BHIVA
British HIV Association

2023 Spring Conference

Mon 24th – Wed 26th April
Gateshead, UK

HIV Medicine

Caroline Sabin

University College London, UK

This educational event is supported by

GILEAD Creating Possible
MSD
ViiV Healthcare

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HIV Medicine Workshop

Caroline Sabin

Conflict of Interest

I have received funding for the membership of Data Safety and Monitoring Boards, Advisory Boards and for the preparation of educational materials from:

- Gilead Sciences
- ViiV Healthcare
- Janssen-Cilag
- Merck Sharp & Dohme

Speakers are required by the Federation of the Royal Colleges of Physicians to disclose conflicts of interest at the beginning of their presentation, with sufficient time for the information to be read by the audience. They should disclose financial relationships with manufacturers of any commercial product and/or providers of commercial services used on or produced for patients relating to the 36 months prior to the event. These include speaker fees, research grants, fees for other educational activities such as training of health professionals and consultation fees. Where a speaker owns shares or stocks directly in a company producing products or services for healthcare this should also be declared.

HIV MEDICINE

Reviewing papers: what to look for in Real World Evidence (RWE) studies

Caroline A. Sabin
Editor-in-Chief, *HIV Medicine*

BHIVA British HIV Association

EACS European AIDS Clinical Society

DAIG Deutsche AIDS-Gesellschaft e.V.

HIV MEDICINE

Reviewing papers: wha… …eal World Evid…

- Are they really ‘real-world’?
- Do they provide strong evidence?

…cine

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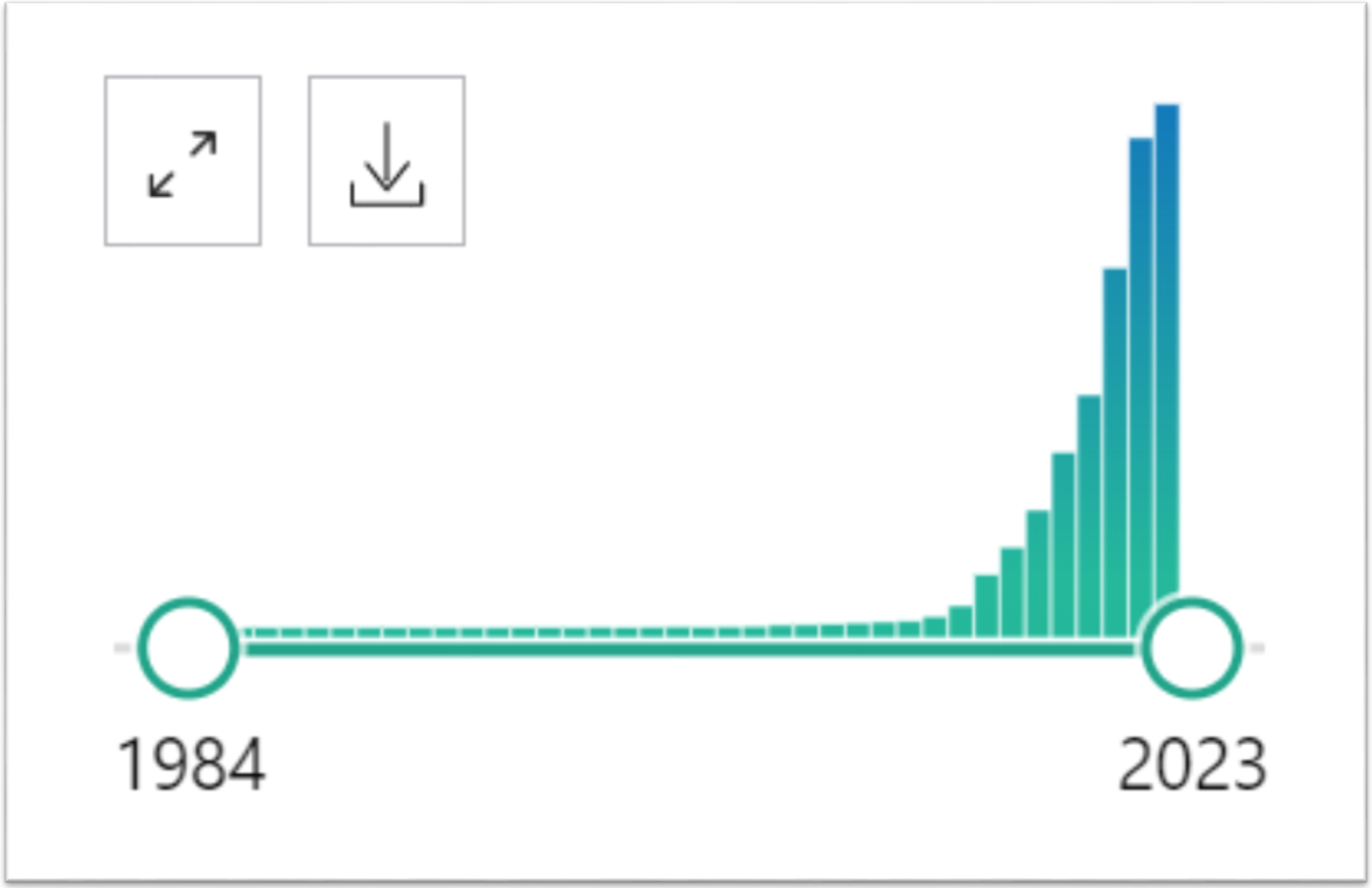
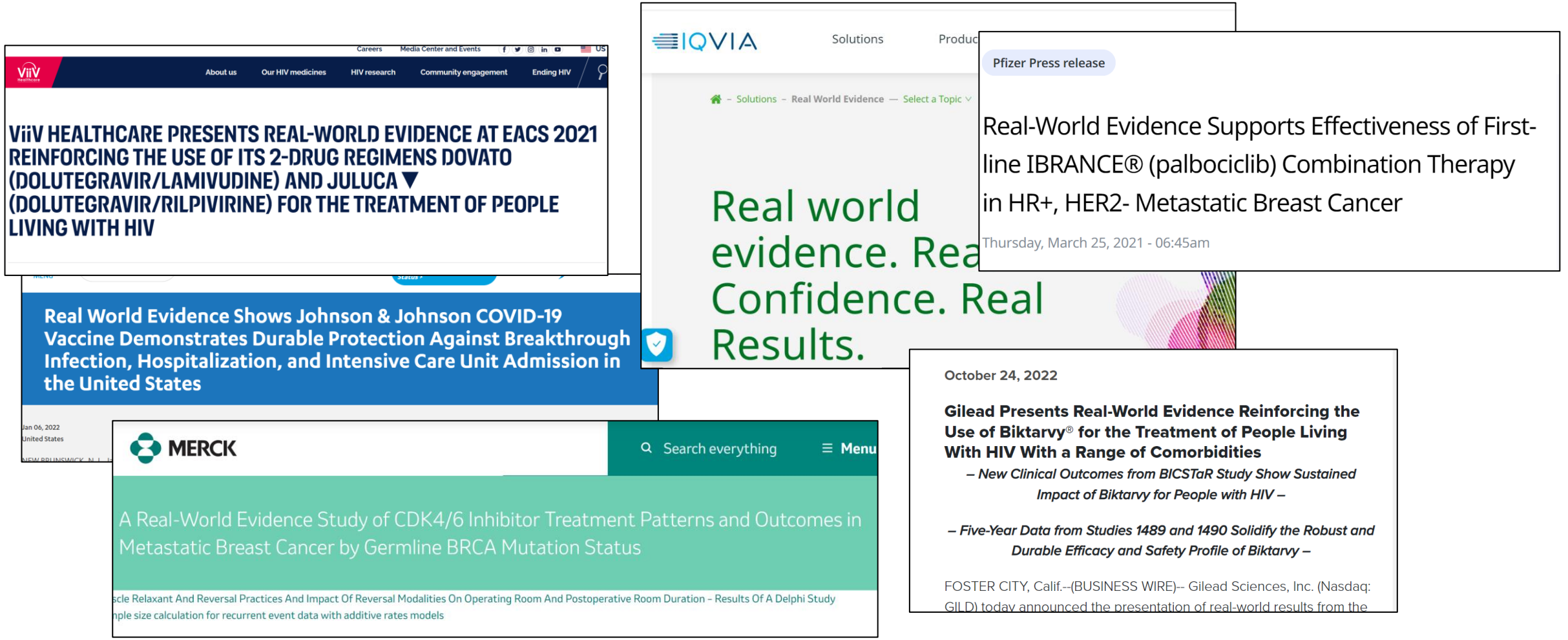
Real World Evidence (RWE) – my reaction

