Leveraging RWD for safety evaluation throughout the lifecycle

PSI Conference 17 June 2026

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RWD eSIG Session

Real-world data – do you know all the opportunities? The key questions they can answer and how.

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

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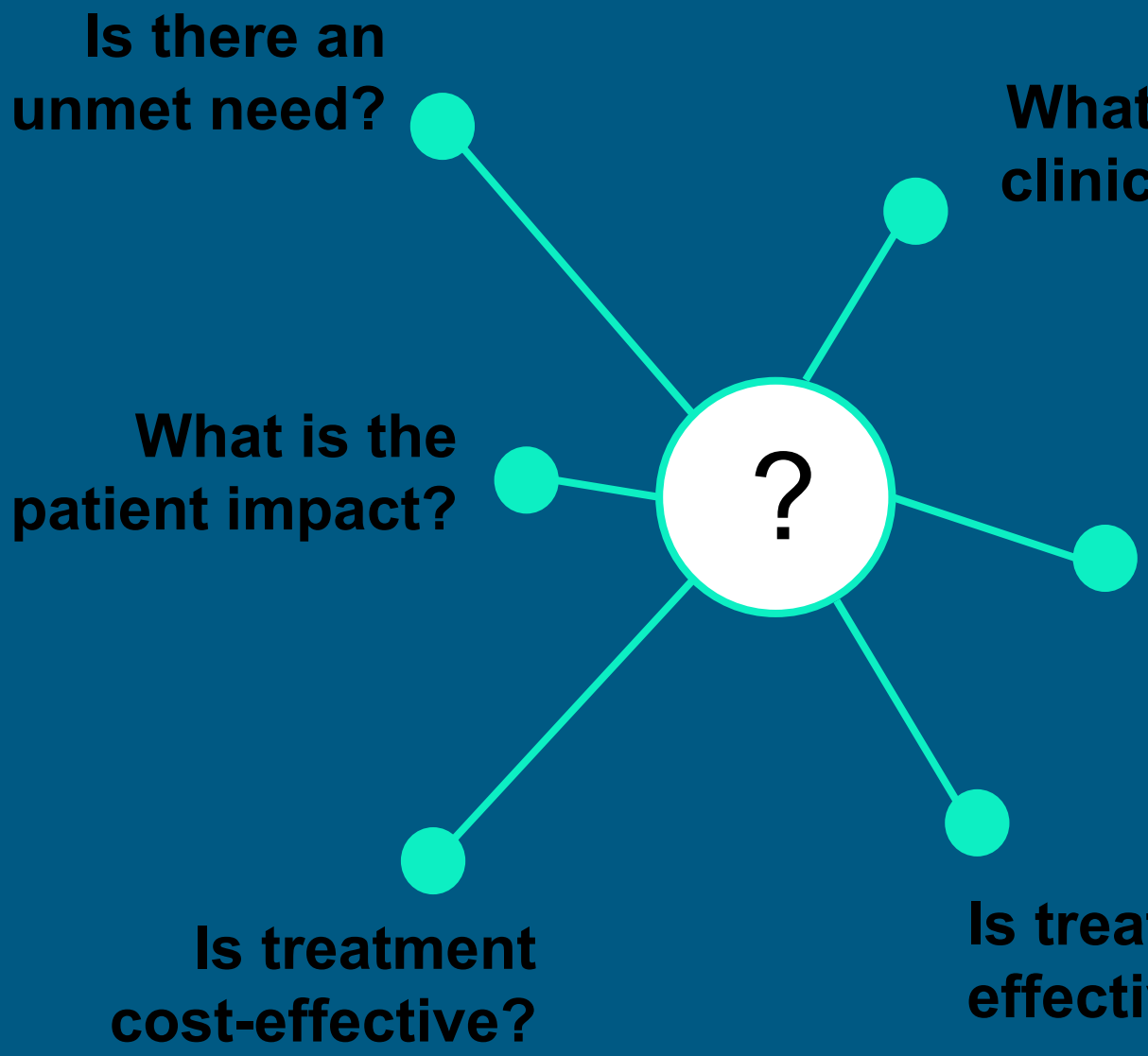
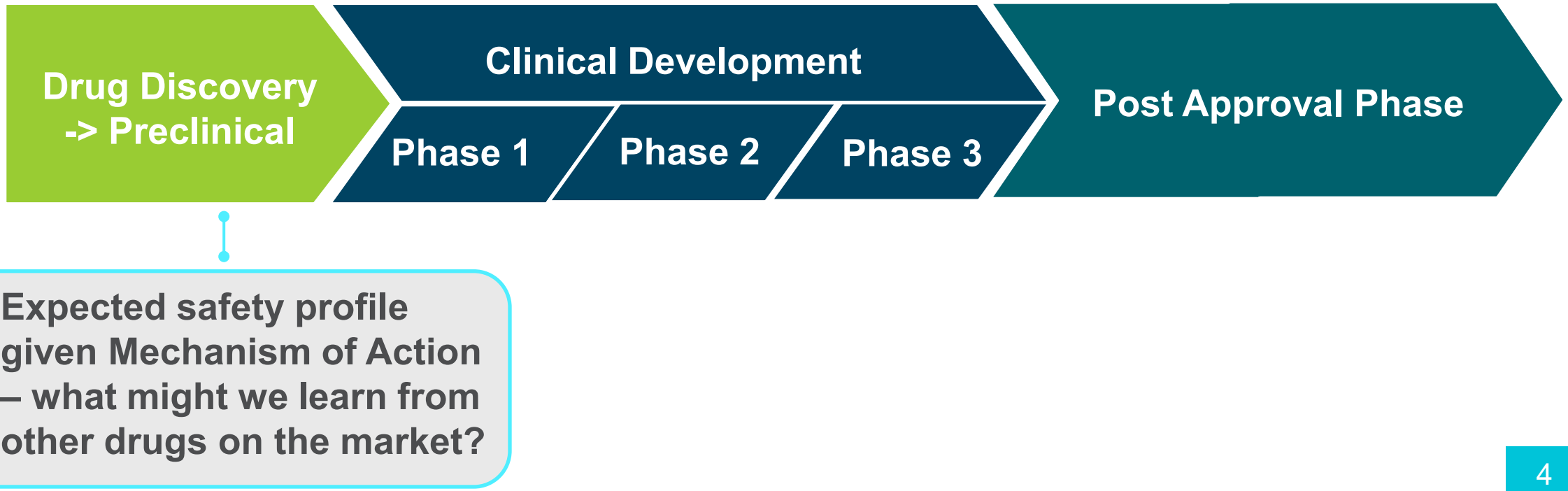


