OHDSI – A global opportunity to produce reliable evidence that improves health for patients around the world

Patrick Ryan, PhD

Johnson & Johnson

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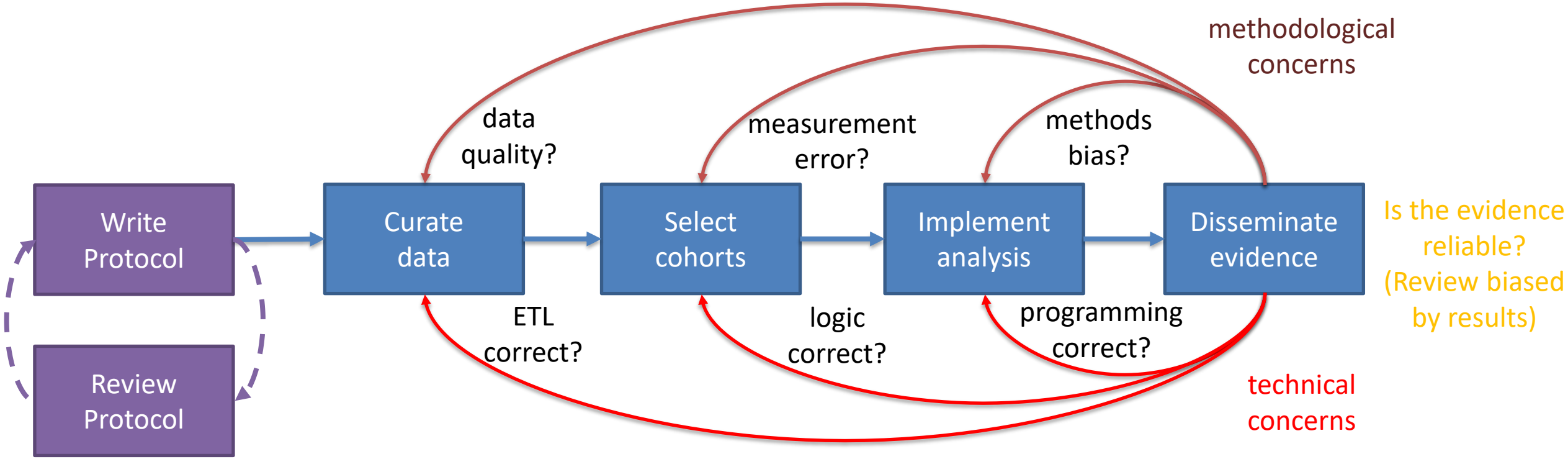
Current status quo in observational research makes it challenging to build trust in evidence

Does the study provide an unbiased effect estimate?
Are the findings generalizable to the population of interest?



Can the study be fully reproduced?
Does the analysis actually do what the protocol said it would do?

Imagine you or a loved one is diagnosed with a disease and offered two alternative treatments A and B. Both treatments are expected to reduce serious complications due to the disease, but may have small risk of other serious adverse events. No randomized clinical trials directly compare those two treatments.

You have a choice:

1. Wait to make your treatment choice until a direct head-to-head RCT is conducted
2. Rely on 'expert opinion' and indirect comparisons between RCTs (which are inconclusive about the comparative benefits and risks)
3. Learn from real-world evidence, compare with existing knowledge, and then make your treatment decision

Real-world evidence from an observational database study

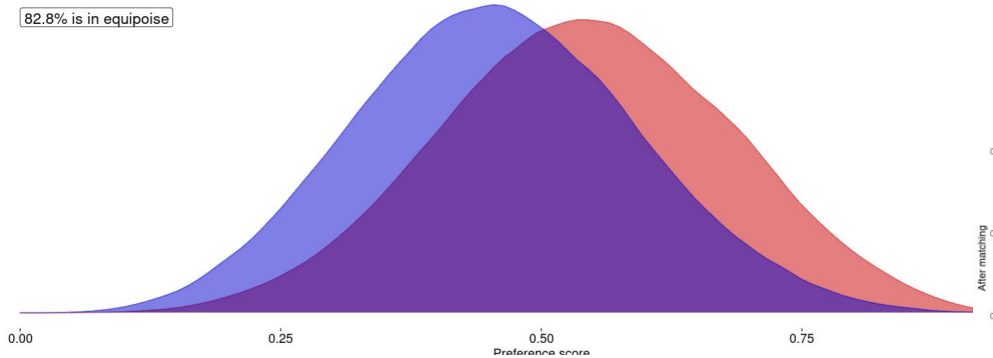
Comparative new user cohort design, propensity score adjustment, Hazard ratio from Cox model applied to a large insurance claims database

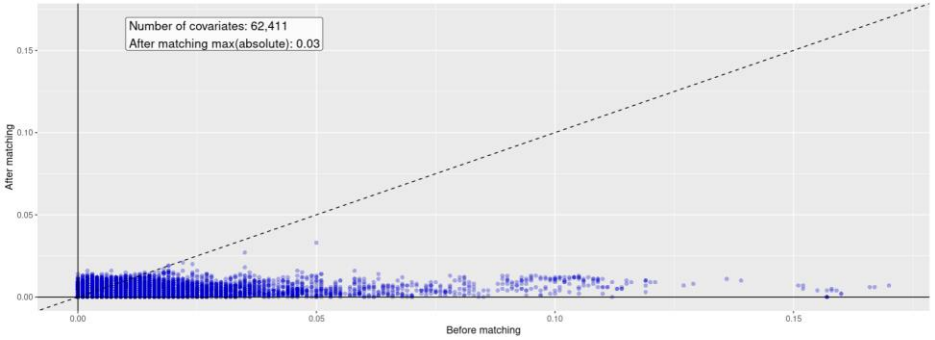
Treatment A vs Treatment B	Relative risk
Benefit	1.33 (1.05 – 1.72)
Risk	3.55 (2.12-6.23)