RWE studies, PubMed, 1984-2023



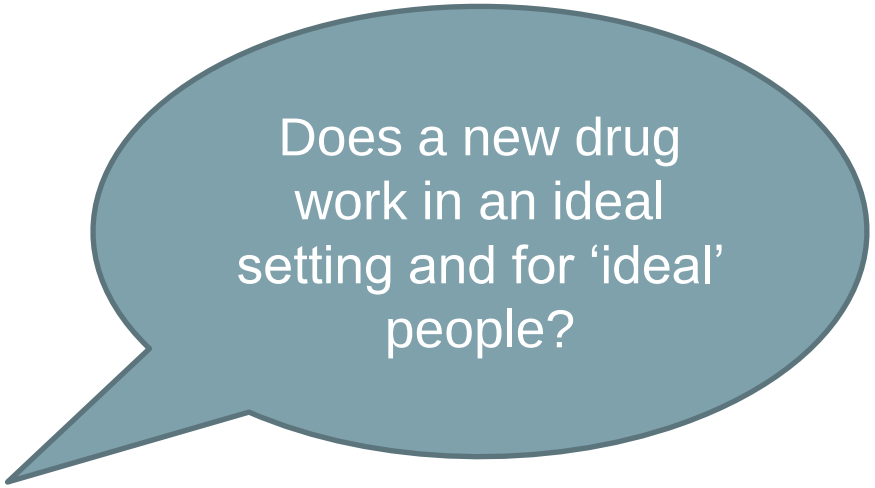
RWE and Pharma



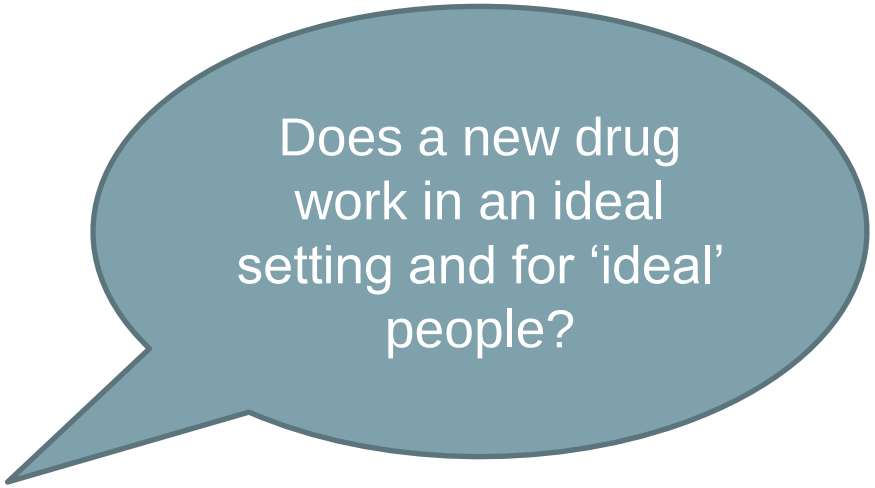
Plan of talk

- How do we ‘assess’ whether a new drug intervention works?
- What is RWE?
- What should you look for when reviewing RWE studies?