Real-world data can help answer key questions

There are safety-related RWD opportunities throughout the lifecycle



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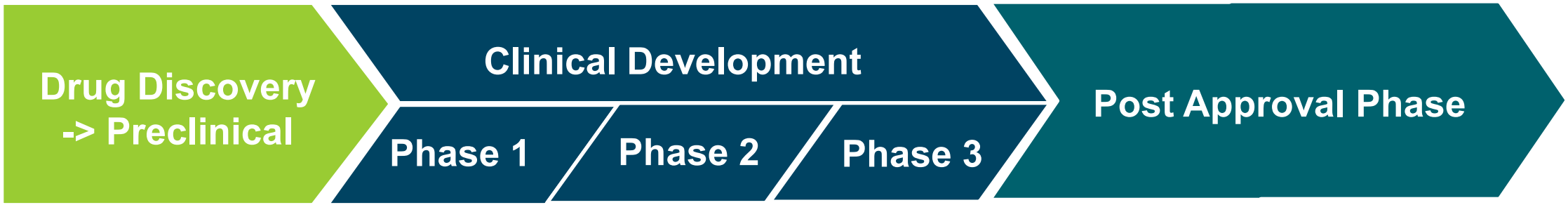
- What is the background incidence of anticipated AEs?
- An unanticipated AE occurs during trial, can we contextualise?



Expected safety profile given Mechanism of Action – what might we learn from other drugs on the market?

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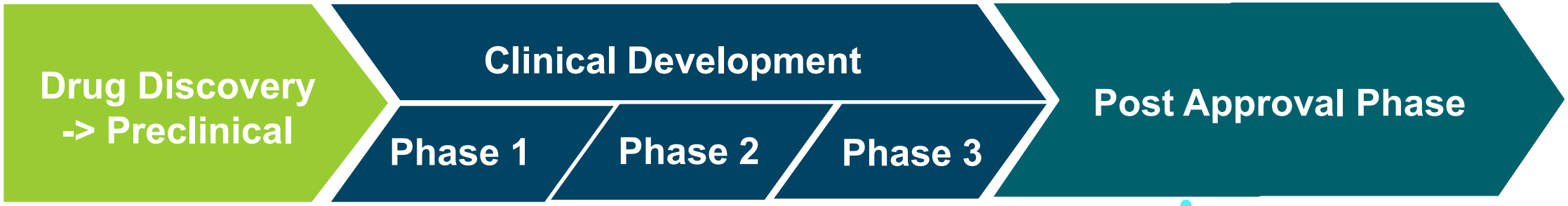

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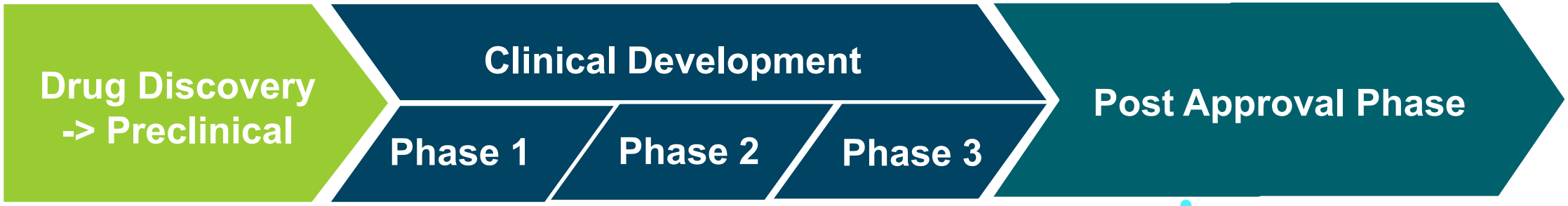

