Risk Characterisation Utilising External Data Sources: A Methodological Consideration for Clinical Trials with High Subject Drop-Out

An Industry Perspective

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Worldwide Research & Development

Disclosure

- Jamie Geier is an employee and shareholder in Pfizer, Inc. The views expressed in this presentation do not necessarily represent those of Pfizer.

Risk Characterisation & Industry

- Epidemiology & Industry
  - Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC)
  - Varenicline (Chantix®)
- The Application of “Virtual Cohorts”
- Lessons Learned

ZODIAC=Ziprasidone Observational Study of Cardiac Outcomes

ZODIAC: Background and Study Rationale

- Ziprasidone is an atypical antipsychotic treatment launched September 2000 in Sweden and March 2001 in the United States
  - Modestly prolongs the QTc interval, but whether this has important clinical relevance was not known
  - Lower incidence of weight gain reported in clinical trials when compared with other antipsychotics
  - Potentially beneficial changes in lipid profiles observed with treatment in clinical development programme

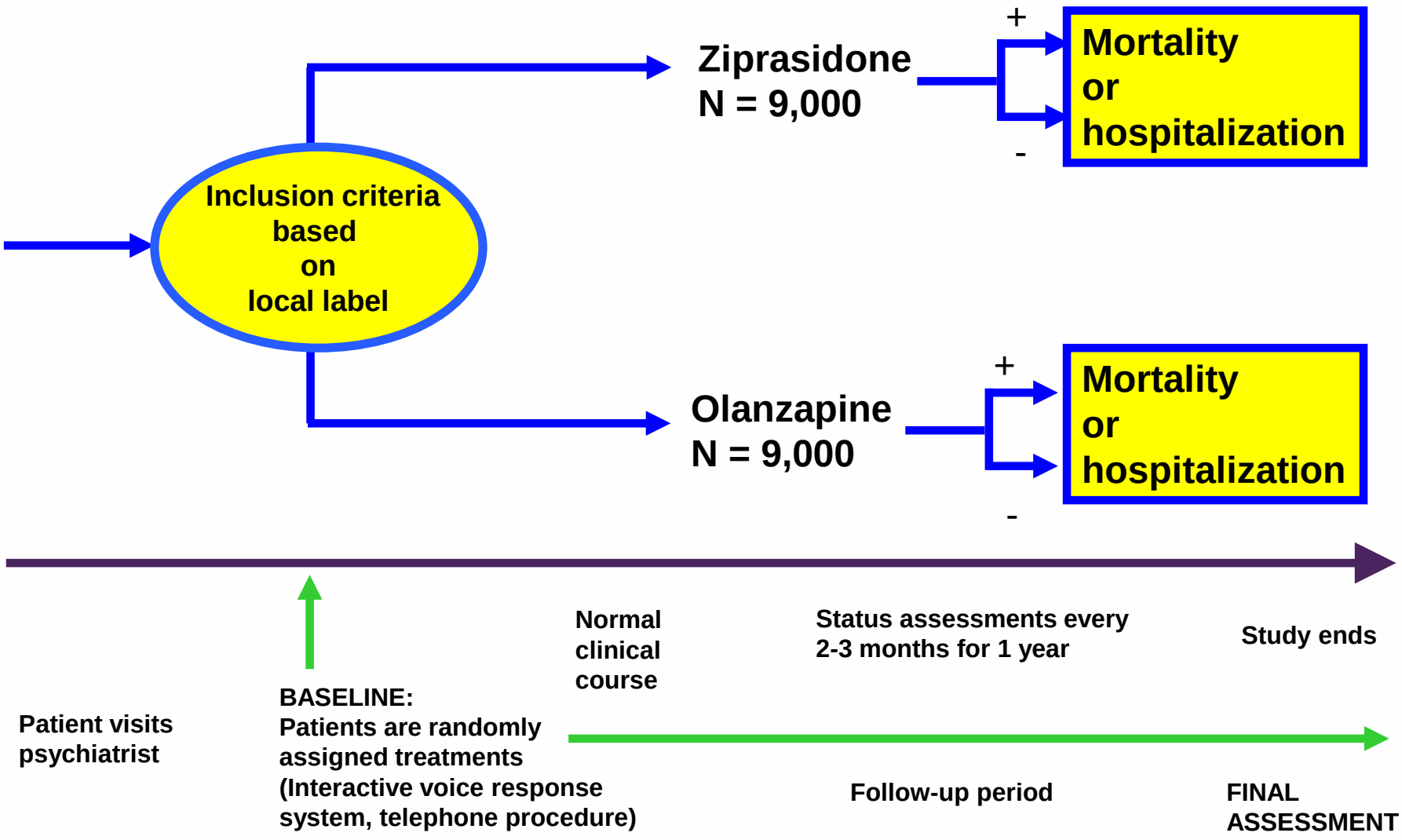
Question of interest to regulators at the time of approval:
Does use of ziprasidone in the "*real world*" increase the risk of clinically meaningful, serious cardiovascular events?

