
    - parathyroidectomy
  - bone fracture
  - retinopathy

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List of Potential Baseline Covariates (2)

- Dialysis vintage (years)
- Dialysate calcium (mmol/L)
- Type of vascular access (*natural fistula*, graft, permanent catheter, other)
- Vitamin D use (*yes*/no*)*
- Phosphate binder type (*calcium-containing*, magnesium-containing, aluminum-containing, Sevelamer or lanthanum carbonate)
- Serum calcium corrected for albumin (mg/dL)
- Serum phosphorus (mg/dL)
- Ca x P $[(mg/dL)^2]$
- PTH (pg/mL)
- BALP (µg/L)
- NTx (nmol/L)

List of Potential Baseline Covariates (3)

- Hemoglobin (g/dL)
- Statin use (*yes*/no*)*
- LDL (mg/dL)
- HDL (mg/dL)
- Total cholesterol (mg/dL)
- Albumin (g/dL)
- Tobacco use (*never*, former, current*)*
- PRO scores (for PRO endpoints only)

Why aren't more studies designed as LSTs?

- Availability of eligible patients, sites, investigators
- Time
- Cost
- Resources
- Optimism around magnitude of treatment effect

Simplicity of design and conduct enables size

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Why aren’t more studies designed as LSTs?

- Need for safety data collection
- Study execution and data collection to meet regulatory requirements
- Interest in more than a single endpoint
- Interest in additional/potential questions

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Advantages and limitations to Consider

	Key parameters	Small study	MCT	LST
1	Complex intervention			
2	Complex endpoint			
	Complex/Precise follow-up			
	Small anticipated treatment effect			
3	Small population			
	Precisely-defined population			
	Expected qualitative interaction			

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When could LSTs be used: 3 key conditions for conducting a LST

1. **Although modest, the anticipated effect size will be considered sufficient for securing a new indication**
   - The aim of LSTs is to detect a meaningful but modest effect on one unambiguous and readily ascertained endpoint (eg death, hospitalization)
2. **If the results confirm the primary hypothesis, no additional analyses will be needed**; in particular:
   - Subgroup analyses, to search for qualitative and quantitative interactions will not be performed
   - Post-hoc explanatory analyses will not be performed
3. **The study will only be expected to minimally inform the safety profile of the therapeutic intervention**

These conditions can often be fulfilled in the context of a post-approval study

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Anatomy of a MCT

	EVOLVE	TREAT	RED-HF
Population	Dialysis	CKD-ND, Type II Diabetic	Heart Failure
Subjects Enrolled	3883	4038	2278
Sites Participating	458	623	619
Countries Participating	22	24	32
Study Duration (years)	5.5	5	6.25
CRF pages*	1,320,077	791,000	540,000
Unique CRF pages /subject	148	178	217
Queries	800,741	116,000	50,802
Potential Endpoints Reported	6,657	4200	3000
Type of Investigational Product	Tablet	Injection	Injection
Doses of IP administered	3,748,241	140,535	61,921

* EVOLVE collected data in an electronic data capture system via eCRF
TREAT and RED-HF used paper case report forms for data collection

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RCTs could be simplified

- **The main barrier for simplifying trials is the desire to collect a large amount of data to address additional or potential questions**
  - Desire to be able to assess the effects of the intervention in different subgroups
  - Desire to be able to conduct explanatory analyses, if needed
  - Willingness to be able to answer all questions from Regulatory agencies
- **Trials could often be simplified if agreement …**
  - Not to ask *a posteriori* for assessment of qualitative and quantitative interactions
  - Not to ask *a posteriori* for explanatory analyses
  - To allow for less extensive collection of AEs after initial approval
  - To be comfortable with limited on-site monitoring

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Dialysis Offers an “Ideal” Venue for LST

- Grievous illness with significant unmet need
  - Even treatments with modest effect will be important for this patient population
- Population seen by HCP TIW
  - Duration of enrollment can be minimized
- High event rate
  - Annual mortality ~20% in the US
  - Allows for relatively short studies
- Almost near complete data-collection in the US
  - Virtually no Lost to F/u
  - Possibility to use EMR for data collection

