Cytel
Shaping the Future of Drug Development

Head-to-head Comparisons using Real-World Data

Design and data source considerations from pilot investigations in CVD

July 28, 2020

Speakers

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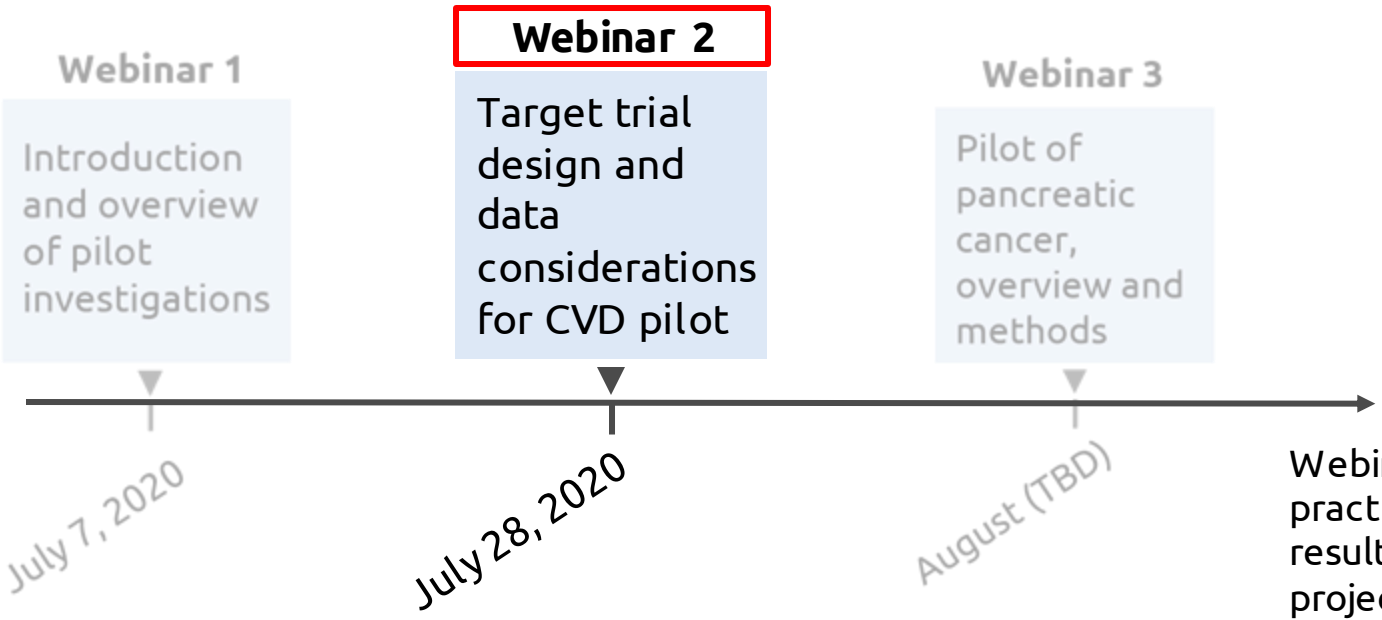
This is a part of a webinar series



Webinars focusing on practical application and results from pilot projects will be hosted in the summer and early fall 2020

Introduction:
Target trial emulation

Randomized clinical trials

- Randomized trials are the standard for comparing effectiveness of interventions
  - Randomization reduces selection bias and confounding
  - Provide causal estimates of effects

- Decision-making and health policy need to be informed by causal knowledge about comparative effectiveness and safety

Treat with drug A, B or C?

Treat with drug B or C if no response to A? Treat now or later?

Which individuals to treat?