ZODIAC: Methodology

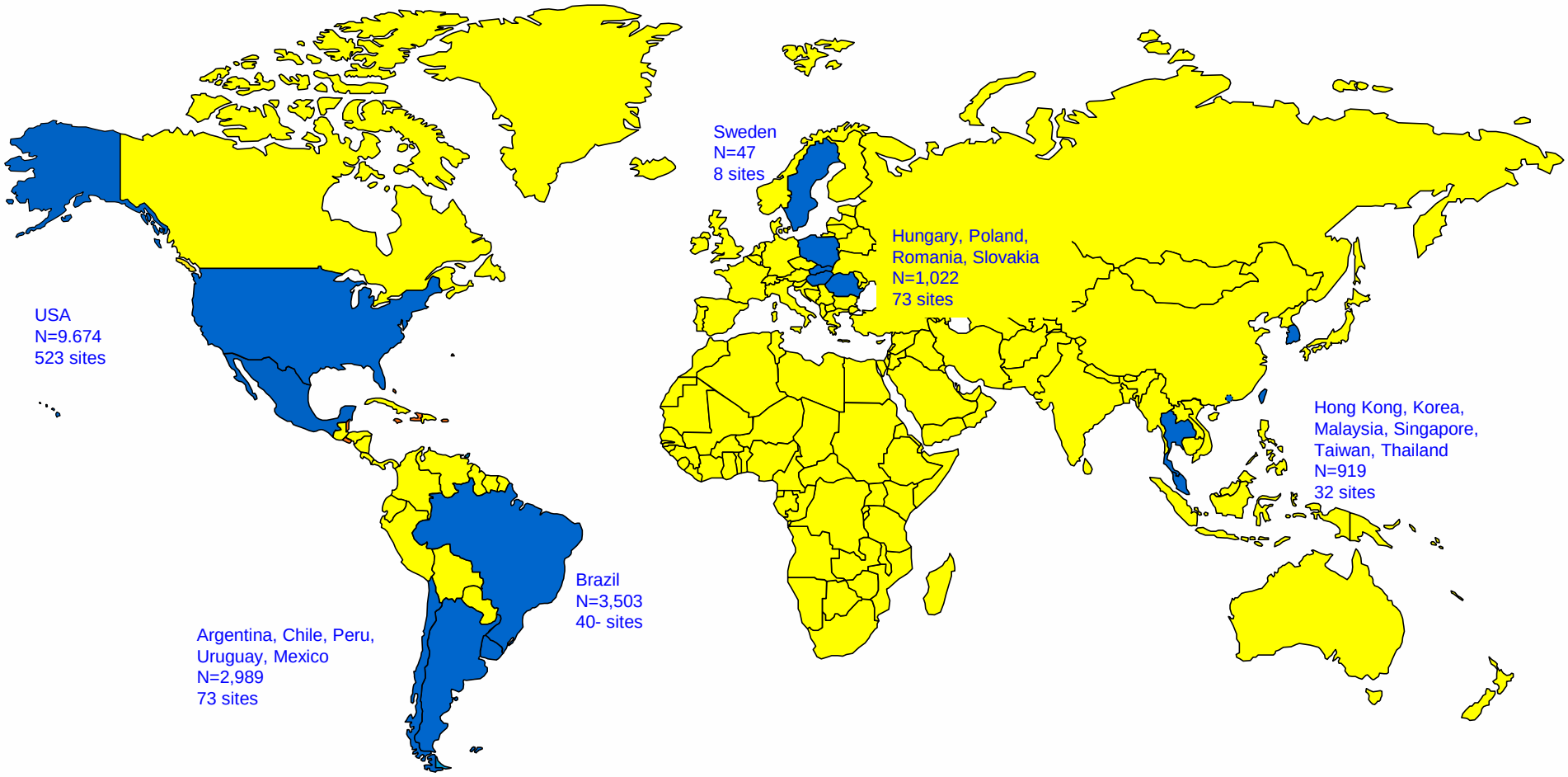
- An international, multicenter, observational study with randomization to compare the cardiovascular safety of ziprasidone and olanzapine
- Study design is “Large Simple Trial”
  - Large, naturalistic, prospective study with random assignment of patients to antipsychotic treatment, to control for channeling bias
  - 18,154 patients randomised to ziprasidone or olanzapine
  - No additional study-required monitoring or tests after randomisation
  - Follow-up during usual care for 1 year
- Both agents to be used as per local product labeling (USPI, SPC etc.)
  - Ziprasidone 40 mg/day starting dose in the United States, 80 mg/day in other countries; maximum 160 mg/day
  - Olanzapine 5-20 mg/day

mg=miligrams; SPC= Summary of Product Characteristics; USPI=United States Product Insert

ZODIAC: Design



ZODIAC: Global Enrollment in 18 Countries



Total Patient Enrollment = 18,154 patients from 749 sites

ZODIAC: Mortality Endpoint Results

Mortality endpoint	Ziprasidone (n= 9,077) n (%)	Olanzapine (n=9,077) n (%)	Relative Risk (95% CI)	Total (N=18,154) n (%)
Non-suicide mortality*	83 (0.91)	81 (0.90)	1.02 (0.76, 1.39)	164 (0.90)
All cause mortality	103 (1.13)	102 (1.12)	1.01 (0.77, 1.33)	205 (1.13)
Sudden death	2 (0.02)	3 (0.03)	0.67 (0.11, 3.99)	5 (0.03)
Cardiovascular mortality†	3 (0.03)	8 (0.09)	0.38 (0.10, 1.41)	11 (0.06)
Suicide mortality	19 (0.21)	16 (0.18)	1.19 (0.61, 2.31)	35 (0.19)

*One death in the ziprasidone group met criteria for both non-suicide and suicide mortality.
† When events classified by Endpoint Committee as cardiovascular mortality with insufficient data conservatively added to definite and possible events, RR = 1.60 (95% CI: 0.84, 3.05) for ziprasidone vs. olanzapine.