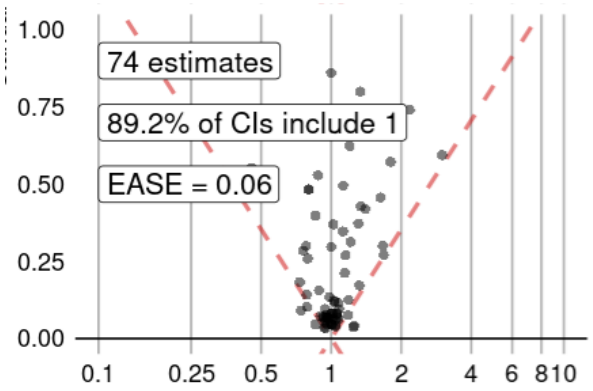
Real-world evidence with supporting diagnostics

Treatment A vs Treatment B	Relative risk
Benefit	1.33 (1.05 – 1.72)
Risk	3.55 (2.12-6.23)

Target subjects	Comparator subjects	Target years	Comparator years	Target events	Comparator events	Target IR (per 1,000 PY)	Comparator IR (per 1,000 PY)	MDRR
168,541	169,189	137,177	150,711	707	655	5.15	4.35	1.16

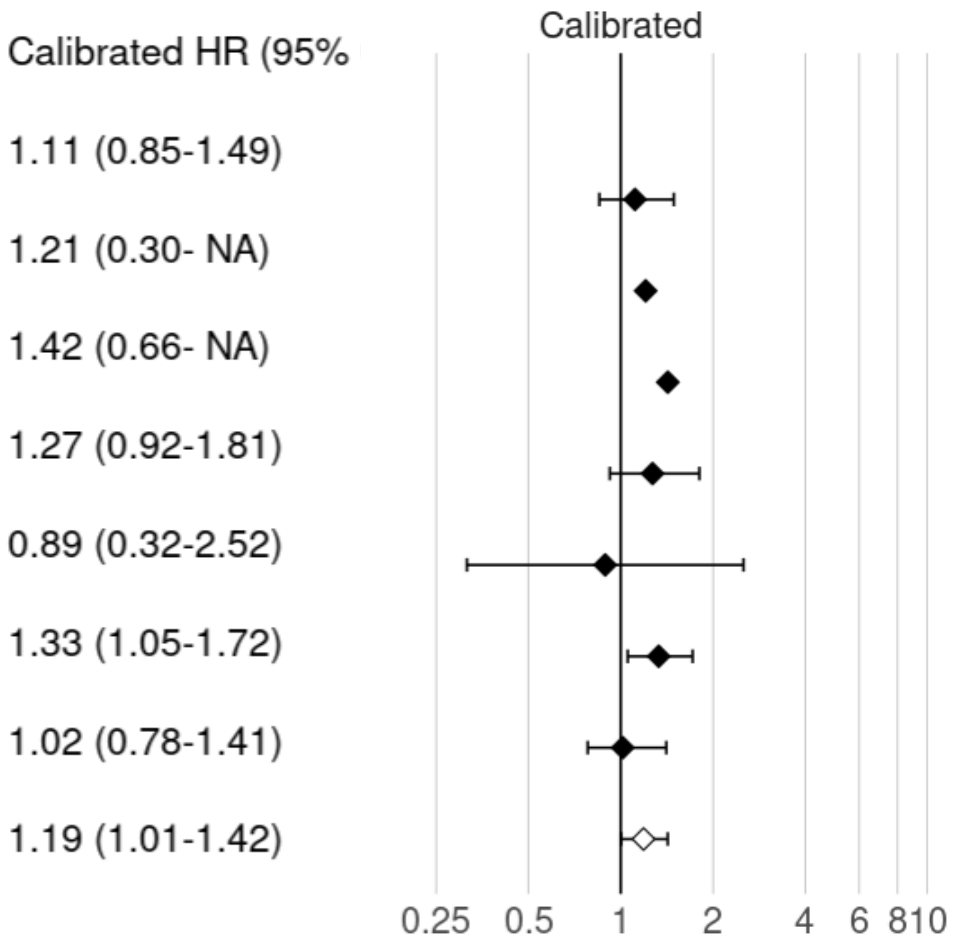






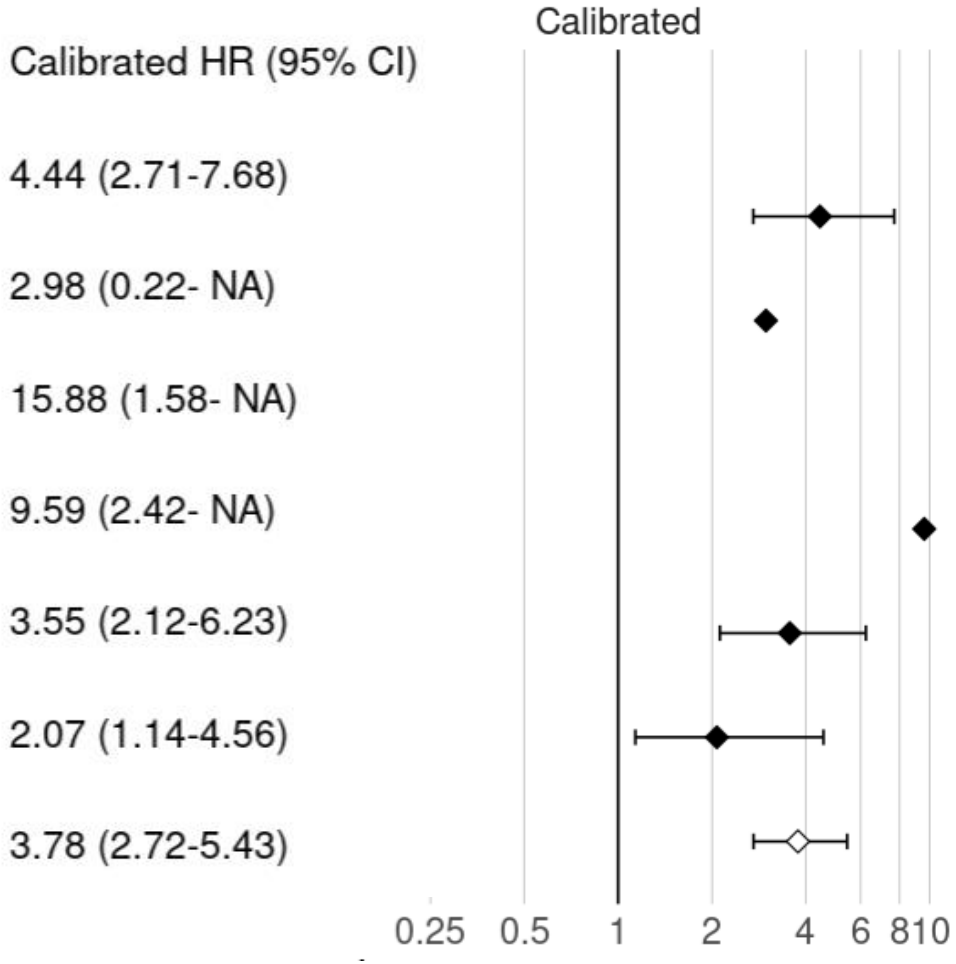
Real-world evidence across a network of databases