Assessing whether a new drug intervention works

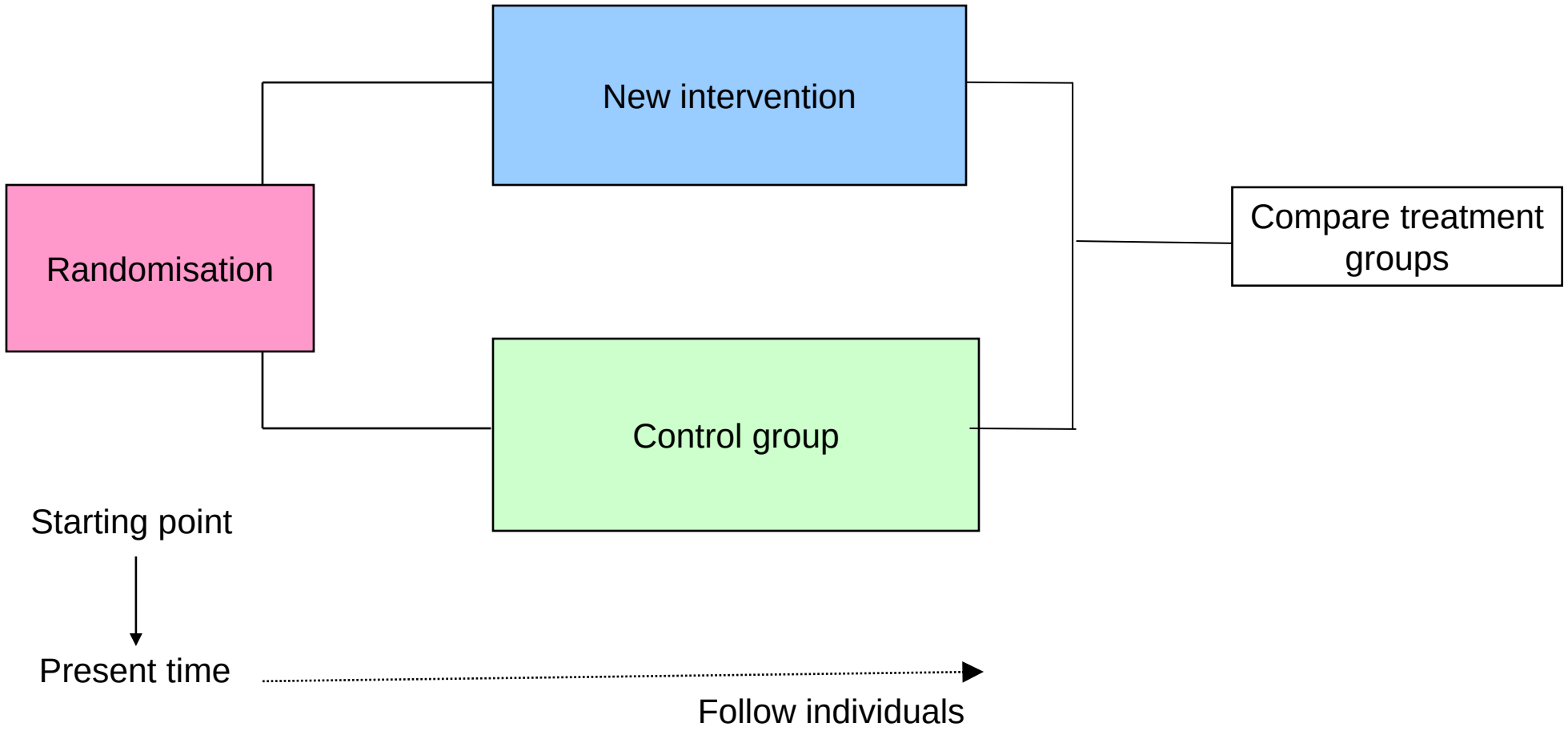


Assessing whether a new drug intervention works



- Test of **efficacy**
- Generally studied in RCT

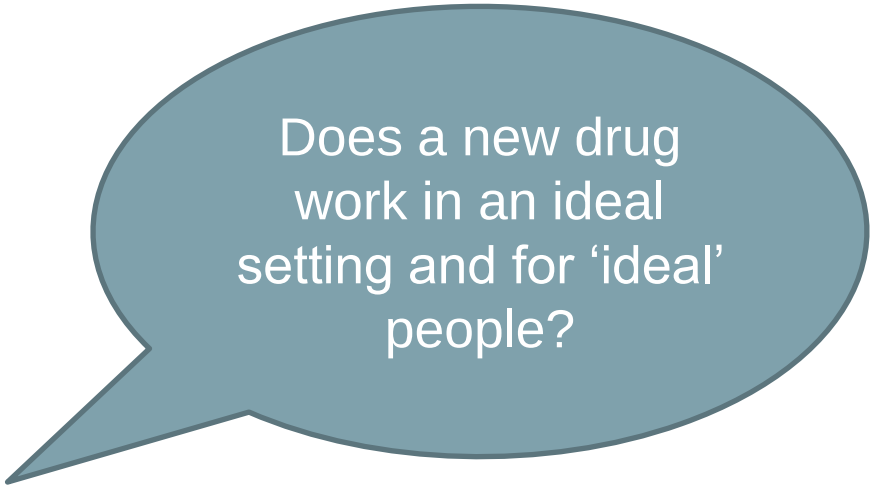
Parallel design RCTs



Other features of RCTs

- Usually fairly strict inclusion/exclusion criteria – population restricted to those most likely to benefit and/or complete trial
- Close attention to uptake of intervention – treatment switches generally ignored (intent-to-treat analysis)
- Regular monitoring of participants
- Losses-to-follow-up recorded and incorporated into analyses appropriately

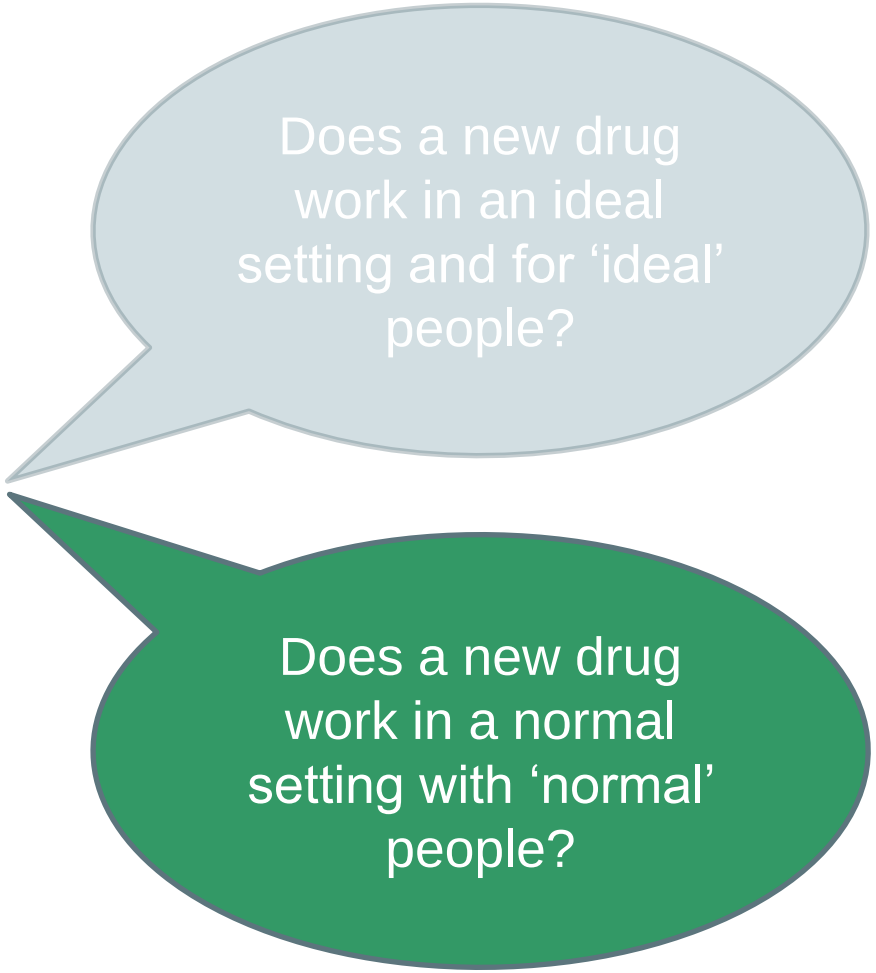
Assessing whether a new drug intervention works