ZODIAC: Readjudication of the Secondary Endpoint of Sudden Death, Three Domains

Witness

- Witnessed
- Not Witnessed
- Insufficient / No Information

Timing

- ≤ 1 hour
- >1 hour to ≤ 24 hours
- > 24 hours
- Insufficient / No Information

Cause

- Cardiac arrhythmia (non-conduction disorder)
- Cardiac arrhythmia (conduction disorder)
- Myocardial Infarction
- Other cardiac cause
- Non-cardiac cause
- Unknown

ZODIAC:
Readjudication Results using ICD-10 Coding

Sudden Death Endpoints	Ziprasidone (n= 9,077) n (%)	Olanzapine (n=9,077) n (%)	Relative Risk (95% CI)	Total (N=18,154) n (%)
Sudden death (original)	2 (0.02)	3 (0.03)	0.67 (0.11, 3.99)	5 (0.03)
NOS (R96 or R96.1 or I46.1)	9 (0.1)	8 (0.1)	1.11 (0.45-2.77)	17 (0.1)
Sensitivity Analyses (R96 or R96.1 or I46.1 or R98 or R99)	20 (0.2)	27 (0.3)	0.73 (0.44-1.22)	47 (0.3)
NOS (R96 or R96.1)	6 (0.1)	5 (0.1)	1.19 (0.37-3.77)	11 (0.1)
Cardiac Death (I46.1)	3 (<0.1)	3 (<0.1)	0.99 (0.20-4.79)	6 (<0.1)
Sensitivity Analysis (R96 or R96.1 or I46.1 or R98 or R99 or "Other")	31 (0.3)	31 (0.3)	0.99 (0.65-1.50)	62 (0.3)

ICD-10= International Classification of Diseases and Related Health Problems, 10th Revision; NOS=not otherwise specified

ZODIAC: Conclusions

- ZODIAC is the largest randomised study of patients with schizophrenia conducted to date
- Readjudication of the sudden death endpoint according to ICD 10 criteria yielded results consistent with the study's initial findings
  - Sudden death NOS (RR=1.11, 95% CI: 0.45-2.77)
  - Sensitivity analyses (RR=0.73, 95% CI: 0.44-1.22)
- Supplemental analyses showed no difference in the risk of sudden death comparing persons randomized to ziprasidone versus olanzapine
- Fatal events occurring outside of a hospital setting often lack the clinical detail needed to apply specific ICD 10 codes

ZODIAC:
Operational Strategies for Patient / Site Retention

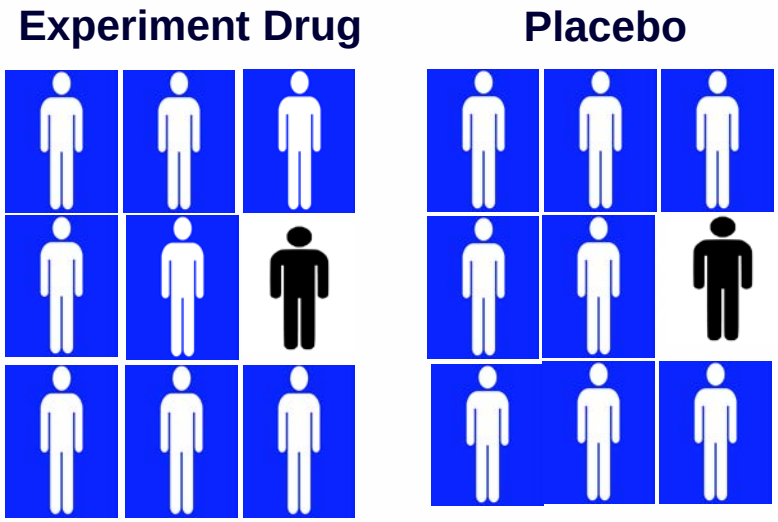
- 18,154 patients were randomized
- 15,194 patients completed the 1 year follow-up (83.3%)
  - 998 withdrew consent
  - 1667 were lost to follow-up

- Strategies implemented to mitigate engagement challenges included:
  - Global study expansion, field coordinator and site relations programs, monthly site newsletters, collection of alternate contact information, NDI searches, and frequent sponsor/CRO/site interactions

CRO=Contract Research Organization; NDI=National death index

Adverse Events Occurrence in Clinical Trial Programmes

- Evaluation of adverse events observed in experimental drug arm can be compared to “placebo” arm of clinical trial
  - No difference suggests adverse events are not uniquely associated with experimental drug



- But what if data in the placebo arm are not available or it is a rare event? What about long-term extension studies or studies that have poor patient retention?