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- Effectiveness of risk-minimization measures

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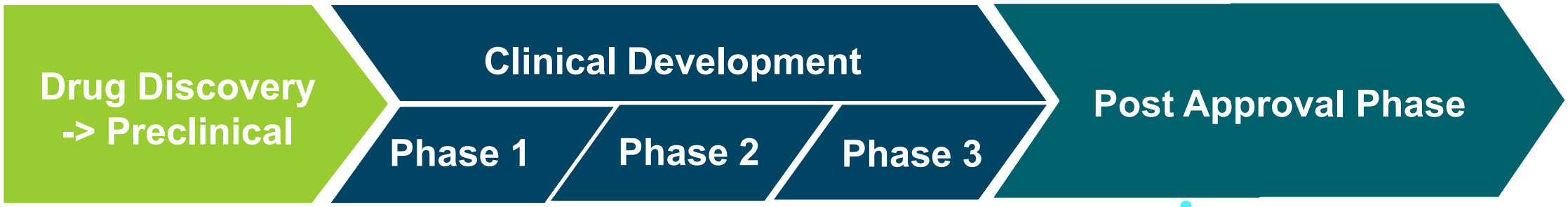
- RW Safety in labelled population
- RW Safety in broader population and subgroups or combinations
- Comparative safety



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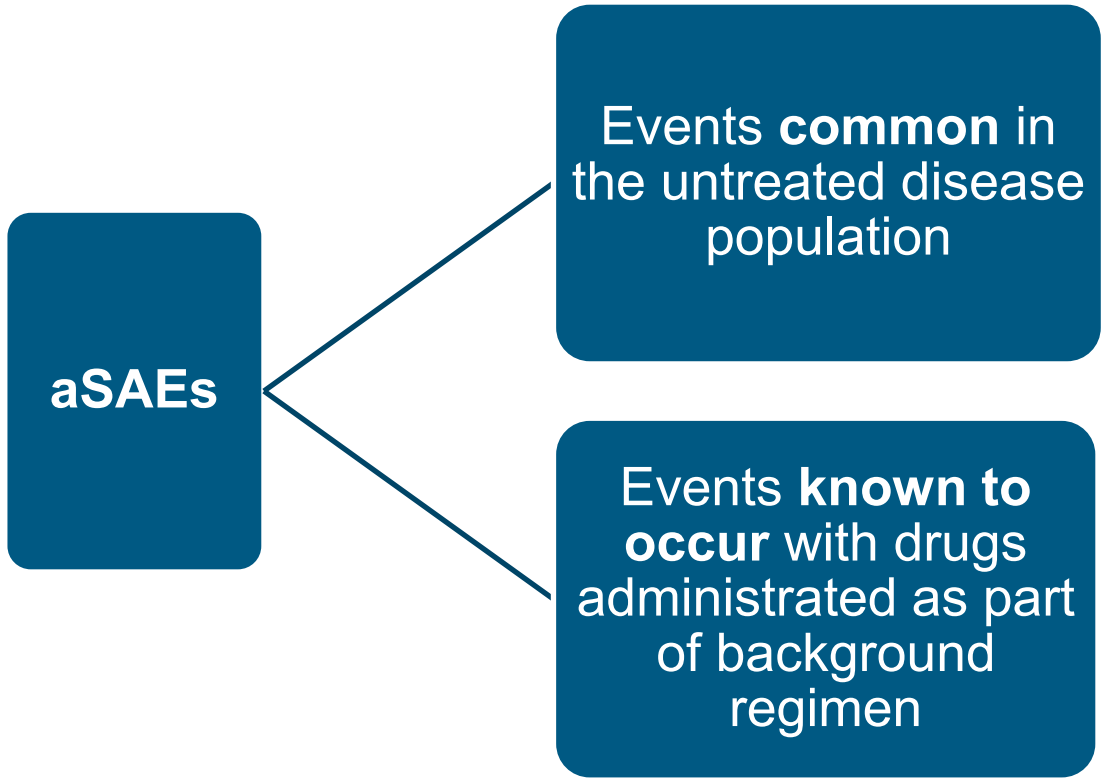
Background Incidence of Anticipated SAEs