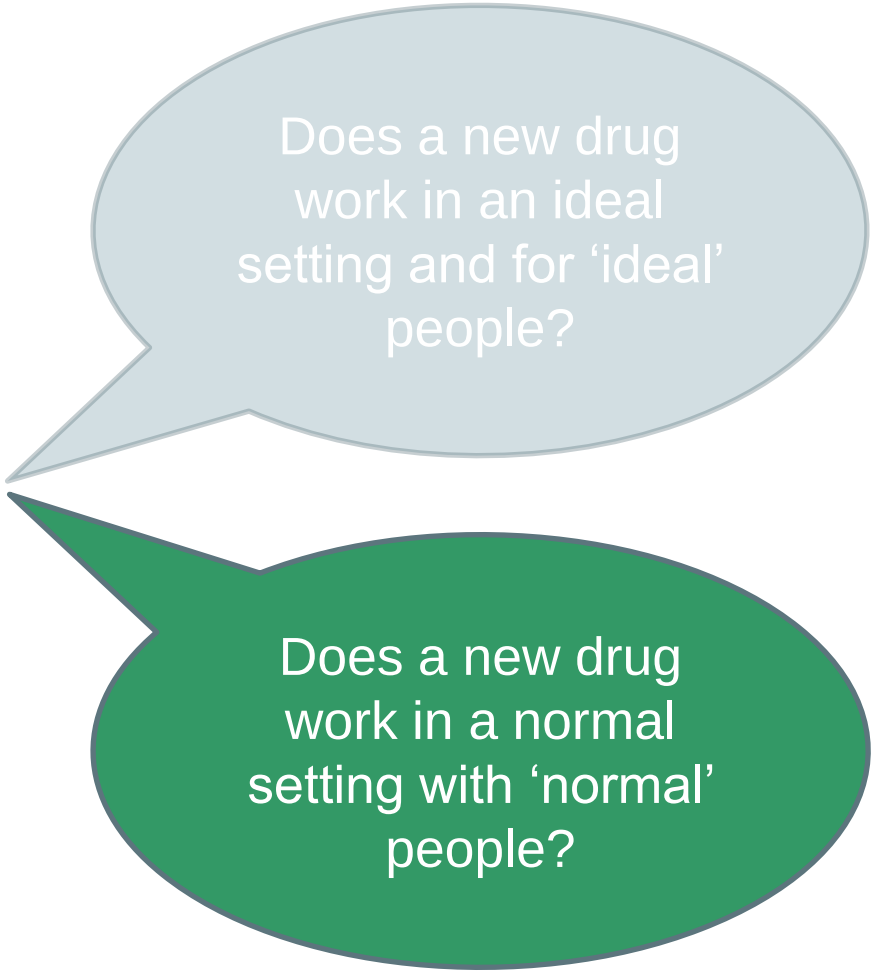
- Test of **efficacy**
- Generally studied in RCT
- Highly selected population
- High fidelity to intervention
- High **internal** validity but **external** validity uncertain

Do we really believe we will see the same treatment effect if the drug is given to a different population with different characteristics?

Assessing whether a new drug intervention works



Assessing whether a new drug intervention works



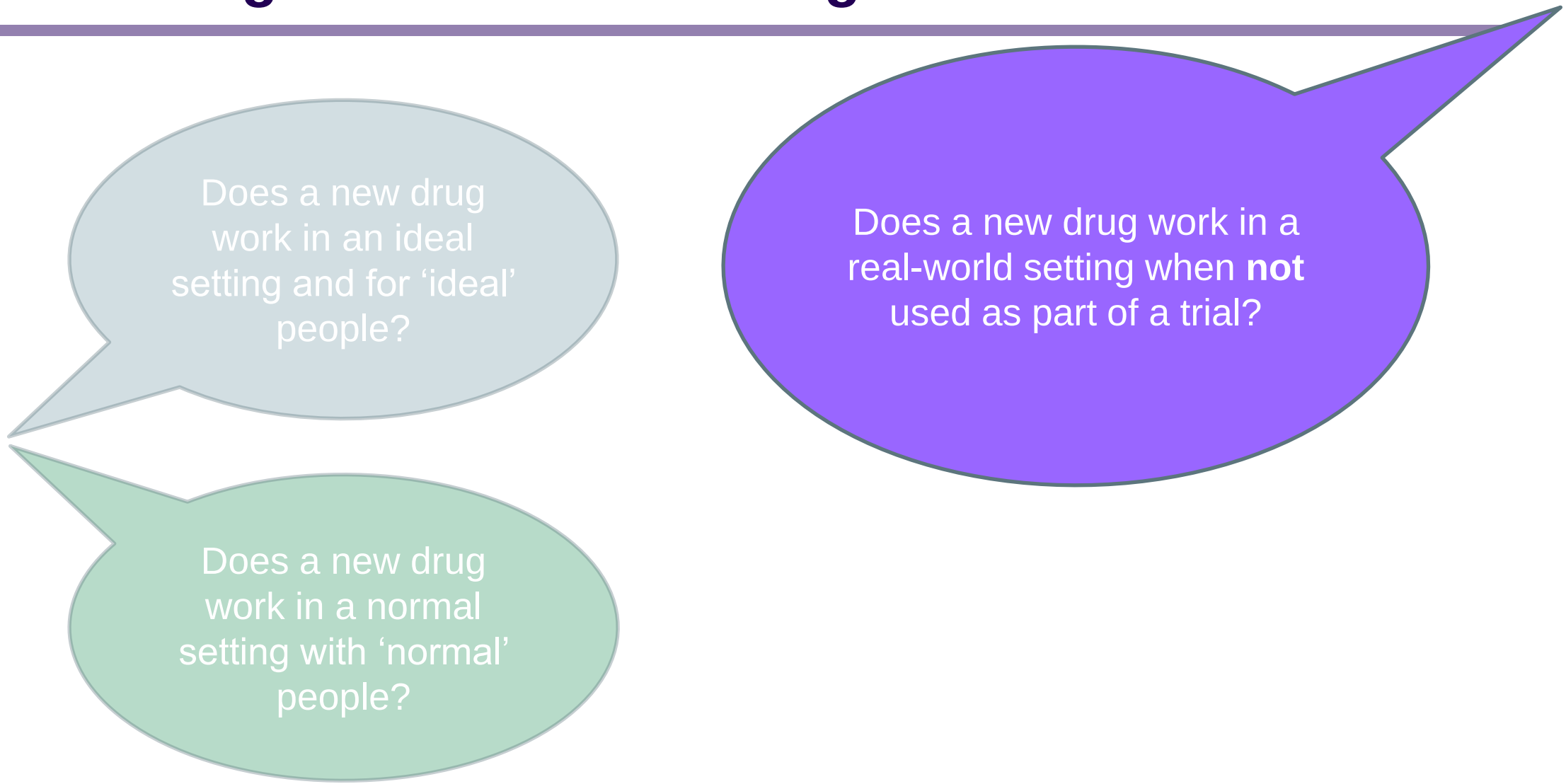
- Test of **effectiveness**
- Still usually studied in RCT
- More representative population
- Realistic fidelity to intervention
- Thus higher external validity