Benefit



Database 1
Database 2
Database 3
Database 4
Database 5
Database 6
Database 7
Meta-analysis

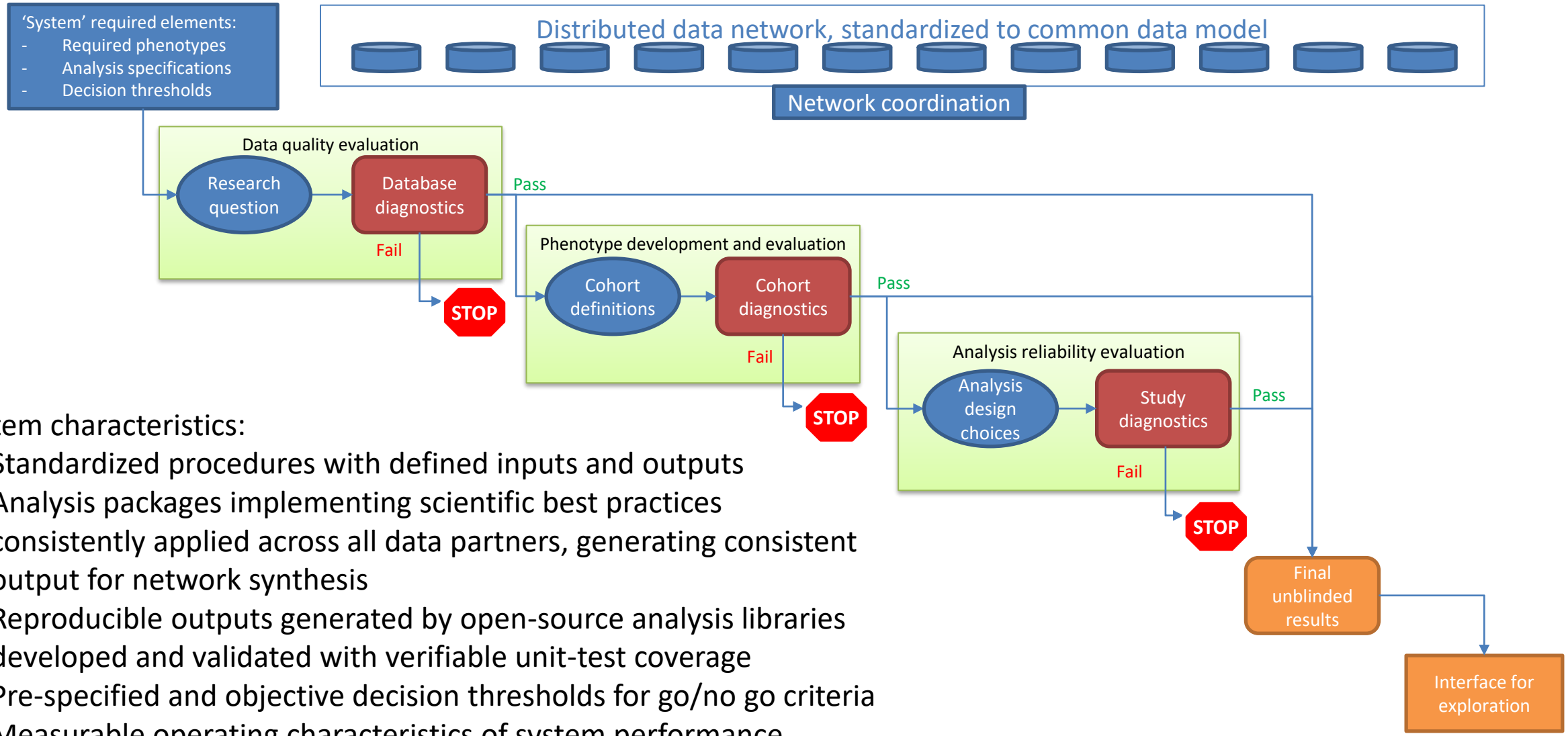
Risk



Desired attributes for reliable evidence

Desired attribute	Question	Researcher	Data	Analysis		Result
Repeatable	Identical	Identical	Identical	Identical	=	Identical
Reproducible	Identical	Different	Identical	Identical	=	Identical
Replicable	Identical	Same or different	Similar	Identical	=	Similar
Generalizable	Identical	Same or different	Different	Identical	=	Similar
Robust	Identical	Same or different	Same or different	Different	=	Similar
Calibrated	Similar (controls)	Identical	Identical	Identical	=	Statistically consistent

Engineering open science systems that build trust into the real-world evidence generation and dissemination process



System characteristics:

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- Analysis packages implementing scientific best practices consistently applied across all data partners, generating consistent output for network synthesis
- Reproducible outputs generated by open-source analysis libraries developed and validated with verifiable unit-test coverage
- Pre-specified and objective decision thresholds for go/no go criteria
- Measurable operating characteristics of system performance

Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND)

Patrick Ryan, Martijn Schuemie, Marc Suchard
on behalf of the LEGEND team

OHDSI Symposium

12 October 2018

What's in a guideline?