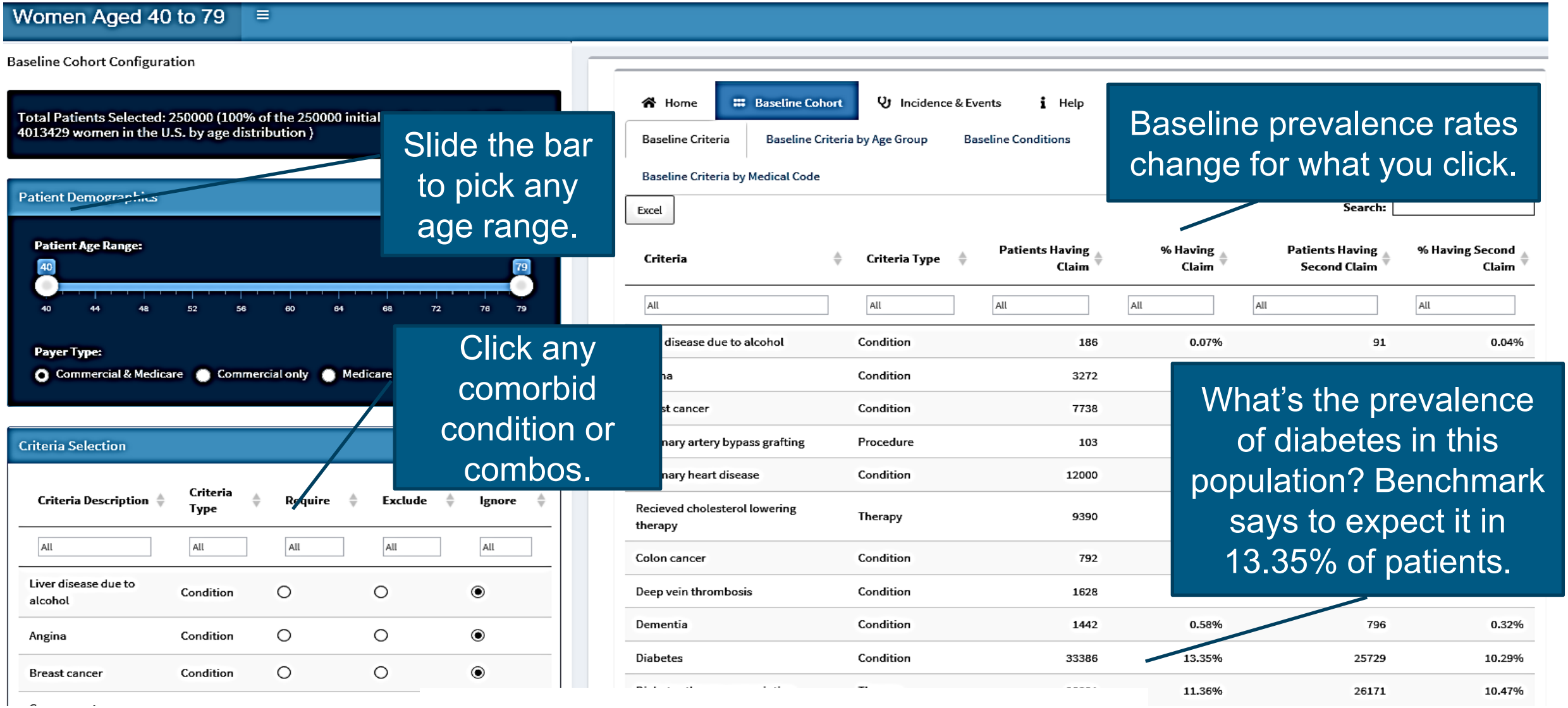
RWD may support a trigger approach for IND safety reporting



- aggregate analysis necessary to determine whether these events meet reporting criteria
- use all available data, including placebo databases, historical data, literature, external epidemiological databases, electronic health records, and disease-specific registries
- a predicted event rate is determined based on information applicable to the study population (e.g., age, comorbidities, concomitant treatments)
- the “trigger” is when the background incidence is exceeded (at which point further investigative action is warranted)

US FDA. “Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies: Guidance for Industry”. Dec 2025.

Example: Interactive RSHINY insurance claims data dashboard combines a dynamic patient selection with events occurring longitudinally



Baseline Cohort Configuration

Total Patients Selected: 2182 (5.2% of the 41578 initial patients)

Patient Demographics

Patient Age Range:

13 50 100

13 22 31 40 49 58 67 76 85 94 100

Patient Gender:

Males & Females | Males only | Females only

Payer Type:

Commercial & Medicare | Commercial | Medicare

Criteria Selection
(Select "Require" for inclusion criteria, "Exclude" for exclusion criteria)

Criteria Type	Criteria Description	Require	Exclude	Ignore
All	All			
Protocol Inclusion	Dry AMD	◉		
Protocol Inclusion	Dry AMD (Second diagnosis 30 days apart)	◉		
Protocol Inclusion	Geographic atrophy (GA)	◉		
Protocol Exclusion	Wet AMD	○	○	◉
condition	Choroidal neovascularization, active	○	○	◉