RCTs of efficacy vs. effectiveness

	Efficacy study	Effectiveness study
Question	Does the intervention work under ideal circumstance?	Does the intervention work in real-world practice?
Setting	Resource-intensive 'ideal setting'	Real-world everyday clinical setting
Study population	Highly selected, homogenous population Several exclusion criteria	Heterogeneous population Few to no exclusion criteria
Providers	Highly experienced and trained	Representative usual providers
Intervention	Strictly enforced and standardized No concurrent interventions	Applied with flexibility Concurrent interventions and cross-over permitted

Singal AT, *et al.* *Clin Trans Gastroenterol* 2014;5(1):e45.

Assessing whether a new drug intervention works



Assessing whether a new drug intervention works

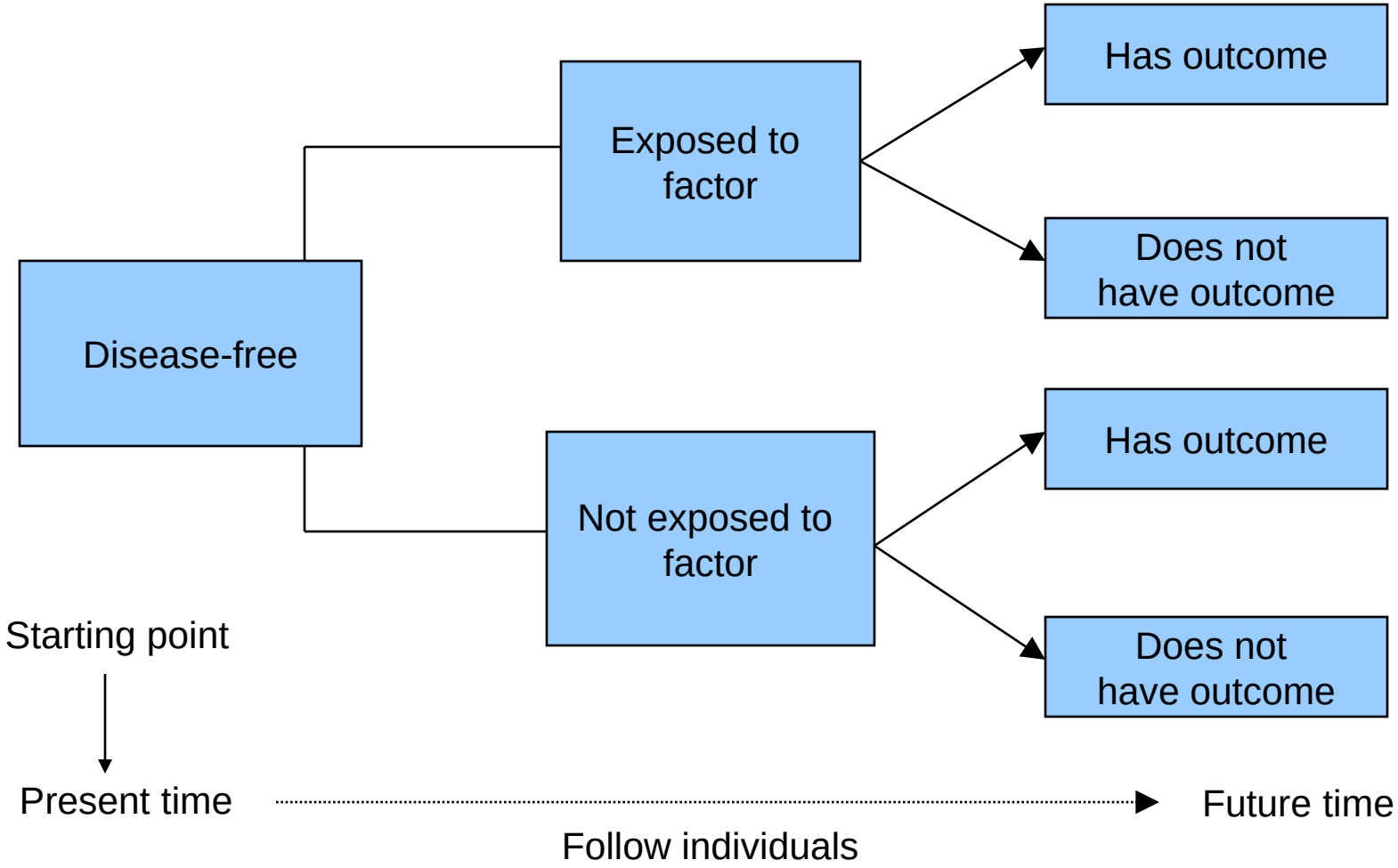
Does a new drug work in an ideal setting and for 'ideal' people?