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Randomized trials are not always feasible

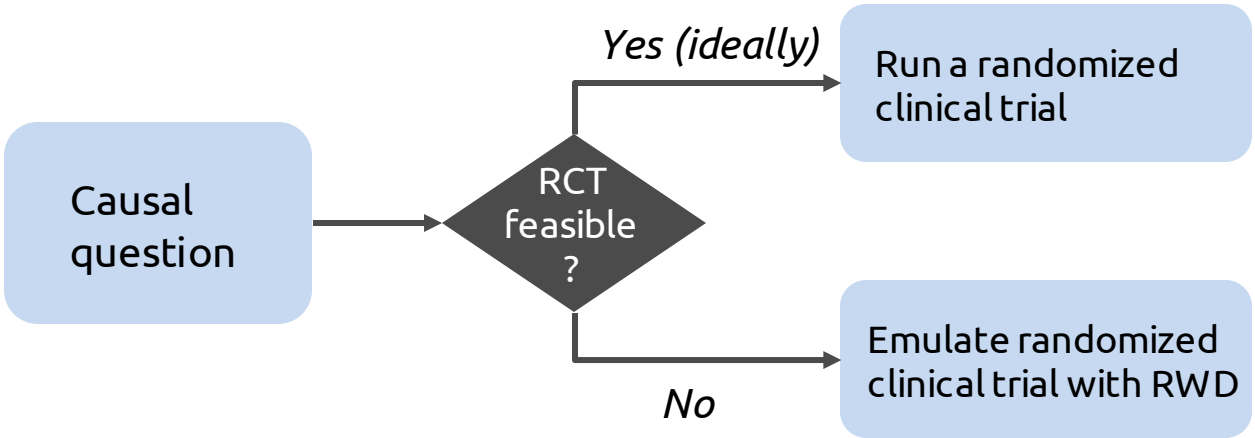
- Possible reasons:
  - Costly
  - Untimely
  - Unethical
  - Impractical

- Trials may be limited in scope
  - E.g. eligibility criteria, outcomes measured
  - Real-world generalizability

- Decisions need to be made even in the absence of a randomized trial to address them – maintaining status quo is also a decision

Plan B: Emulate a randomized trial using RWD

- Try to emulate a hypothetical randomized clinical trial using observational data
- Limitations:
  - Can not emulate placebo, blinding, or force adherence
  - Limited by data available (e.g. only approved therapies)



Target trial framework

Step 1: Ask a causal question

- Equivalent to specifying the protocol of the analogous randomized trial explicitly

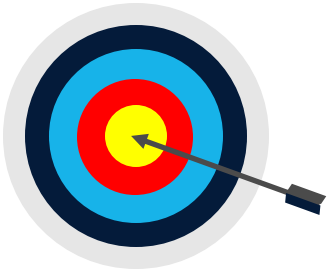
Step 2: Answer the causal question

- Identify a suitable RWD source
- Try and emulate the randomized trial using RWD

- Usually, it is necessary to cycle between steps 1 and 2 iteratively to tune them due to practical limitations, e.g. by restricting eligibility criteria