Proxy trial entry criteria

Home | Baseline Cohort | Incidence & Events | Help

Incidence Density | Incidence Density by Age Group

Excel

Flexible, instant benchmarks for safety monitoring

Criteria	Criteria Type	Patients Having Claim	Patients Having Claim per 1,000 person-years (Standardized)	Patients Having Second Claim
All	All	All	All	All
Dry AMD	Protocol Inclusion	1,684	1,350	1,321
Geographic atrophy (GA)	Protocol Inclusion	1,351	788	956
Wet AMD	Protocol Exclusion	[illegible]	[illegible]	684
Choroidal neovascularization, active	condition	[illegible]	[illegible]	533
Choroidal neovascularization, inactive	condition	[illegible]	[illegible]	223
Intraocular inflammation, Endophthalmitis	condition	[illegible]	[illegible]	2
Intraocular inflammation, Uveitis	condition	[illegible]	[illegible]	11
Optic Ischemic Neuropathy	condition	[illegible]	[illegible]	7
Alcohol abuse	Comorbidity	[illegible]	[illegible]	16
Atherosclerosis coronary artery	Comorbidity	[illegible]	[illegible]	416
Cerebrovascular disease	Comorbidity	440	151	209
Cerebrovascular disease sequelae	Comorbidity	82	25	38
Chronic pulmonary disease	Comorbidity	483	173	315
Heart failure	Comorbidity	543	199	365
Hyperlipidemia	Comorbidity	1,524	994	1,224
Hypertension complicated	Comorbidity	708	273	427
Hypertension uncomplicated	Comorbidity	1,701	1,436	1,475

Where baseline prevalence rates are cross-sectional, incidence looks forward.

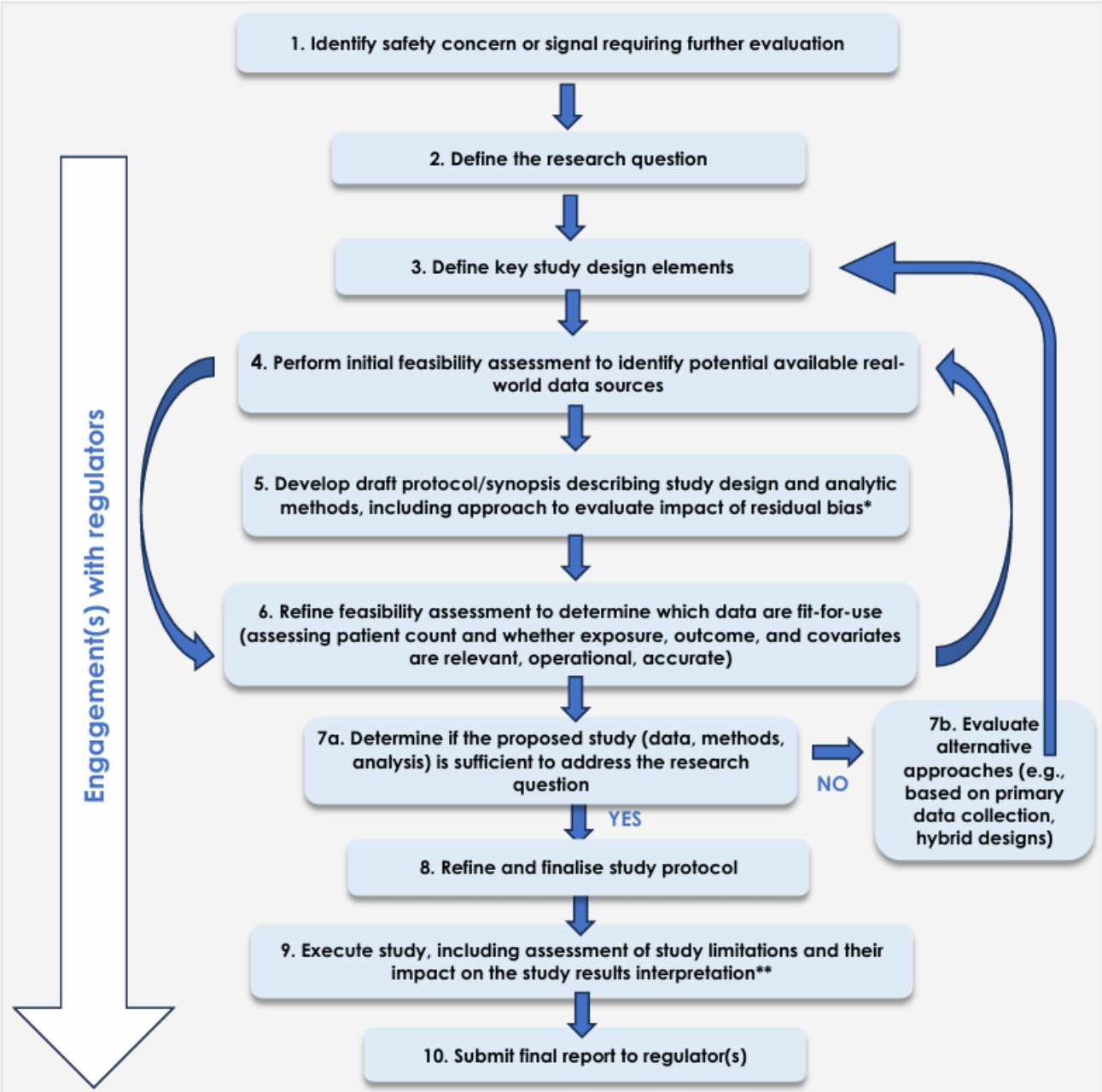
Require continuous enrollment in baseline period, not for follow-up period