Clinical Practice Guideline: Executive Summary

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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56 pages containing **106** recommendations

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12 Oct 2018

Table 18. Oral Antihypertensive Drugs

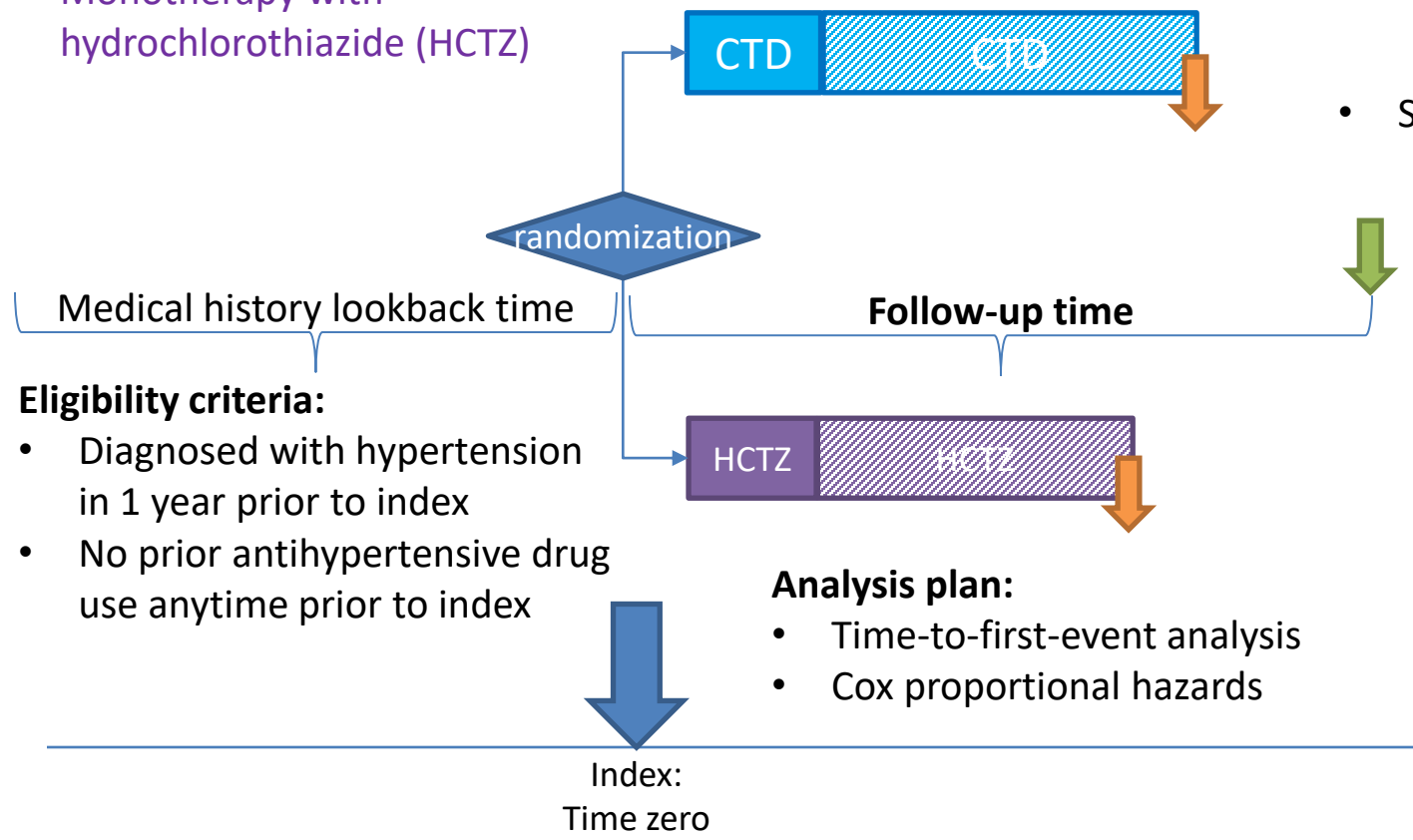
Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
Thiazide or thiazide-type diuretics	Chlorthalidone	12.5–25	1	• Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD. • Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. • Use with caution in patients with history of acute gout unless patient is on uric acid–lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Indapamide	1.25–2.5	1	
	Metolazone	2.5–10	1	
ACE inhibitors	Benazepril	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ACE inhibitors. • Avoid in pregnancy.
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–10	1 or 2	
	Trandolapril	1–4	1	
ARBs	Azilsartan	40–80	1	• Do not use in combination with ACE inhibitors or direct renin inhibitor. • There is an increased risk of hyperkalemia in CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. • Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
CCB—dihydropyridines	Amlodipine	2.5–10	1	• Avoid use in patients with HF*r*EF; amlodipine or felodipine may be used if required. • They are associated with dose-related pedal edema, which is more common in women than men.
	Felodipine	5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	5–20	1	
	Nifedipine LA	60–120	1	
	Nisoldipine	30–90	1	
CCB—nondihydropyridines	Diltiazem SR	180–360	2	• Avoid routine use with beta blockers because of increased risk of bradycardia and heart block. • Do not use in patients with HF*r*EF. • There are drug interactions with diltiazem and verapamil (*CYP3A4* major substrate and moderate inhibitor).
	Diltiazem ER	120–480	1	
	Verapamil IR	40-80	3	
	Verapamil SR	120–480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100–480	1 (in the evening)	

What would the 'target trial' look like to compare efficacy of two initial therapies?

12 Oct 2018

Treatment strategies:
- Monotherapy with chlorthalidone (CTD)
- Monotherapy with hydrochlorothiazide (HCTZ)

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect



Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure
- Safety:
  - Known or potential adverse events, e.g.
  - Acute renal failure
  - Angioedema
  - Cough
  - Diarrhea
  - Fall
  - Gout
  - Headache
  - Hyperkalemia
  - Hyponatremia
  - Hypotension
  - Impotence
  - Syncope
  - Vertigo

What is the Diuretic Comparison Project study design?