Step 1

Step 2



Problems with naïve analysis of RWD

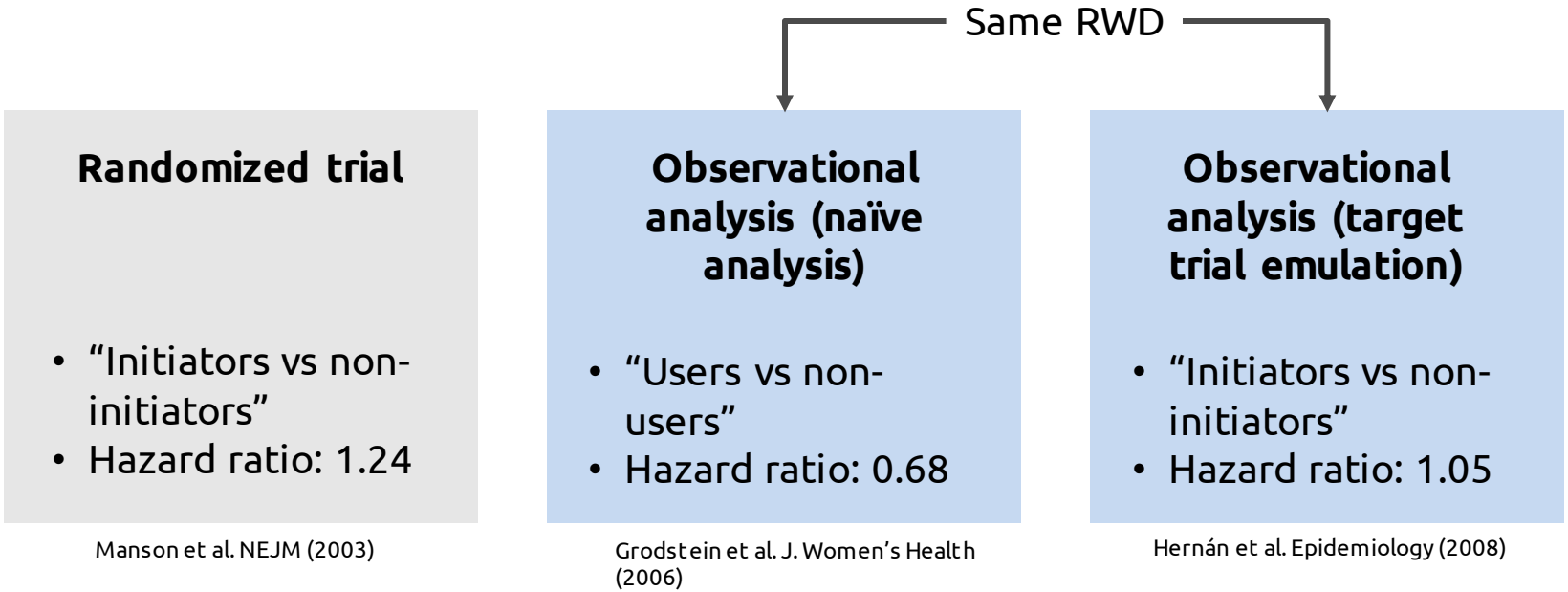
- Asking the "wrong" or a poorly-defined causal question
  - Explicit representation of the causal question as a target trial prevents this

- Answering the causal question incorrectly
  - Not accounting for various biases that may arise
  - Not adjusting for relevant confounders/adjusting where we shouldn't
  - Not using the appropriate methods

- **Result: biased effect estimates, wrong conclusions**

Example: post-menopausal hormone therapy and CHD

- Effect of post-menopausal hormone therapy on risk for coronary heart disease?



Use cases for target trial emulation

- Generation of efficacy or safety evidence for conditional regulatory approval or post-market assessment
- Providing a comparison when network meta-analysis is not possible
- Expanding the scope (e.g. eligibility criteria) of a randomized trial
- Refining aspects of an existing treatment protocol
- Enabling a comparison to identify optimal treatment regimen

Pilot project: Head-to-head comparison of second-line therapies for type 2 diabetes