Epidemiological Data Sources for Risk Characterisation

- Literature Review of Observational Studies
  - Patient characteristics
  - Capture of time (calendar and patient follow-up)
- Meta-analysis of Clinical Trials
  - Endpoint definitions & reporting conventions
  - Small numbers of patients & events
  - Short duration of follow-up
- Virtual Cohorts Using Pre-Existing Observational Databases
  - Sample size advantage allows stratification by patient characteristics
  - Operationalisation of endpoints
  - Methodological differences between data sources (if multiple sources are used)

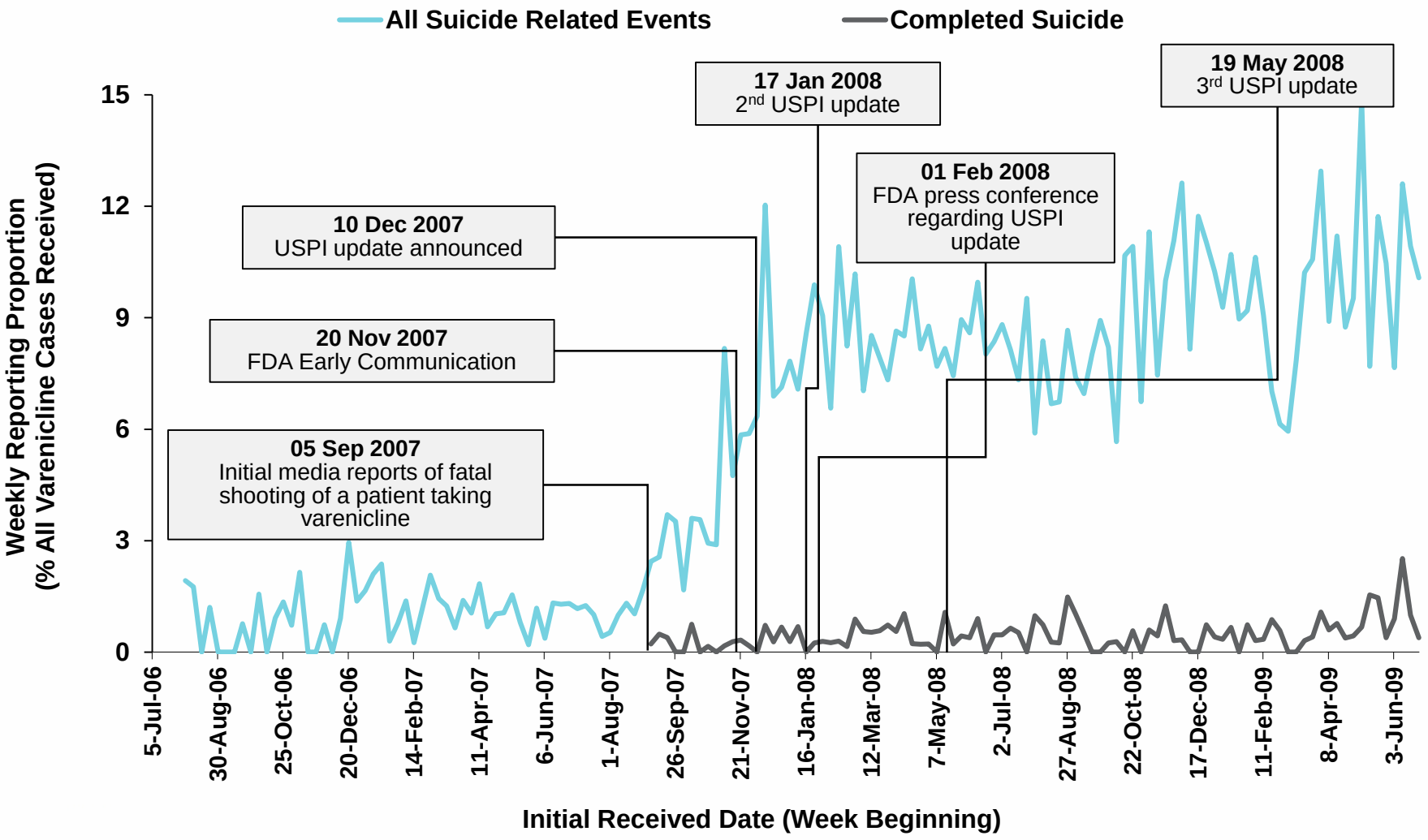
Varenicline (Chantix®)

- Postmarketing spontaneous reports raised a safety concern regarding serious neuropsychiatric (NPS) adverse events
- Available data did not support the existence of a causal relationship between varenicline and serious NPS
- Results of randomized clinical trials and observational studies have recently been added to the Warnings and Precautions section of the Chantix label