Does a new drug work in a normal setting with 'normal' people?

Does a new drug work in a real-world setting when **not** used as part of a trial?

- 'Real-word' **effectiveness**
- Usually studied in cohort/registry
- Representative population
- Little attention on fidelity to intervention

Cohort studies



But why rely solely on RCTs or cohorts?

- Many clinics collect information on those attending their service
- People are treated and monitored following standard protocols
- Includes those not normally be considered for inclusion in a RCT
- Why not use this information to learn about how a drug works in a fully representative and unselected, population?

What is RWE?

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., et al.

"‥ information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, produce and disease registries, and data gathered through personal devices and health applications."

Sherman RE, et al. *NEJM* 2016; **375**: 2293-2297.

Example: Real-life experience with bictegravir (BIC) /emtricitabine (FTC)/tenofovir anafenamide (TAF)

- Observational, retrospective, single-centre study in Barcelona
- All adults with HIV starting BIC/FTC/TAF from 8/6/2018
- Viral suppression (<50 copies/ml) rates (on-treatment)
  - M6: ART-naïve 77% ART-experienced 94%
  - M12: ART-naïve 92% ART-experienced 93%
- Suppression rates were not as high as those observed in RCTs of treatment-naïve people treated with BIC/FTC/TAF

Ambrosioni J *et al.* *J Antimicrob Chemother* 2022 https://doi.org/10.1093/jac/dkab481

Example: Impact of switch to DTG vs. continuation of PI/r in people at risk of prior NRTI resistance

- Quebec HIV Cohort of 10,219 people with HIV
- Inclusion: all PWH with virologic failure or exposure to mono/dual NRTI therapy who were virologically suppressed on PI/r-based regimen for >6 months (n=532)
- 216 (40.6%) changed regimen to DTG+2NRTIs; 316 (59.4%) remained on PI/r+2NRTIs
- Weighted hazard ratio for effect of DTG switch on virologic failure: 0.57 (95% CI 0.21, 1.52)

N'dongo Sangare M *et al.* *Open For Infect Dis* 2020; 7(11): ofaa404

RWE studies to investigate drug adverse events

- RCTs maybe limited in their ability to detect relatively infrequent adverse events due to lack of power and/or duration of trial
- Observational/RWE datasets may offer a means to identify adverse drug events
- But results must always be interpreted with caution, particularly where adverse events are unexpected

Example:Integrase strand transfer inhibitor (INSTI) use and diabetes mellitus (DM)

- Used IBM MarketScan databases to identify PWH newly starting antiretroviral therapy (ART)
- Primary outcome: new-onset DM/hyperglycemia in 6 months after ART initiation
- INSTI use associated with increased risk of new-onset DM/ hyperglycaemia (HR 1.31 (95% CI 1.15-1.48))

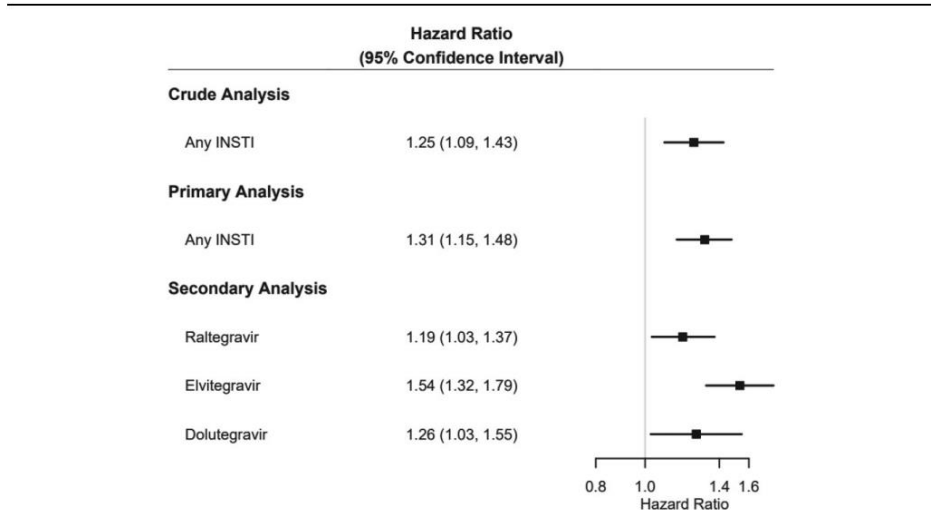


Figure 2. Hazard ratio estimates of new-onset diabetes/hyperglycemia in adults initiated on ART from July 2007 to June 2019. ART, antiretroviral therapy.

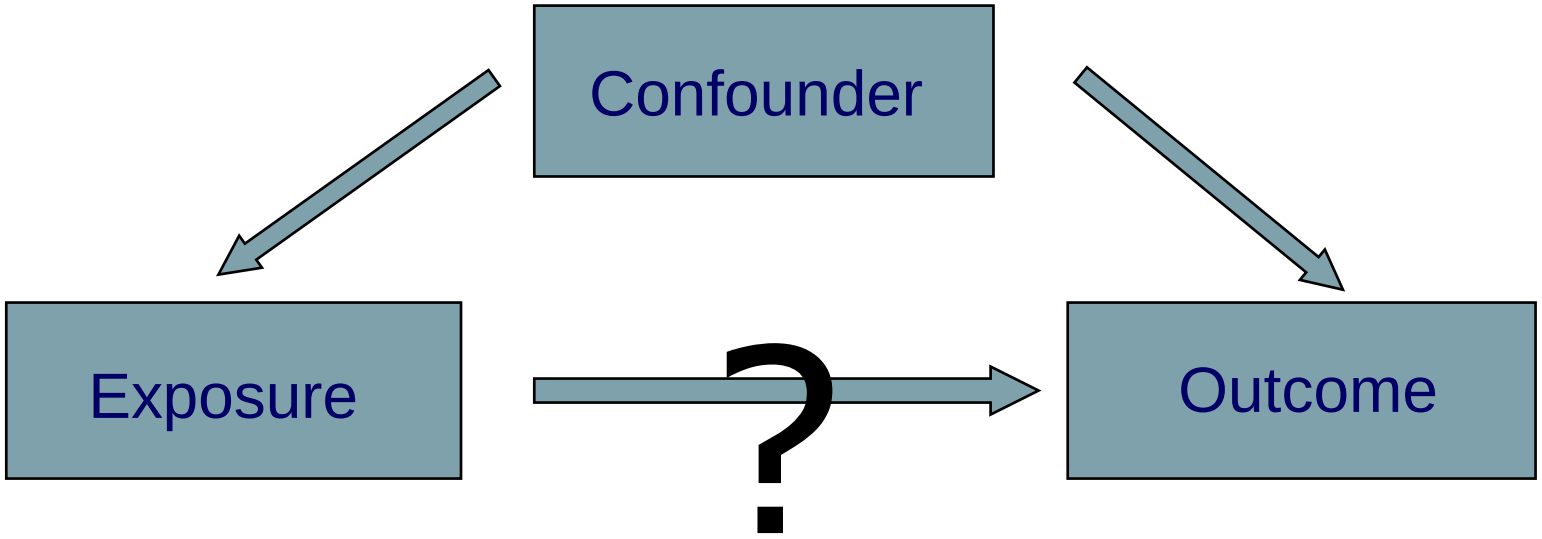
O'Halloran JA *et al.* *Clin Infect Dis* 2022 (on-line, ahead of print)