Considerations for protocol design and data source

Overview

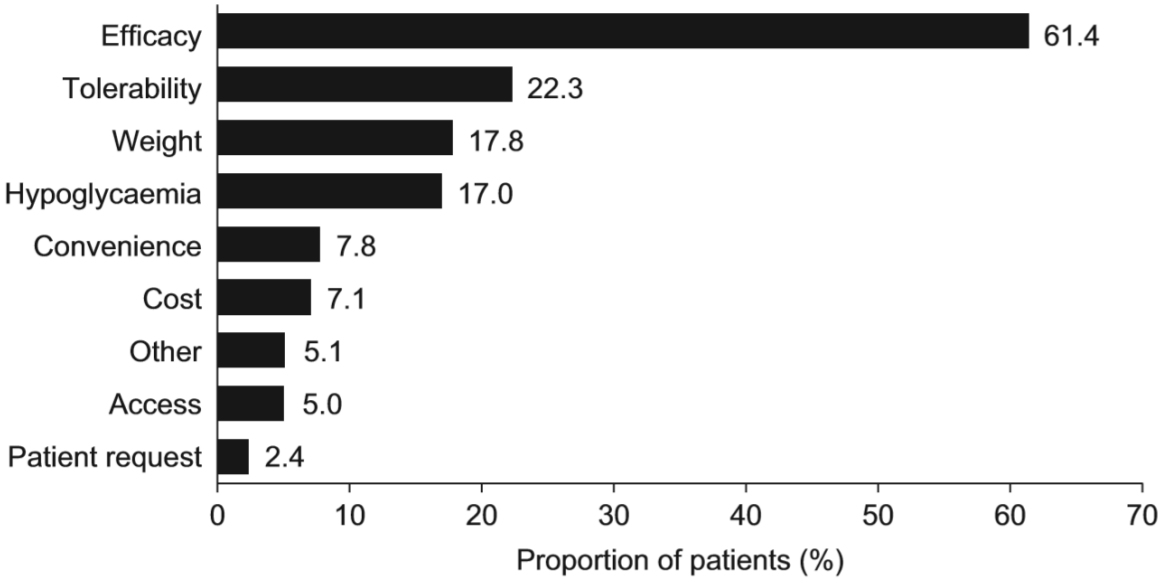
- Patients with type 2 diabetes on metformin often fail to achieve/maintain glycemic control and require second-line therapy

- >6 classes of anti-diabetic drugs have been approved for use
  - A head-to-head comparison of effectiveness, safety is lacking
  - Choice of second-line agent varies across clinical practices

- There is a need for comparative effectiveness evidence to guide choice of second-line agent
  - To reduce detrimental effects, improve cost-effectiveness
  - Guide personalized therapy

Efficacy is the main driver in prescription practices globally

Reason for choice of second-line therapy by investigators for type 2 diabetes

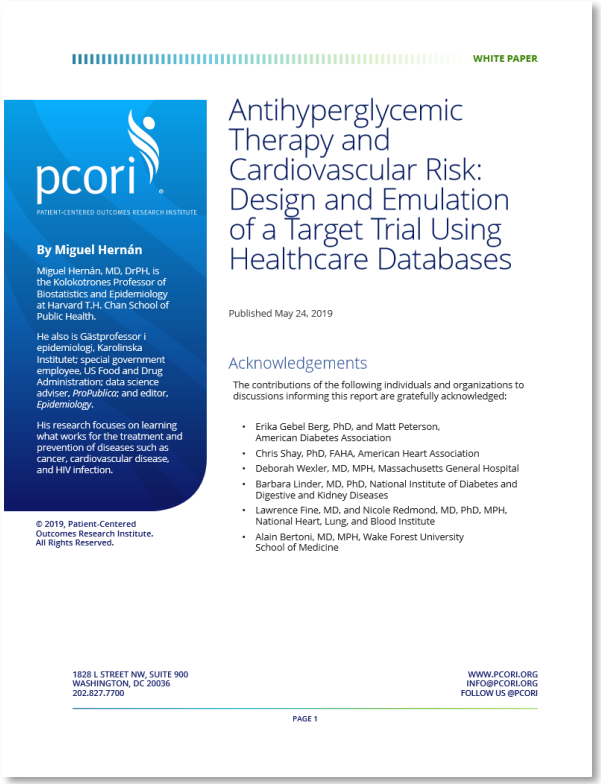


Gomes, Marilia B., et al. "Treatment of type 2 diabetes mellitus worldwide: baseline patient characteristics in the global DISCOVER study." *Diabetes research and clinical practice* 151 (2019): 20-32.

Step 1 – asking the causal question

- Framing the causal question explicitly in the form of a target trial protocol

- Considerations for protocol design:
  - Who needs to be involved?
  - What are the roles for those involved?
  - How do you define the data/variables necessary for emulation?
  - How do you refine the protocol given practical limitations (e.g. data)?