Varenicline: Developed Specifically to Address Nicotine Dependence

- Varenicline binds with high affinity to α4β2 nicotinic acetylcholine receptors (nAChRs)
  - nAChRs are widely distributed in the brain
  - Activation of α4β2 nAChRs in the ventral tegmental area plays a key role in mediating reinforcement- and dependence-producing effects of nicotine via dopamine release
- Varenicline is a partial agonist that
  - Has a higher α4β2 nAChR binding affinity than nicotine and outcompetes nicotine from binding to α4β2 nAChRs
  - Produces less dopamine release than nicotine
- These properties are thought to
  - Provide sustained, low-level dopamine release during a quit attempt
  - Inhibit the full agonist effect of nicotine during a smoking relapse

Varenicline: Possible surveillance bias



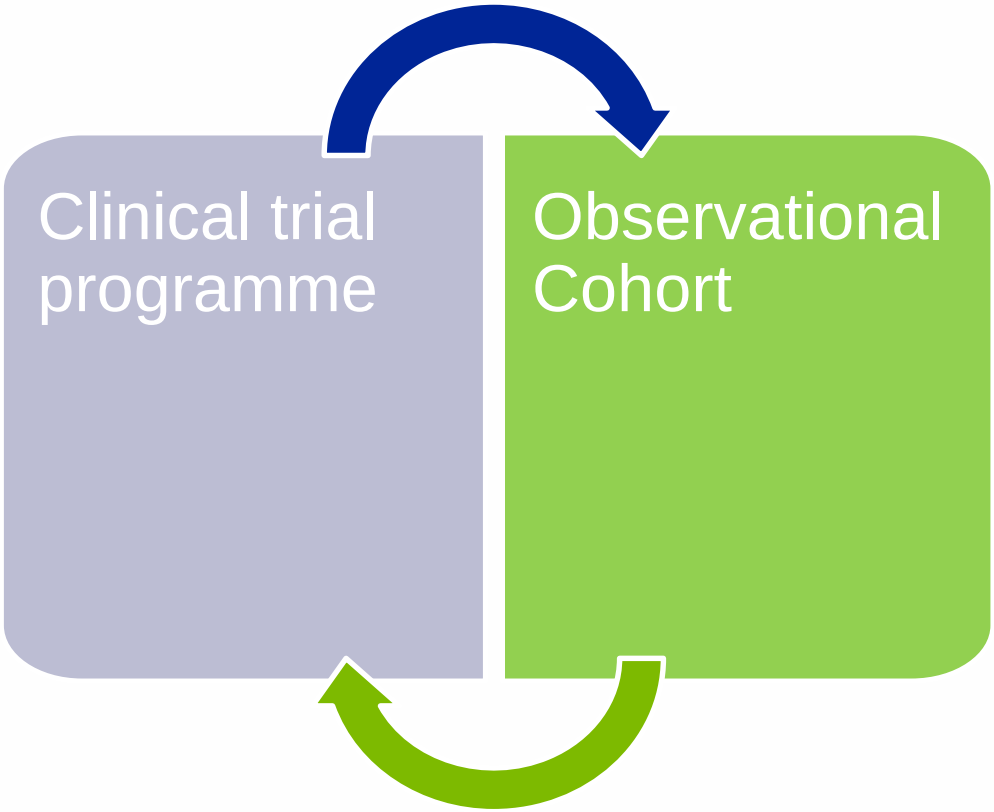
Varenicline:
Observational Studies of Fatal/Non-Fatal Self Harm

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
Suicide attempt	Cunningham	0 / 11,774	0 / 23,548	NA	NA	NA
Suicide	Thomas	2 / 30,352	6 / 78,407	NA	NA	NA
Fatal Or Non Fatal Self Harm	Thomas	19 / 30,352	69 / 78,407	0.88	0.52	1.49
	Kotz	119 / 51,450	540 / 106,759	0.56	0.46	0.68
	Molero	657 / 69,757	NA	1.00	0.72	1.37