Limitations of RWE studies

- Data are not usually collected for research purposes and there may be issues around data quality/accuracy
- Observational studies subject to many different sources of bias, including:
  - Bias resulting from confounding/channelling
  - Missing/incomplete data
  - Monitoring bias
  - Attrition bias
  - Misclassification bias
  - Survivorship bias
  - Lead-time bias

Bias due to confounding

Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome

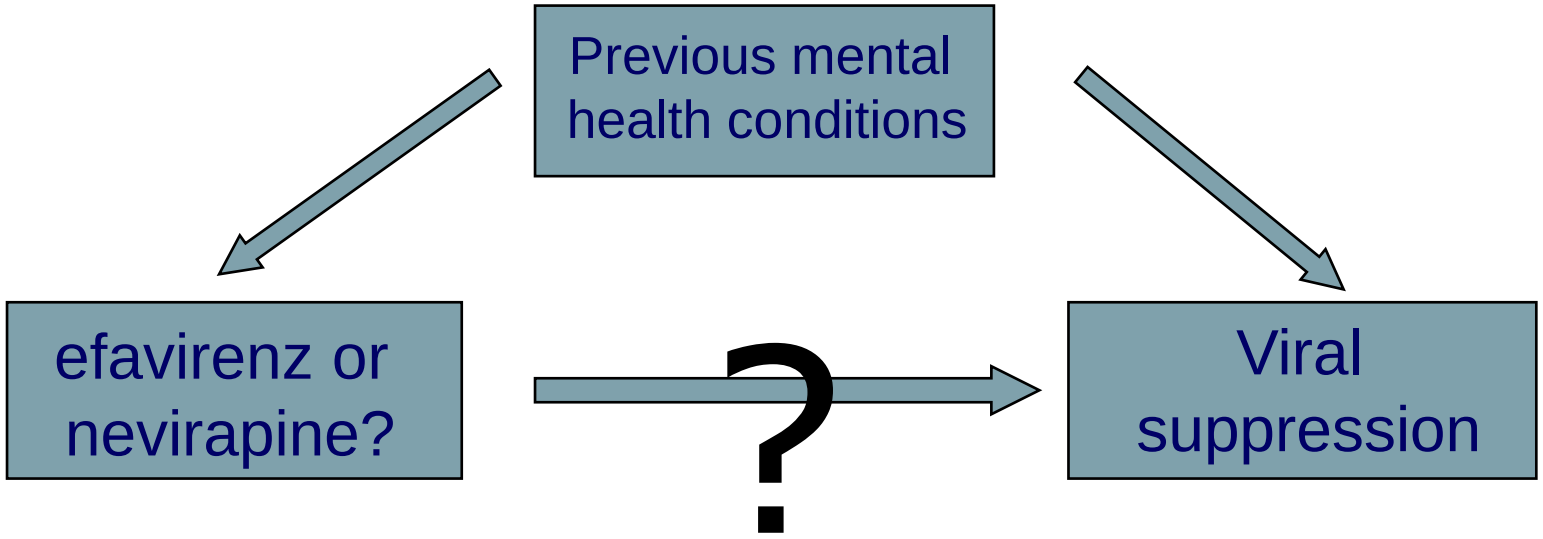


Example: is nevirapine associated with poorer virological outcomes than efavirenz?

- Several cohorts had reported that those receiving nevirapine had a poorer virological outcome than those receiving efavirenz
- Efavirenz may cause anxiety/depression and sleep disturbances, and is not recommended for use in those with mental health problems
- The presence of mental health problems is a known risk factor for poor drug adherence
- At that time, few cohort studies were able to collect high quality data on prior mental health problems in their participants

‘Channelling’ in RWE studies

ART drugs are not given randomly…



Defining endpoints in RCTs vs RWE studies

- RCT endpoints:
  - Defined in advance
  - Capture the ‘most important’ aspects of disease progression
  - Able to discriminate between treatment arms
  - Mindful of regulatory requirements
- But in a cohort/registry, may have concerns relating to:
  - Missing data
  - Infrequent and/or irregular measurements
  - Changes in laboratory methods over time
  - Selection of patients and monitoring bias
- Intent to treat (ITT) analyses
  - - What do these mean in the context of a non-randomised study?

Defining endpoints (2)

- Have to define endpoints differently

Example: HIV RNA at 48 weeks

RCT: HIV RNA at week 48 visit (+/- 7 days)

Cohort/registry: nearest HIV RNA to 48 weeks (+/- 6 weeks)

- Are these really comparable endpoints?

Example: Real-life experience with bictegravir (BIC) /emtricitabine (FTC)/tenofovir anafenamide (TAF)

- All adults receiving BIC/FTC/TAF after 8th June 2018
- Effectiveness, HIV RNA <50 copies/mL
  - On-treatment (OT): discontinuation/missing=excluded
  - Modified intention-to-treat (mITT): discontinuation=failure, missing=excluded
  - Intention-to-treat (ITT): discontinuation/missing=failure
- But what does ITT mean if there is no randomisation?
- Does missing really equal virological failure?
- Are the results really directly comparable to those from RCTs?