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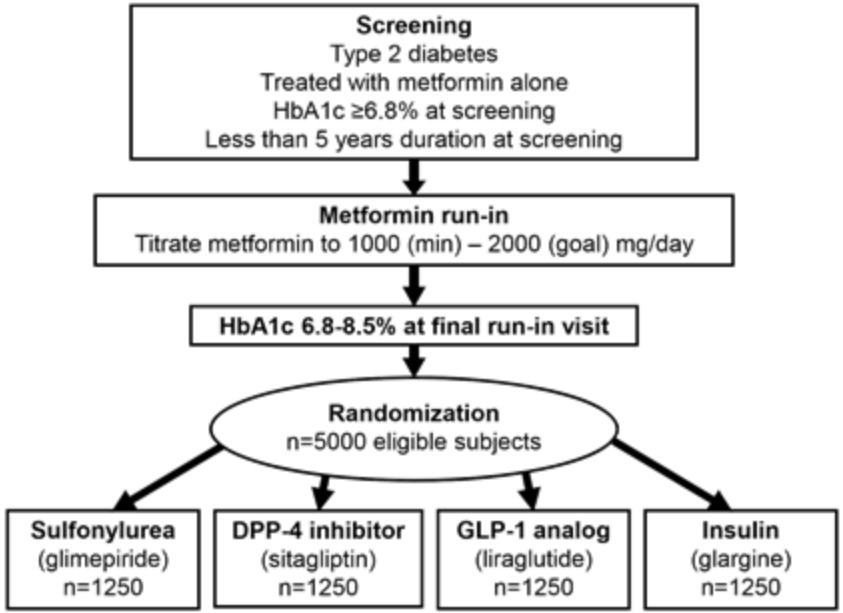
GRADE trial

- Ongoing open-label randomized trial for comparative effectiveness of second-line therapy in type 2 diabetes
  - Started in 2013
  - Est. primary completion in July 2021

- Outcomes
  - HbA1C (primary)
  - Cardiovascular, microvascular side effects, adherence-tolerability

- No SGLT-2 inhibitor arm



Nathan, David M., et al. "Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE)." *Diabetes care* 36.8 (2013): 2254-2261.

Data considerations for target trial emulation

- Data from combination of EMR/EHR, claims data, clinician notes

- Brief checklist:
  - "Big" data – sufficiently large sample size, large number of variables
  - Representative sample covered
  - Bias/irregularities in capture of study variables
  - Long follow up
  - Database expertise
  - Access to clinical practitioners familiar with data
  - Data normalization, harmonization, de-identification
  - Cohort generation – minimizing bias, false positives/negatives

Hall, Gillian C., et al. "Guidelines for good database selection and use in pharmacoepidemiology research." *Pharmacoepidemiology and drug safety* 21.1 (2012): 1-10.

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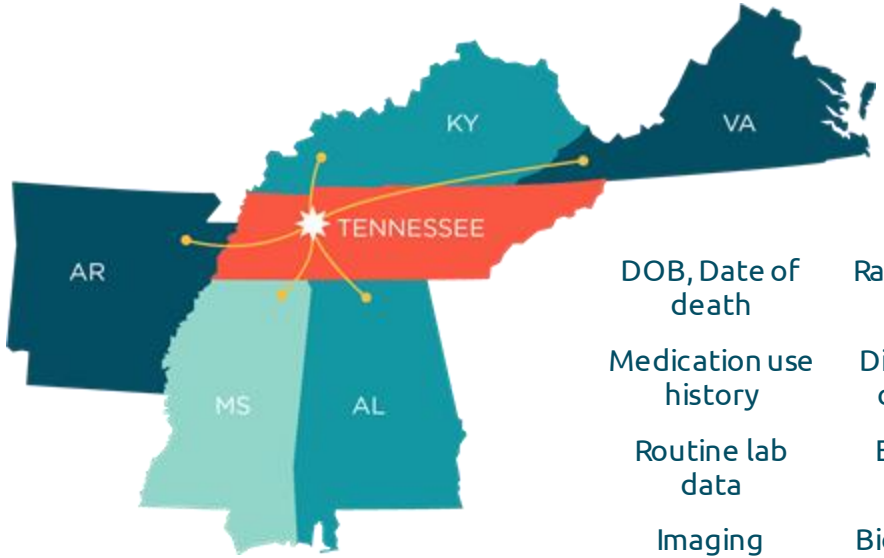
Partnership with Nashville Biosciences for RWD