CI=confidence interval; NA=not applicable

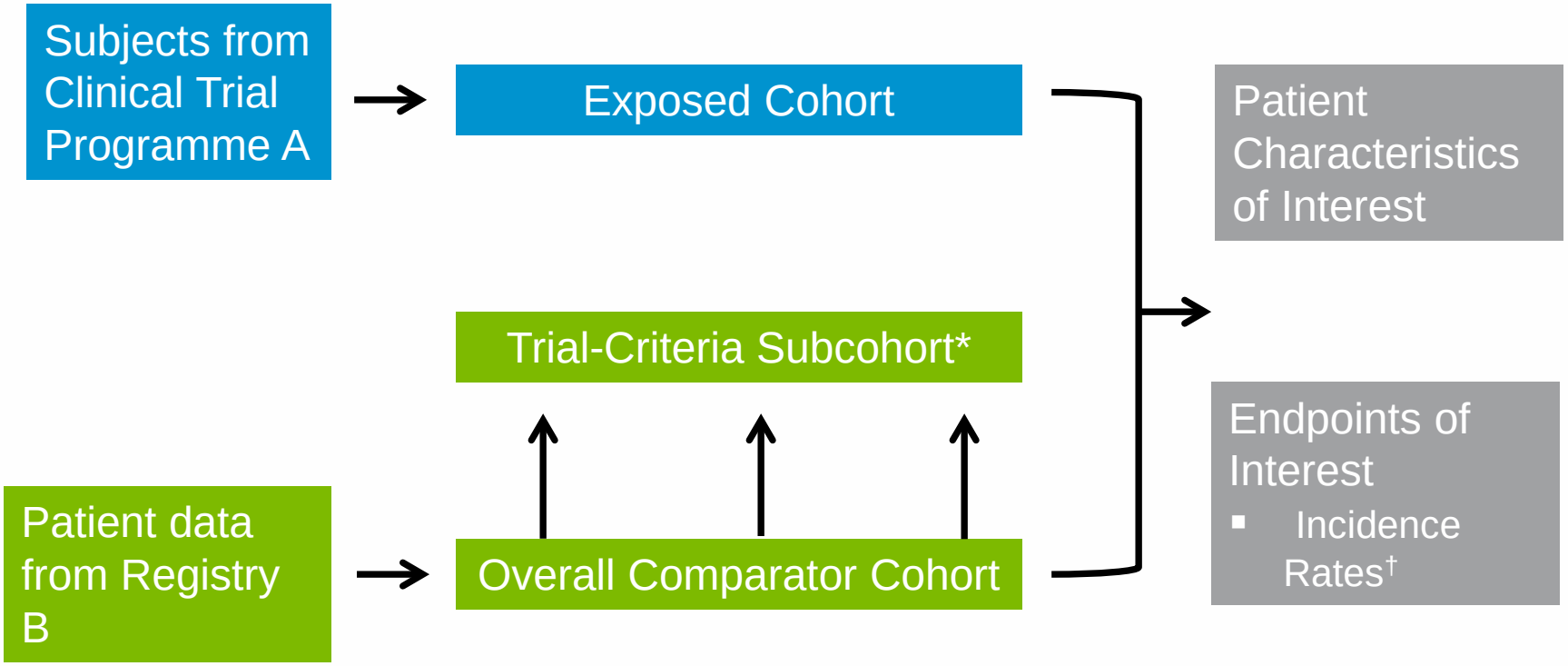
Inter-relationship between a Clinical Trial Programme & External Patient Cohorts

Need to characterise target population according to co-morbidities, complications and safety concerns