12 Oct 2018

Treatment strategies:

- Monotherapy with chlorthalidone (CTD)
- Monotherapy with hydrochlorothiazide (HCTZ)

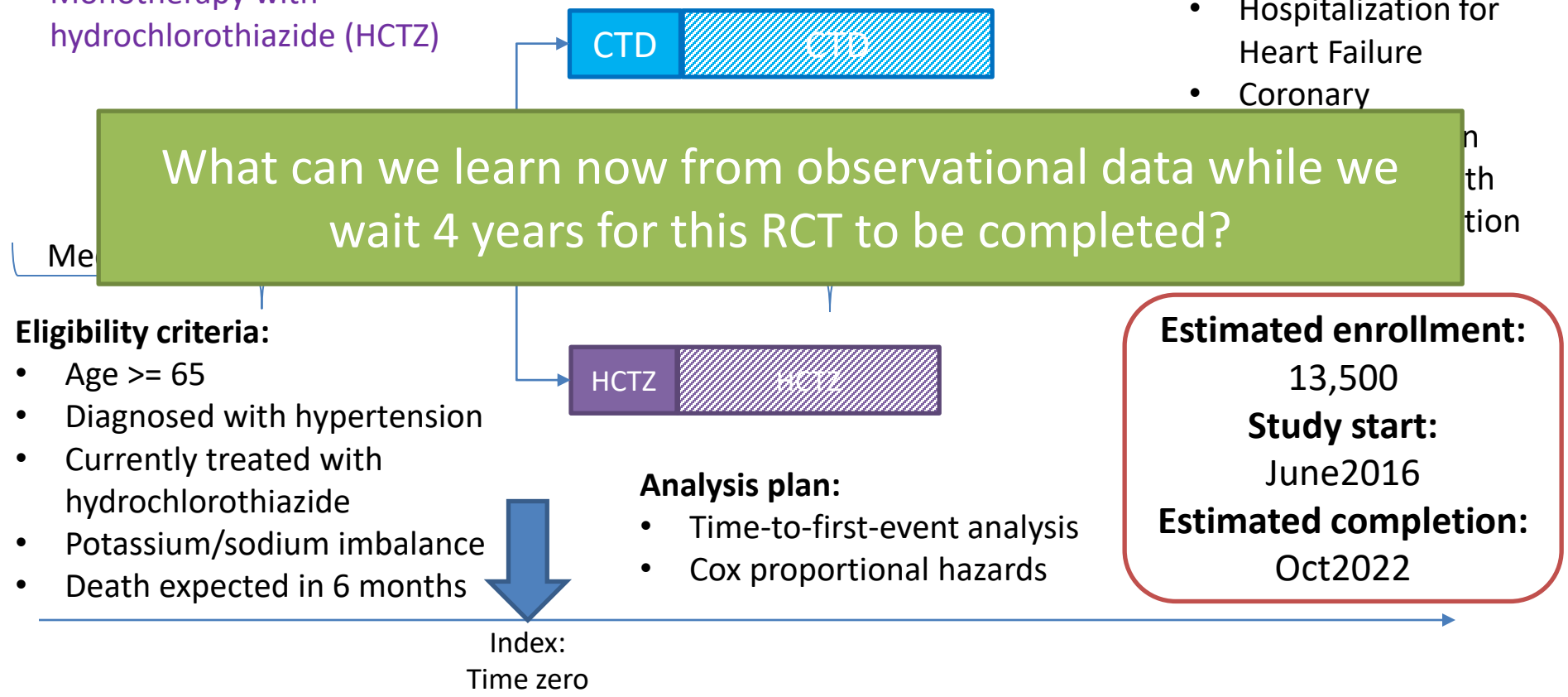
Causal contrasts of interest:

- Intent-to-treat effect

Outcomes:

- Myocardial infarction
- Stroke
- Hospitalization for Heart Failure
- Coronary

What can we learn now from observational data while we wait 4 years for this RCT to be completed?



Eligibility criteria:

- Age >= 65
- Diagnosed with hypertension
- Currently treated with hydrochlorothiazide
- Potassium/sodium imbalance
- Death expected in 6 months

Analysis plan:

- Time-to-first-event analysis
- Cox proportional hazards

Estimated enrollment:
13,500
Study start:
June2016
Estimated completion:
Oct2022

https://clinicaltrials.gov/ct2/show/NCT02185417

Research

17 Feb 2020

JAMA Internal Medicine | Original Investigation

Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension

George Hripcsak, MD, MS; Marc A. Suchard, MD, PhD; Steven Shea, MD; RuiJun Chen, MD; Seng Chan You, MD; Nicole Pratt, PhD; David Madigan, PhD; Harlan M. Krumholz, MD, SM; Patrick B. Ryan, PhD; Martijn J. Schuemie, PhD

Supplemental content

IMPORTANCE Chlorthalidone is currently recommended as the preferred thiazide diuretic to treat hypertension, but no trials have directly compared risks and benefits.

OBJECTIVE To compare the effectiveness and safety of chlorthalidone and hydrochlorothiazide as first-line therapies for hypertension in real-world practice.

DESIGN, SETTING, AND PARTICIPANTS This is a Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND) observational comparative cohort study with large-scale propensity score stratification and negative-control and synthetic positive-control calibration on databases spanning January 2001 through December 2018. Outpatient and inpatient care episodes of first-time users of antihypertensive monotherapy in the United States based on 2 administrative claims databases and 1 collection of electronic health records were analyzed. Analysis began June 2018.

JAMA Internal Medicine | Original Investigation

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17 Feb 2020

Table 2. Effectiveness by Outcome (Propensity Score Stratification, On-Treatment)