ICH M14 came into effect in March 2026

General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilise Real-World Data for Safety Assessment of Medicines

- Harmonised guidance for non-interventional studies using RWD
- Aims to improve consistency and reduce duplication across regions and support regulatory decision-making with real-world evidence (RWE)
- Early interaction with regulators encouraged
- Frameworks from non-governmental groups mentioned
  - (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, The Sentinel Innovation Center with the PRINCIPLED framework, ISPE/ISPOR's HARmonized Protocol Template to Enhance Reproducibility (HARPER) Initiative

Figure 1. A conceptual framework for generating adequate evidence using fit-for-use real-world data to address regulatory questions on the safety of medicines



- Start with a clearly defined research question – causal/descriptive
- Target Trial Emulation referred to
- Initial scan to narrow data options
- Concept & operational definitions for exposure, outcomes, covariates
- Can data support operational definitions? Reference to SPIFD.
- Reliability and relevance. Data to fit the study not the study to fit the data
- Aim to calculate unbiased estimate, address confounding. DAG.
- Study Registration
- Be transparent what's post-hoc

Primary & Secondary Non-Interventional Evidence Generation

- “Real-world” data emerges from where treatments are chosen by patients or providers (as in routine practice)
- The terms prospective and retrospective less preferred

Secondary use of data, aka “Retrospective”

← Time Horizons →

Primary Data collection, aka “Prospective”

Administrative claims data
Direct and indirect costs, comparative effectiveness/safety, adherence and persistence

Medical records
Disease severity, treatment rationale, side effects, effectiveness

RWE

RWE = real-world evidence

Prospective Longitudinal studies
Disease Registries, long-term observational studies