Findings Inform Clinical Trial Programmes

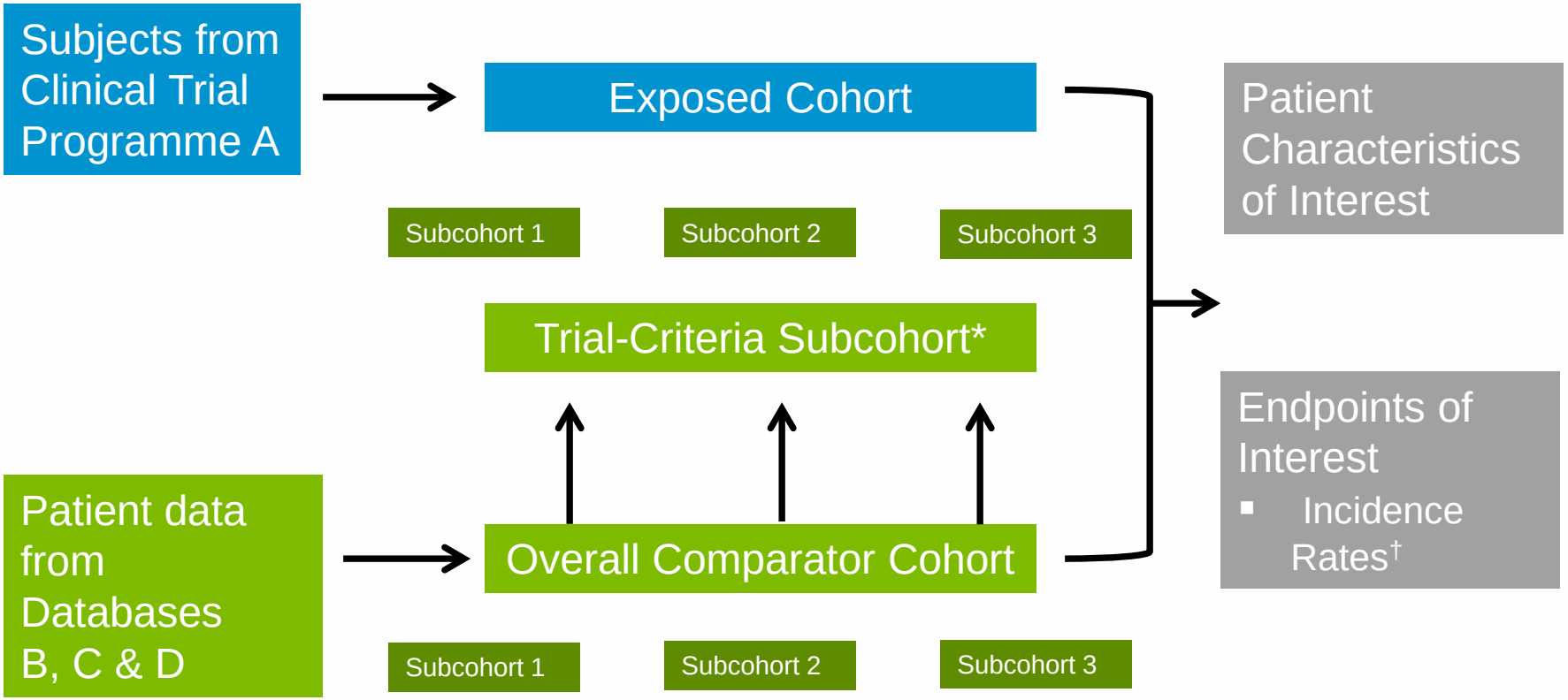
Case Study #1: Primary Care Therapy A



*To capture patients with similar demographic and clinical characteristics to the clinical programme under study (i.e., disease severity, age group, median/mean follow-up time, comorbidities)

†Age- and sex-standardised

Case Study #2: Specialty Care Therapy A



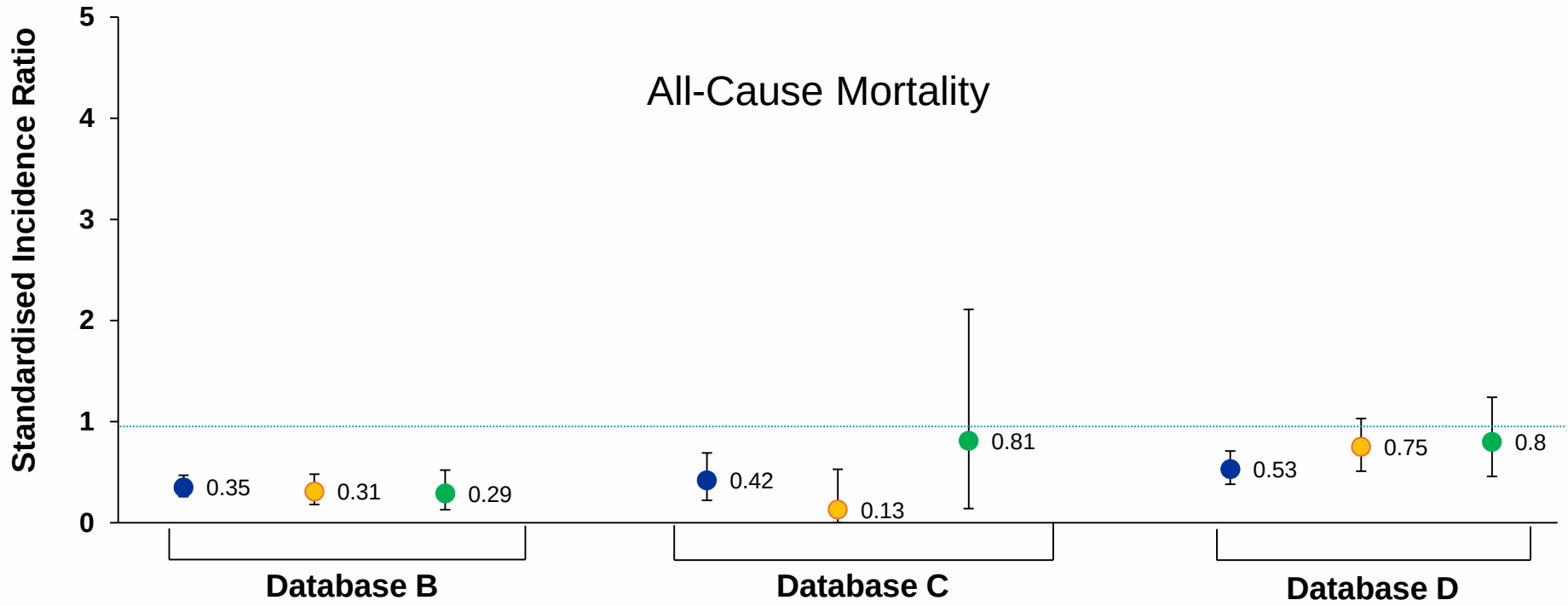
*To capture patients with similar demographic and clinical characteristics to the clinical programme under study (i.e., disease severity, age group, median/mean follow-up time, comorbidities)

†Age- and sex-standardised

Data Comparisons: Observed/Expected Analyses

- Standardised Incidence Ratios (SIR)
  - Standardised against the age & sex distribution of a comparator population
  - Interpreted like an RR or OR
    - >1.0 is increased risk, <1.0 decreased risk
- Data Sources
  - Electronic health records and patient registries
  - Long-standing history of safety evaluations & regulatory application
  - Sample sizes & endpoint operationalisation
- Events of interest
  - All-cause mortality & cardiovascular events

Standardised Incidence Ratios and 95% CIs Comparing Pfizer Drug X Subjects with Trial-Criteria Register Subcohorts of Patients Initiating their 1st, 2nd or 3rd therapy within 3 External Databases