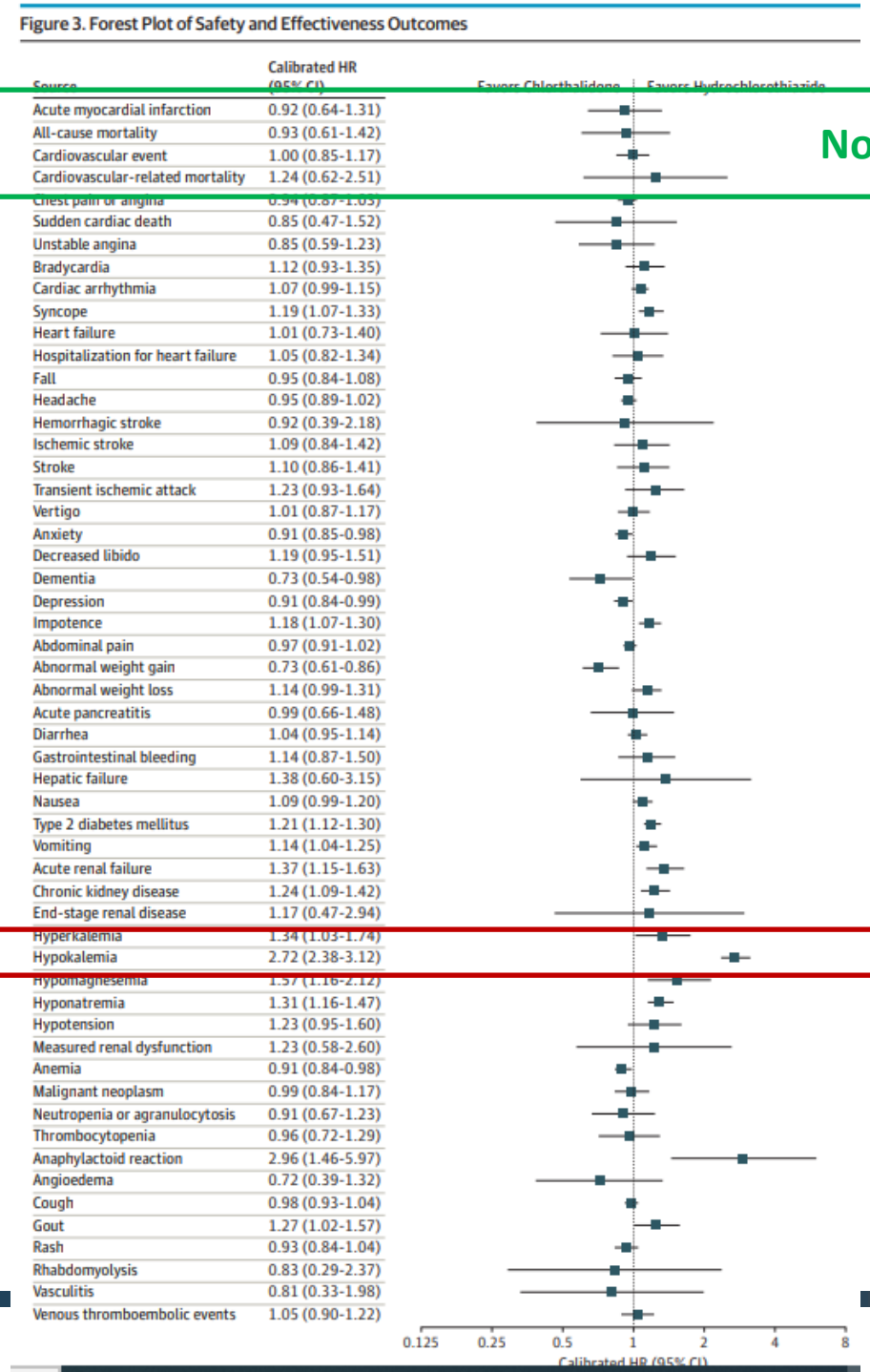
	Chlorthalidone, Total No.		Hydrochlorothiazide, No. (%)		Hazard Ratio (95% CI)[a]	
Outcome	Events	Patients[b]	Events	Patients[b]	Uncalibrated	Calibrated
Acute myocardial infarction	41	36 859	952	692 371	0.93 (0.63-1.36)	0.92 (0.64-1.31)
Hospitalization for heart failure	62	36 833	1248	691 409	1.07 (0.82-1.39)	1.05 (0.82-1.34)
Stroke	60	36 755	1141	689 698	1.13 (0.86-1.47)	1.10 (0.86-1.41)
Composite cardiovascular disease[c]	149	36 628	3089	687 106	1.01 (0.86-1.20)	1.00 (0.85-1.17)

[a] Hazard ratio for chlorthalidone vs hydrochlorothiazide (lower hazard ratio favors chlorthalidone).

[b] Number of patients exposed varies by outcome owing to differences in whether database has hospitalization information and outcome-specific preexposure exclusions.

[c] Composite cardiovascular disease includes the first 3 outcomes and sudden cardiac death.

17 Feb 2020



No difference in cardiovascular effects

Increased risk of hypokalemia

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17 Feb 2020

Figure 1. Comparability of the Populations for Commercial Claims and Encounters Database (CCAE)