Population surveys
Standalone, linked to database

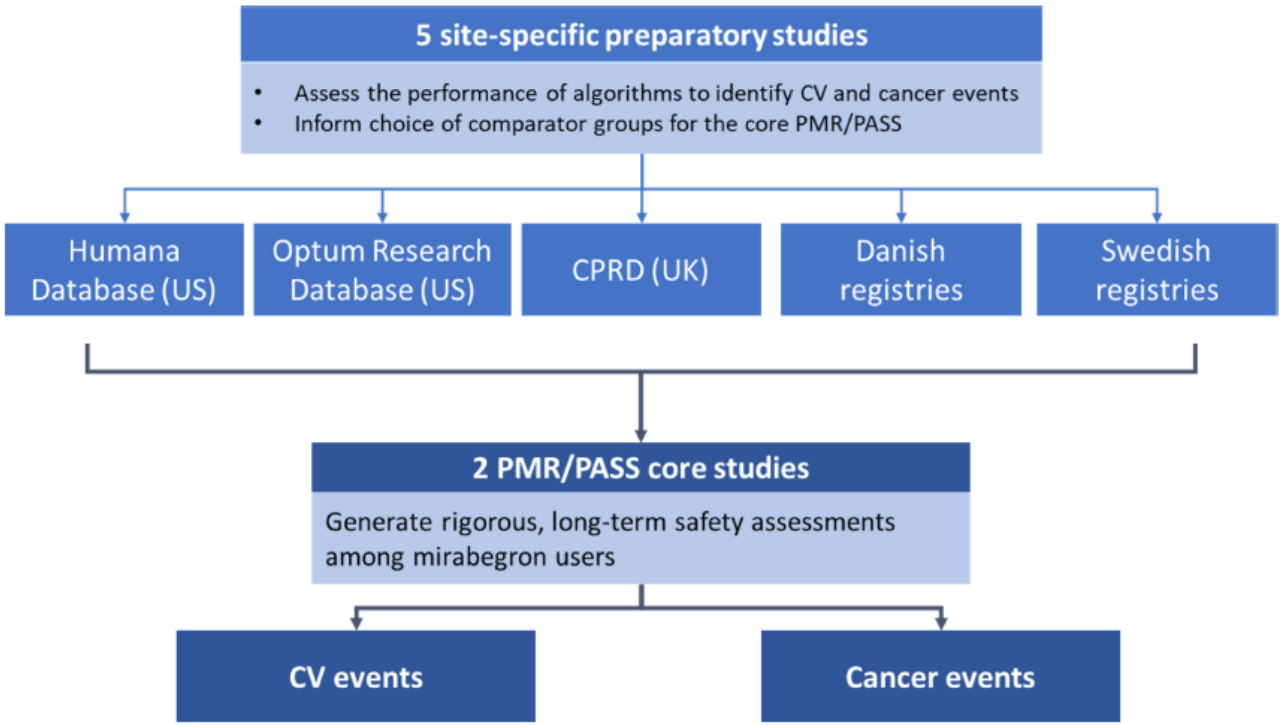
Biases

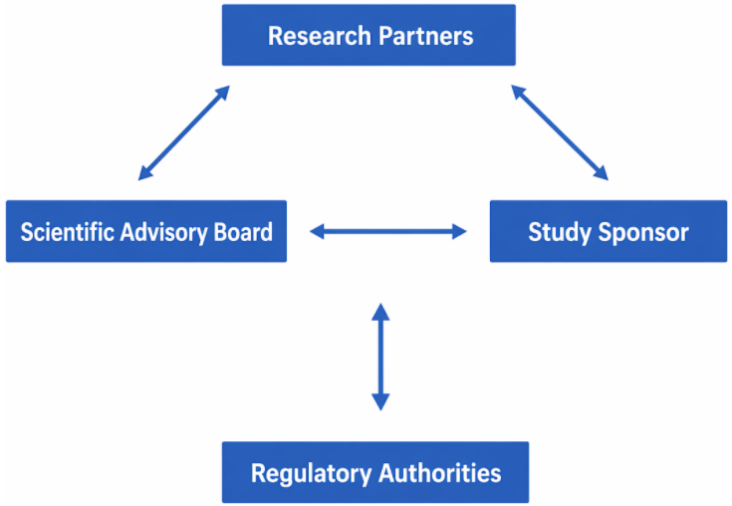
Selection bias
Information bias – recall, protopathic, surveillance/detection
Misclassification
Volunteer or interviewer bias
Referral bias, self-selection bias
Prevalent user bias
Time-related bias – immortal time, immeasurable time
Confounding (time-varying, measured, unmeasured, controlled, residual)

…Quantitative bias analysis

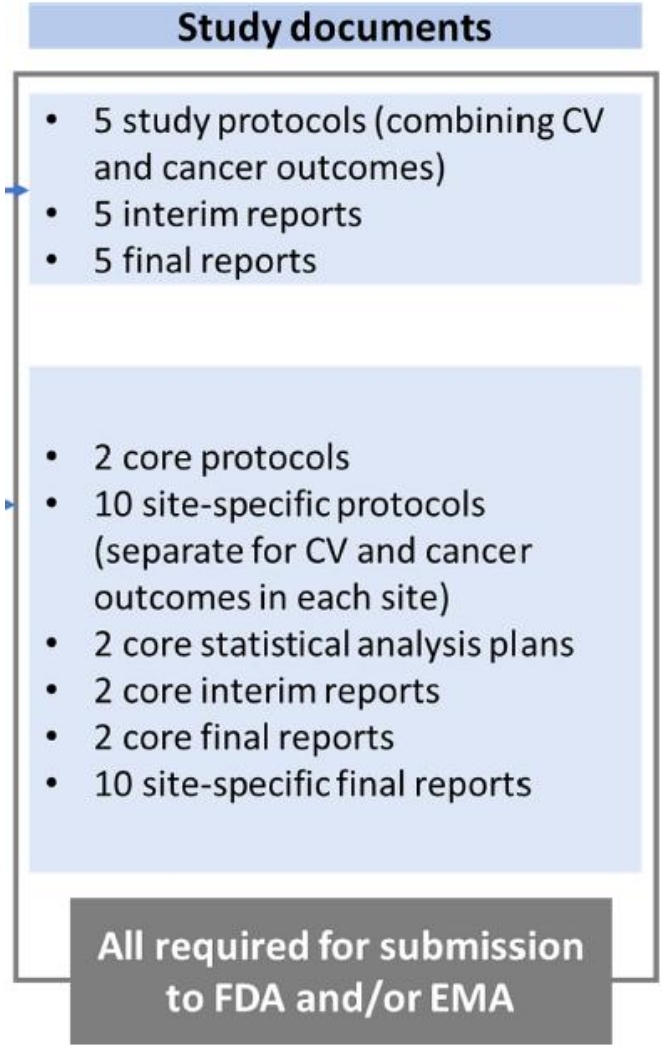
Example: NI-PASS Program

- Product approved for treatment of overactive bladder. In phase 3 trials, potential safety concerns were identified.
- Post-marketing requirements were issued.