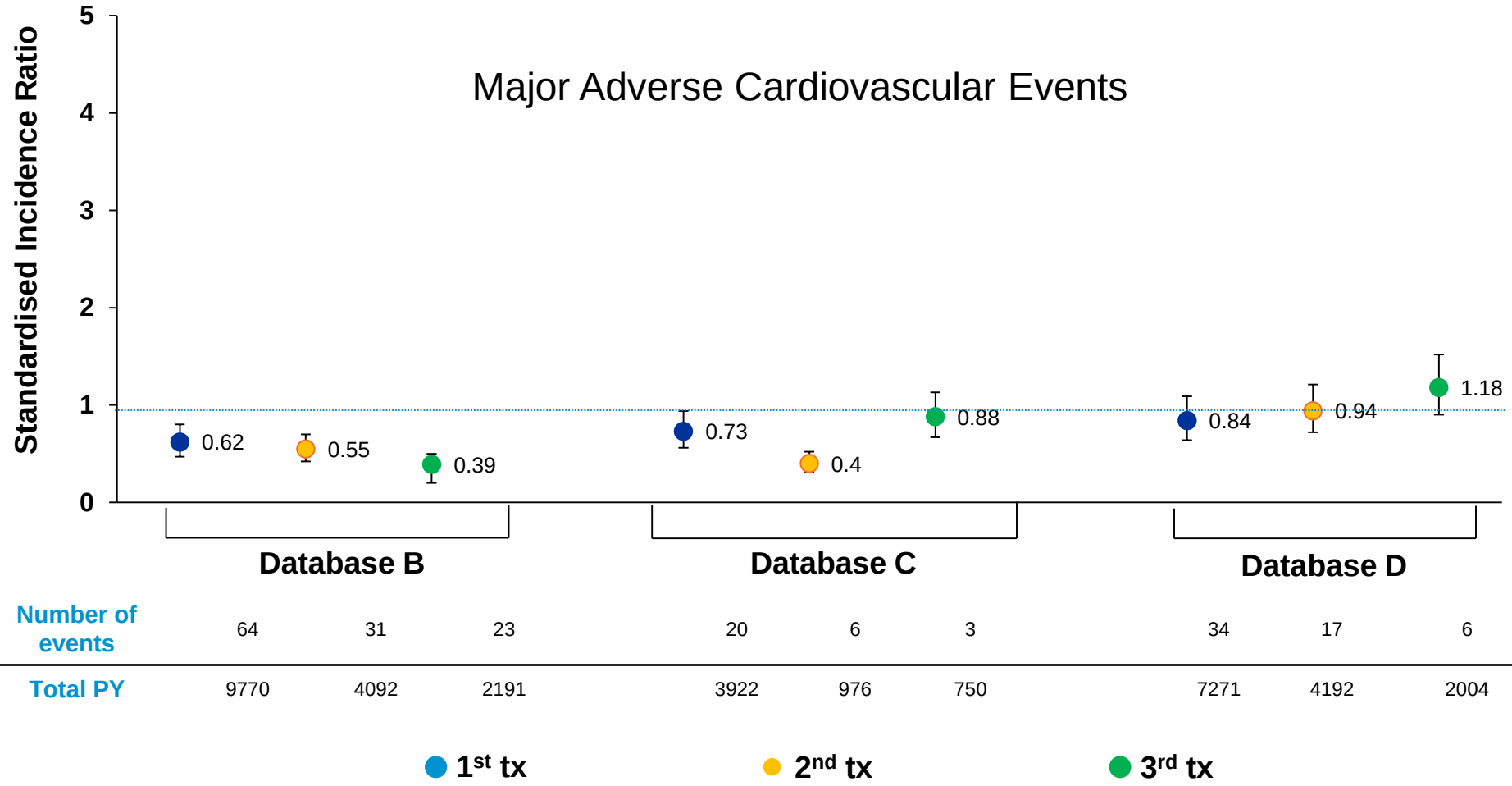


	Database B			Database C			Database D		
Number of events	46	18	9	13	1	3	41	35	20
Total PY	14605	6527	3605	3922	976	750	8349	5691	3356

● 1st tx ● 2nd tx ● 3rd tx

CI=confidence interval; PY=patient-years; tx=treatment

Standardised Incidence Ratios and 95% CIs Comparing Pfizer Drug X Subjects with Trial-Criteria Register Subcohorts of Patients Initiating their 1st, 2nd or 3rd therapy within 3 External Databases



CI=confidence interval; PY=patient-years; tx=treatment

Learnings

- What worked well
  - Common protocol
  - Common statistical plan (with formatted tables)
  - Common endpoint operationalisation
  - Face-to-face meetings
- Knowledge gained
  - Adequate operational and scientific support is critical, both internally and externally
  - Ad hoc queries happen
- Challenges
  - Pooling of data for rare events across registries
  - Methodological differences in data sources
  - Data confidentiality
  - Timelines

Conclusions

- Registries and other patient databases provide viable options for risk characterisation

- While collaborations between databases and industry are possible, success is contingent on:
  - Timelines
  - Established protocols/statistical analysis plans
  - Methodological differences between data sources
  - Sample sizes
  - Operational and scientific support (i.e., programming & statistics)

- Additional work is needed to help address rare diseases and outcomes (i.e., pooling data sources, meta-analytic techniques, etc.)

Thank you.