- Subsidiary of Vanderbilt University Medical Center (VUMC)
- Leverages a large de-identified EMR, biospecimen repository BioVU®
  - E.g. 163,000 EMRs for type 2 diabetes
- Also provide scientific, clinical expertise

Source of data

- 6100+ providers and 68 hospital locations accepting ~2.5 million patients annually



Nashville Biosciences.

VANDERBILT HEALTH

DOB, Date of death	Race, Ethnicity, Gender	Visit & EMR events	Vitals (hr, weight, BMI)
Medication use history	Disease billing codes (ICD)	Procedure codes (CPT)	Insurance status
Routine lab data	Esoteric lab data	Genotype data	Disease-specific registries
Imaging reports & images	Biopsy reports	Visit & clinical consult notes	History and physicals

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Target trial protocol – checklist

- Eligibility criteria
- Treatment strategies
- Causal contrasts of interest
- Confounders for assignment to treatment strategies
  - Other confounding variables will need to be defined depending on treatment strategies and causal contrasts (e.g. for adherence)
- Outcomes
- Follow-up
  - Start and end time
  - Defining time zero
- *Analysis plan (will be discussed in next webinar)*

Eligibility criteria

Criterion	Available in NB data?	Source
T2DM diagnosis	Yes	ICD, ICD+meds+labs
Age (>45 years)	Yes	DOB
Antihyperglycemic monoTx with metformin for >3 months in 2014/later	Yes	Rx records, self-reported drug use
Suboptimal glycemic control after metformin initiation (>7% HbA1c)	Yes	Labs
No suspected T1D or other reasons for hyperglycemia (rare disorder, pancreatic surgery)	Yes (?) – depends on start of care at VUMC relative to treatment start date	
Not pregnant	Yes	ICD, CPT

Treatment strategies

- Initiation of second-line therapy within 12 months of persistent inadequate HbA1c control with metformin use from one of:
  - GLP-1 RA
  - SGLT-2 inhibitor
  - DPP-4
  - Sulfonylureas
  - (TZD, insulin)
- Other strategies depend on data:
  - Sustained treatment with, addition of a third-line therapy
- Limitations:
  - Limited to drugs prescribed at/dispensed at VUMC pharmacy

Causal contrasts

- Intention-to-treat effect
  - Effect of being assigned to treatment strategy at baseline
  - Of interest in the GRADE trial
  - Requires adjustment for non-random allocation at baseline + non-random loss to follow-up

- Per-protocol effect
  - Effect of adhering to assigned treatment strategy
  - Also requires adjustment for non-adherence (pre + post-baseline factors, e.g. treatment discontinuation)
  - May be feasible depending on availability of sufficient relevant data on adherence

Confounders for treatment assignment at baseline*

Predictor	Available in NB data?	Source/comments
Type of medical insurance	Yes	For most
History of CVD	Yes	
Physician comfort level/perception of drug	Unknown	May need help of treating physician or their Rx histories
HbA1c levels	Yes	Labs
Contraindications	Yes	Rx records
BMI	Yes	
Frailty/tolerability	(?) – Depends on how we define this, may involve practitioners	

*How can we tell if we have adjusted sufficiently, appropriately?

Outcomes

- Metabolic
  - HbA1C levels (may not be a patient-important outcome)
  - BMI
- Macrovascular
  - MACE
  - Heart failure
- Microvascular
  - Glomerular filtration rate (eGFR)
  - Retinopathy

Gandhi, Gunjan Y., et al. "Patient-important outcomes in registered diabetes trials." *Jama* 299.21 (2008): 2543-2549.