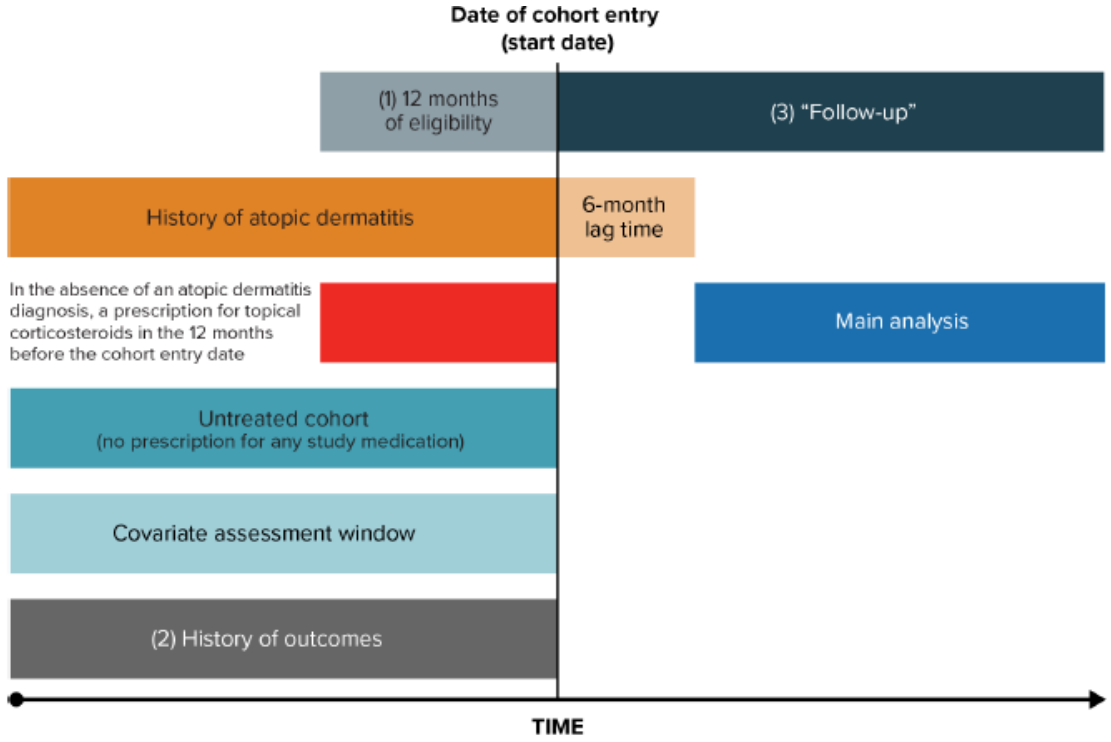
Example: design elements of statistical interest



- Outcome & key covariate validation
- New user design
- Mixed treatment comparator
- Propensity score matching
- Interim power assessment
- Meta-analysis

Example 2

- Product approved for atopic dermatitis, PASS for lymphoma
- Protopathic bias (reverse causation), confounding by indication
- Type of prescriber (1st prescription) proxy for indication severity.
  - Corrected for in CPRD and Denmark Using Probabilistic Bias Analysis



Availability of Characteristic	UK-CPRD GOLD	NL-PHARMO	Danish Health Registers	Swedish National Registers
Drug indication	Yes (ish)	No	No	No
Type of prescriber info	No (GP only)	Yes	No	Yes
Cancer data linkage	Partial	Yes	Yes	Yes

Regulators also have infrastructure to use RWD for safety assessment

https://www.sentinelinitiative.org/

https://darwin-eu.org/
Data Analysis and Real-World Interrogation Network

If you are a project statistician and RWD-based safety info passes your desk, consider these issues..

- For “simple” analyses
  - Choice of denominator can make a large difference to estimates
  - How conditions are coded/grouped etc will make a big difference to the rates – translation across coding dictionaries isn’t easy..
- For rigorous studies
  - Are the required covariates available/included for adjustments
  - Avoid/quantify those biases!

Thanks for listening and supporting responsible data collection & re-use!

OR

References

- ICH M14 guideline: “General principles on plan, design, conduct and interpretation of non-interventional studies using real world data for regulatory purposes” (Step 2 draft). 2023. https://www.ich.org
- US FDA. “Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies: Guidance for Industry”. Dec 2025. https://www.fda.gov/media/150356/download
- de Vogel S, Seeger JD, Arana A, et al. Lessons learned from a multi-data source research collaboration: The mirabegron post-authorization safety study program. *Pharmacoepidemiol Drug Saf*. 2024;33(5):e5799. doi:10.1002/pds.5799 [in turn includes references to publications of the studies in the program]
- Jordi Castellsague, Josephina G Kuiper, Anton Pottegård, Ingegärd Anveden Berglind, Daniel Dedman, Lia Gutierrez, Brian Calingaert, Myrthe PP van Herk-Sukel, Jesper Hallas, Anders Sundström, Arlene M Gallagher, James A Kaye, Carolina Pardo, Kenneth J Rothman & Susana Perez-Gutthann (2018) A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (Joint European Longitudinal Lymphoma and Skin Cancer Evaluation – JOELLE study), *Clinical Epidemiology, 299-310*, doi: 10.2147/CLEP.S146442
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Q & A

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