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REVOLVE- A Hypothetical LST

REVOLVE
A Hypothetical LST

Objective: To determine the efficacy of a secondary HPT treatment regimen including cinacalcet compared to a treatment regimen not including cinacalcet (placebo) on time to all-cause mortality

Study Population

- Adult
- Hemodialysis
- iPTH ≥ 600 pg/mL
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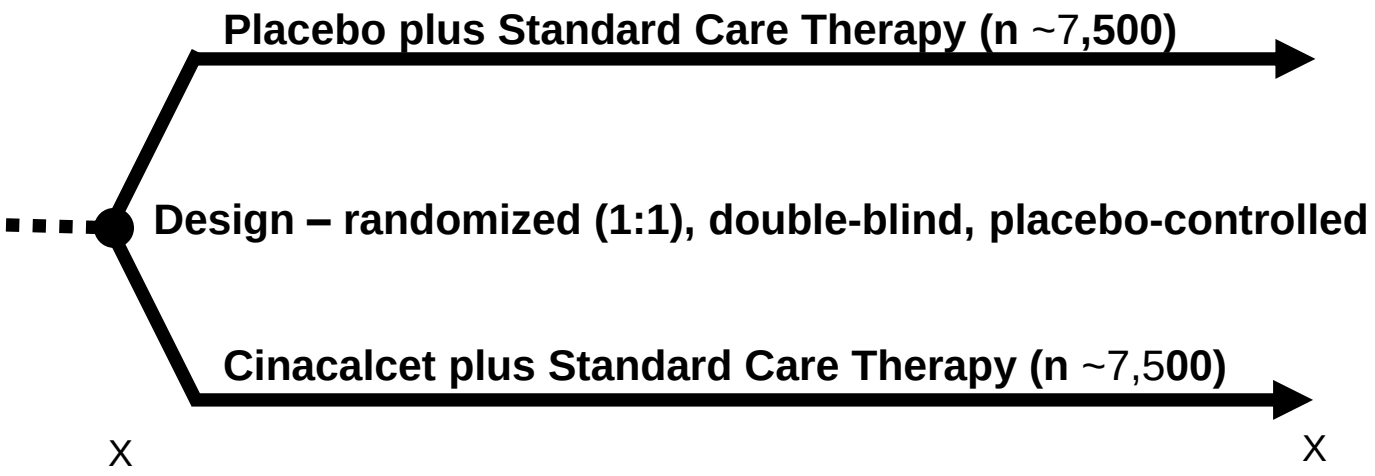

Primary Endpoint

Time to all-cause mortality

Mock Results

	Cinacalcet (N=1948)	Placebo (N=1935)	Hazard Ratio*	P value
Primary endpoint	N/A	N/A	N/A	N/A
Death	XX (aa)	YY (bb)	.AA (BB, CC)	.ZZ
CHF***	N/A	N/A	N/A	N/A
MI***	N/A	N/A	N/A	N/A
HAMI	N/A	N/A	N/A	N/A
Secondary endpoints				
CV death	N/A	N/A	N/A	N/A
Stroke	N/A	N/A	N/A	N/A
Bone fracture	N/A	N/A	N/A	N/A
Parathyroidectomy	N/A	N/A	N/A	N/A

EVOLVE vs REVOLVE Facts and Hypothetical Estimates

	EVOLVE	REVOLVE
How many inclusion/exclusion criteria	17	4
How many countries	22	~35
How many sites	458	~800
How many CRFs per patient	340	~5
How many CRFs in total	1.320 M	~75,000
How many DCFs	800,741	~45,000
How many endpoints submitted	6,657	~7,500
How long from FPE to LPLV	5.5 years	~6-7 years

Summary

- Large trials are enabled by simplicity of design and conduct, without which large trials would not be feasible given time, cost and resource considerations.
- LSTs are appropriate in some, but not all settings. Predicates for LSTs may include
  - Moderate sized, but clinically important treatment effect
  - Prevalent disease
  - In the context of drugs/biologics
    - Post-approval
    - One time intervention or if chronic, easily administered, non-titratable intervention
  - Consequences of reduced monitoring, data collection accepted by all

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