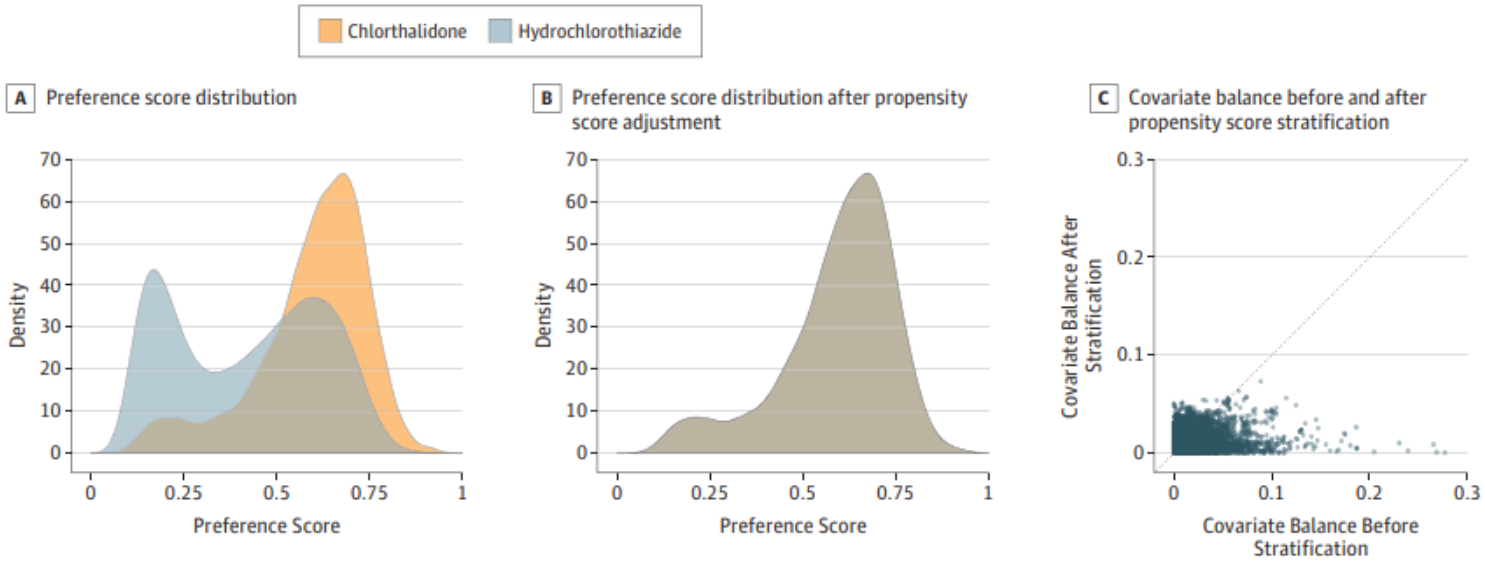
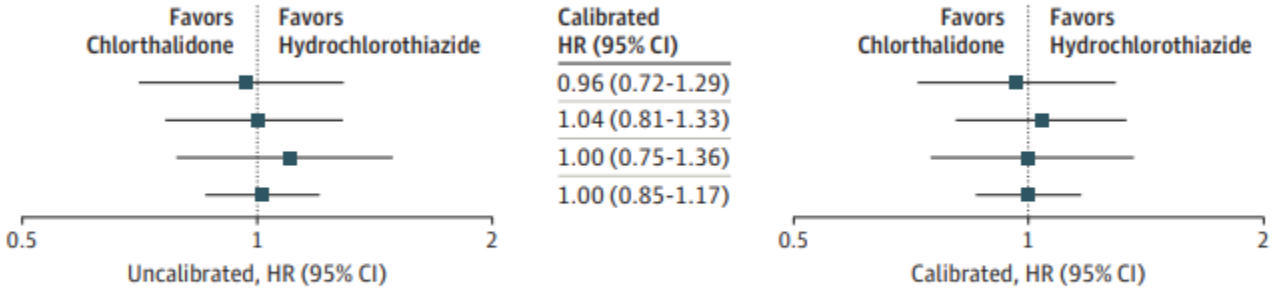


Figure 2. Homogeneity on Effectiveness

Source	Uncalibrated HR (95% CI)	Calibrated HR (95% CI)
CCAE	0.96 (0.70-1.29)	0.96 (0.72-1.29)
Optum	1.00 (0.76-1.28)	1.04 (0.81-1.33)
PanTher	1.10 (0.79-1.49)	1.00 (0.75-1.36)
Summary (I^2 <0.01)	1.01 (0.86-1.20)	1.00 (0.85-1.17)



Hazard ratios (HRs) and forest plot of the 3 databases and the meta-analysis for chlorthalidone vs hydrochlorothiazide on the composite cardiovascular disease outcome. The 3 databases showed excellent agreement. CCAE indicates Commercial Claims and Encounters Database.

eFigure 2. Sensitivity to balancing on baseline blood pressure in the PanTher database. We show effectiveness and safety outcomes for the PanTher database for propensity models that exclude (blue triangle) and include (red circle) baseline systolic and diastolic blood pressure in the propensity model. There are no major shifts in outcome.

Comment & Response

June 22, 2020

22 June 2020

Chlorthalidone and Hydrochlorothiazide for Treatment of Patients With Hypertension

Andrew E. Moran, MD, MPH[1,2]; Paul K. Whelton, MD, MSc[3]; Thomas R. Frieden, MD, MPH[1]

Chlorthalidone and Hydrochlorothiazide for Treatment of Patients With Hypertension

To the Editor Hripcsak et al[1] compared cardiovascular and safety outcomes of chlorthalidone and hydrochlorothiazide in the treatment of patients with hypertension. Chlorthalidone is recommended over hydrochlorothiazide because it has a longer duration of effect (24 vs 6-12 hours) and has been more extensively documented as effective in randomized clinical trials to reduce cardiovascular events and mortality.[2] Prior meta-analyses and observational comparisons suggest that chlorthalidone is superior in preventing cardiovascular events.[3,4] However, to our knowledge there are no published randomized trials comparing chlorthalidone and hydrochlorothiazide; such a trial is ongoing in the US Veterans Affairs system, with results expected in 2023.[5]

Moderately strong prior evidence suggests the superiority of chlorthalidone over hydrochlorothiazide, and there is substantial likelihood that residual confounding accounts for the lack of an observed difference in cardiovascular end points in the Hripcsak et al[1] study. For this reason, it is imperative to await the more definitive VA trial results in 2023[5] before changing clinical practice recommendations on diuretic choice.

Andrew E. Moran, MD, MPH
Paul K. Whelton, MD, MSc
Thomas R. Frieden, MD, MPH

Diuretic Comparison Project - DCP

Nov 05, 2022

Author/Summarized by Author:	Dharam J. Kumbhani, MD, SM, FACC
Summary Reviewer:	Deepak L. Bhatt, MD, MPH, FACC

Trial Sponsor:	U.S. Department of Veterans Affairs
Date Presented:	11/05/2022
Date Published:	11/05/2022

Principal Findings:

The primary outcome, major adverse cardiovascular events (MACE), for chlorthalidone vs. HCTZ: hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.94-1.16 (p = 0.4).

- For patients with prior stroke: HR 0.73, 95% CI 0.57-0.94 (p for interaction = 0.035)

Secondary outcomes for chlorthalidone vs. HCTZ:

- First hospitalization for MI: HR 1.01, 95% CI 0.80-1.28 (p = 0.91)
- First hospitalization for stroke: HR 1.0, 95% CI 0.74-1.36 (p = 1.0)
- First hospitalization for heart failure: HR 1.04, 95% CI 0.87-1.25 (p = 0.4)
- Hypokalemia: 6.0% vs. 4.4% (p < 0.001)