Follow up

- Defining time zero
  - Time of treatment prescription

- Patients are followed from time zero until diagnosis of outcome or loss to follow-up due to various factors
  - E.g. due to discontinuation of pharmacy benefits, medical insurance etc.
  - Ideally, minimize loss to follow-up
  - Possible ways include only including patients with a history of regular visits

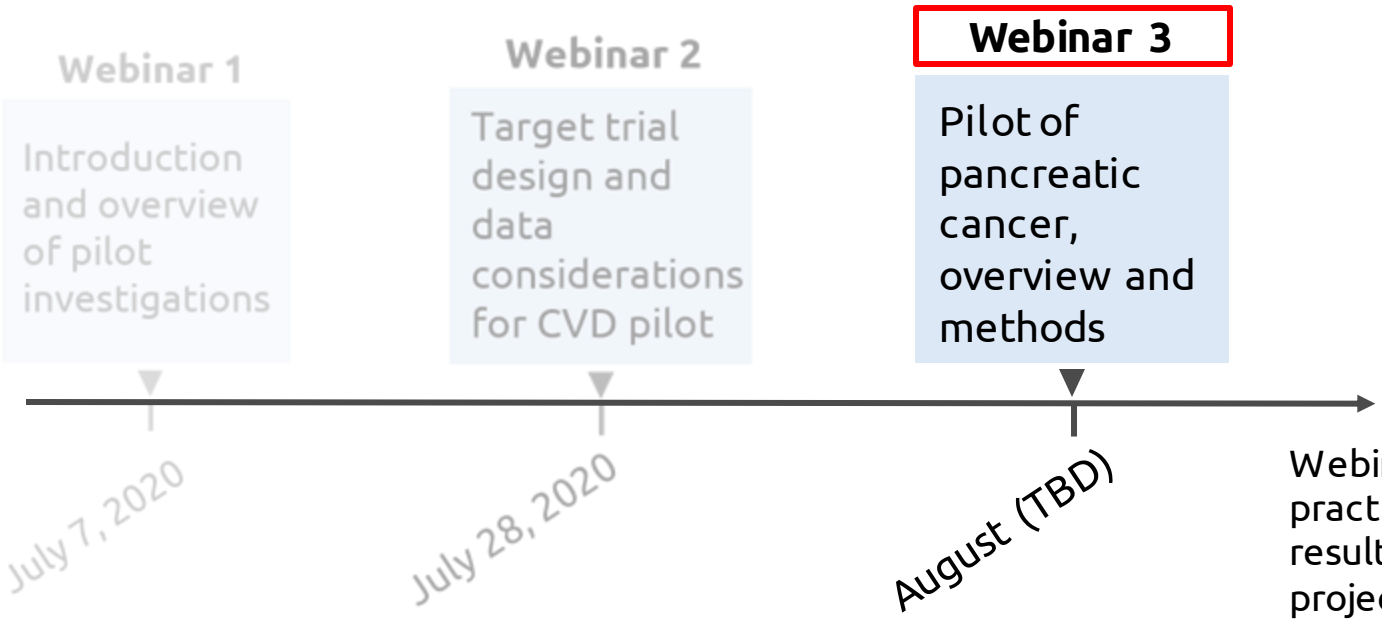
Next steps

- Cohort extraction and sample size estimation
- Iterative tuning of protocol given data limitations
- Definition of final protocol and analysis plan
- Trial emulation
  - Results – survival curves, relative risk estimates
  - Subgroup analyses
- Sensitivity analysis
- Benchmarking against results from GRADE if possible

Conclusion

- In the absence of a randomized clinical trial, we can try to emulate a hypothetical randomized trial using RWD
  - Can also complement existing trials
  - Fraction of time and cost
- Considerations discussed today:
  - Trial protocol design
  - Suitable high-quality RWD for emulation
- Trial design may need to be refined iteratively due to practical constraints
- Multiple parties are needed to successfully define protocol and interact with big data (e.g. for data validation, database expertise)

Next webinar



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Questions?