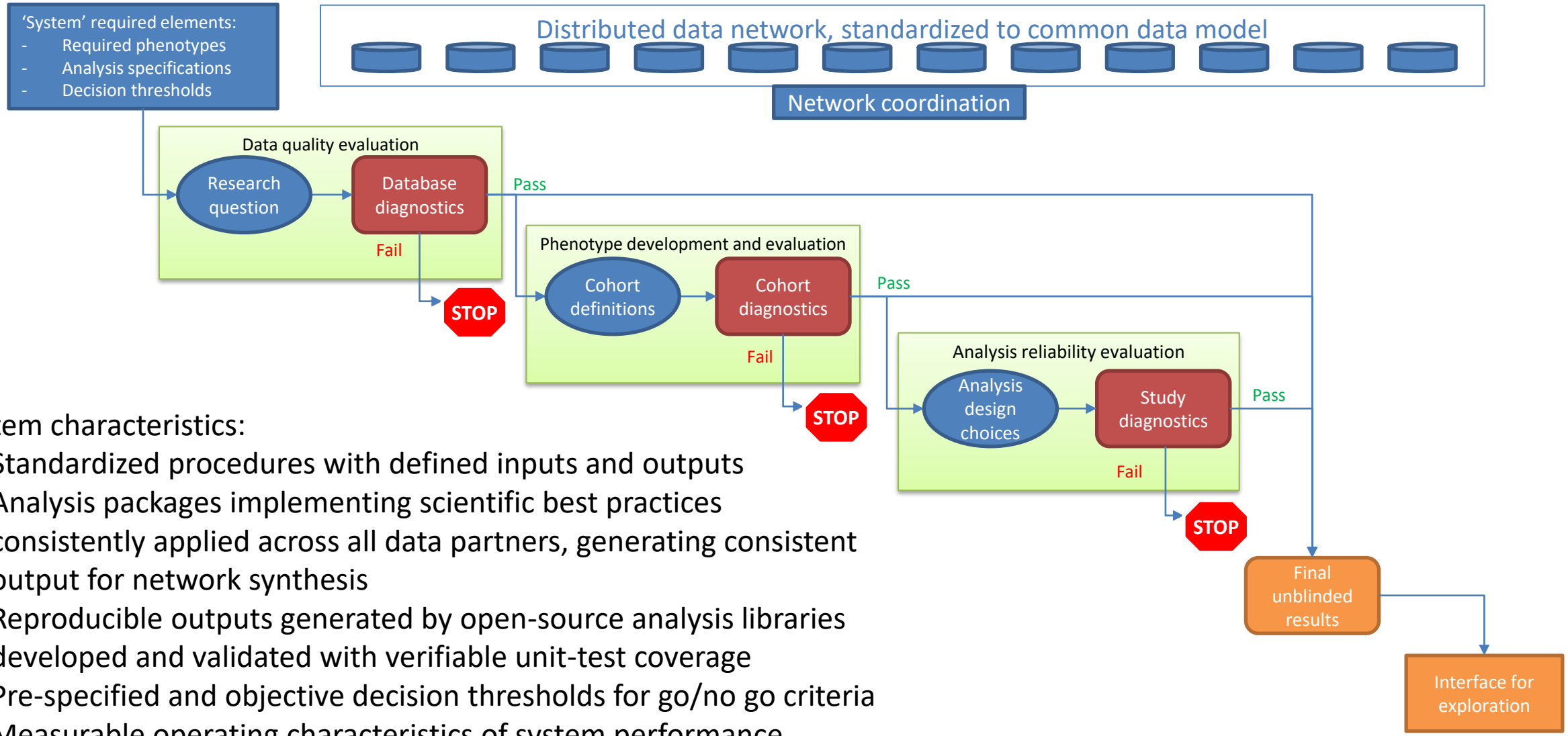
Interpretation:

The results of this trial show that there are no differences in cardiovascular outcomes between chlorthalidone and HCTZ among elderly veterans with hypertension. Among patients with prior MI, a benefit was observed. This is a hypothesis-generating finding and has to be viewed in the context of an overall negative trial. Hypokalemia was more common with chlorthalidone.

Comparing reliable real-world evidence with randomized trial results

	OHDSI's LEGEND in 2018/2020	Diuretic Comparison Project RCT in 2022
Cardiovascular events	1.00 (0.85-1.17)	1.04 (0.94-1.16)
Hospitalization for Acute myocardial infarction	0.92 (0.64-1.31)	1.01 (0.80-1.28)
Hospitalization for Stroke	1.10 (0.86-1.41)	1.00 (0.74-1.36)
Hospitalization for Heart failure	1.05 (0.82-1.34)	1.04 (0.87-1.25)
Hypokalemia	2.72 (2.38-3.12)	p<0.001

Engineering open science systems that build trust into the real-world evidence generation and dissemination process



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- Pre-specified and objective decision thresholds for go/no go criteria
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Level of proactivity in delivering real-world evidence

Time-to-evidence			
~seconds	Anticipatory	Generate and deliver insights without being asked; answer questions before requested by 'pushing' relevant pre-computed evidence to potential evidence consumers	Standardized dissemination +
~minutes	Prepared	Produce pre-computed evidence to enable answer retrieval in 'real time' by qualified users when requested; standardized analysis packages executed across network generate results 'at-scale' across many target, outcome cohorts	Standardized analysis configurations +
~hours	Responsive	Enable fast evidence generation by using interface that allow qualified users to set defined input parameters, execute standardized analyses, and view results upon request.	Standardized analysis tools +
~days	Enabled	Design and execute standardized analysis packages that apply validated statistical libraries with defined input parameters and fixed output to compile summary results across a network standardized to a common data model	Standardized data, network execution
~weeks, months, years	Reactive Bespoke	Service bespoke project requests by convening team to align on problem statement, author protocol/analysis plan documents, implement statistical programming code to custom specification, execute analysis across databases, iteratively review results and request post hoc analyses, write summary of results as report, and deliver to decision-maker to ensure it meets their needs	

Concluding thoughts

- Enabling use and establishing value of real-world evidence requires building trust across stakeholders – evidence generators and consumers
- People and processes need to be augmented with science, technology and engineering
  - Research network = people + data + analytic tools + best practices
- Open science systems that promote transparency and reproducibility can increase reliability and efficiency
- Community efforts today can enable a more proactive future tomorrow
  - Standardized data network and data quality assessment
  - Phenotype development and evaluation
  - Standardized analytic tool development
  - Global collaboration on clinical evidence generation to fill the gaps in medicine