Ambrosioni J *et al.* *J Antimicrob Chemother* 2022 https://doi.org/10.1093/jac/dkab481

Example: Real-life experience with bictegravir (BIC) /emtricitabine (FTC)/tenofovir anafenamide (TAF)

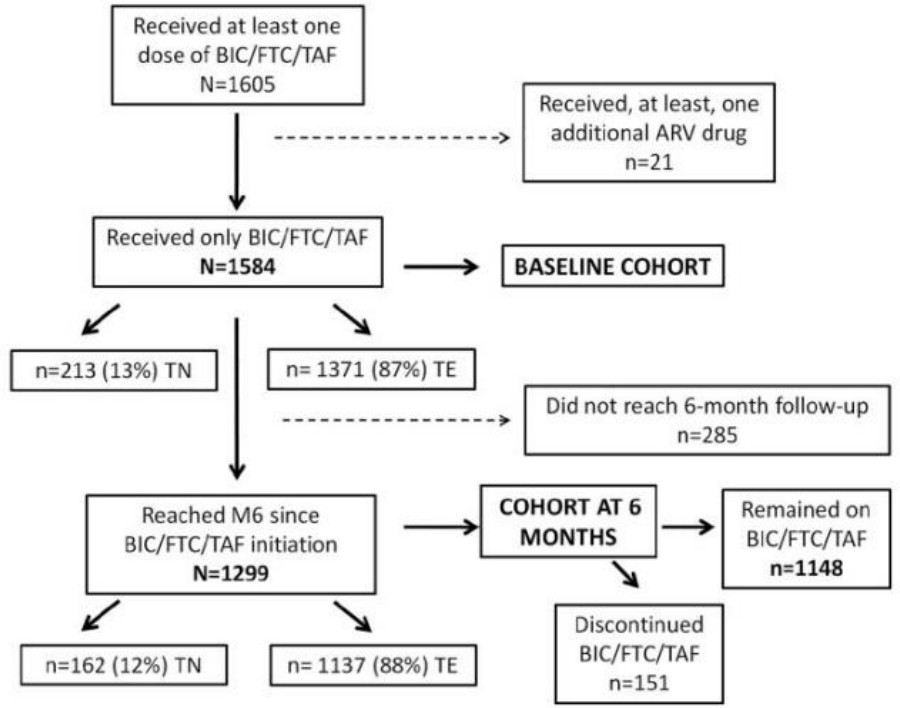
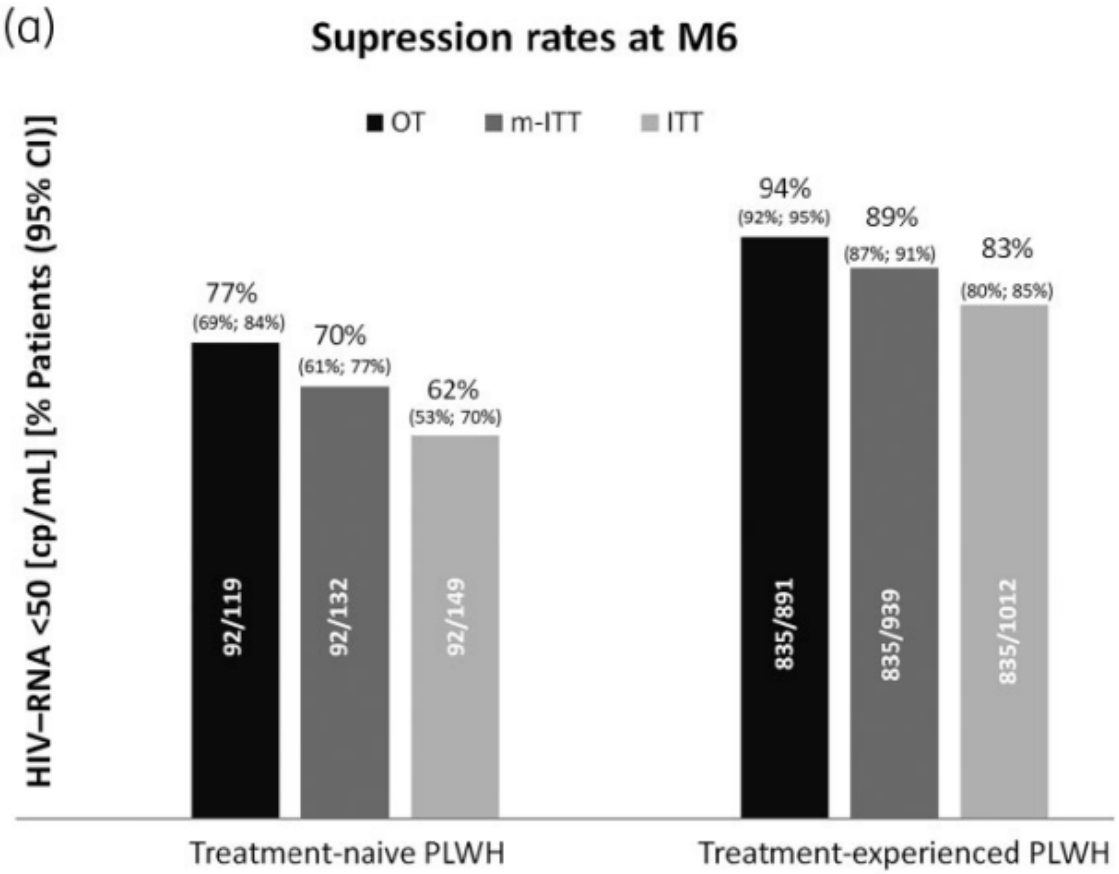


Figure 1. Flow chart of the cohort of PLWH who received at least one dose of BIC/FTC/TAF.



Ambrosioni J *et al. J Antimicrob Chemother* 2022 https://doi.org/10.1093/jac/dkab481

The possibility of monitoring bias

- If you look for something more often, you'll detect it sooner…
- Are people all monitored equally and at the same frequency?
- Examples:
  - renal function among people starting ART
  - sleep disturbances
  - monitoring of weight/BMI
  - Assessment for diabetes mellitus
- What impact does this have on reported associations with outcomes?

So can we trust the results of ALL RWE studies?

"However, the confluence of large datasets of uncertain quality and provenance, the facile analytic tools that can be used by nonexperts, and a shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions."

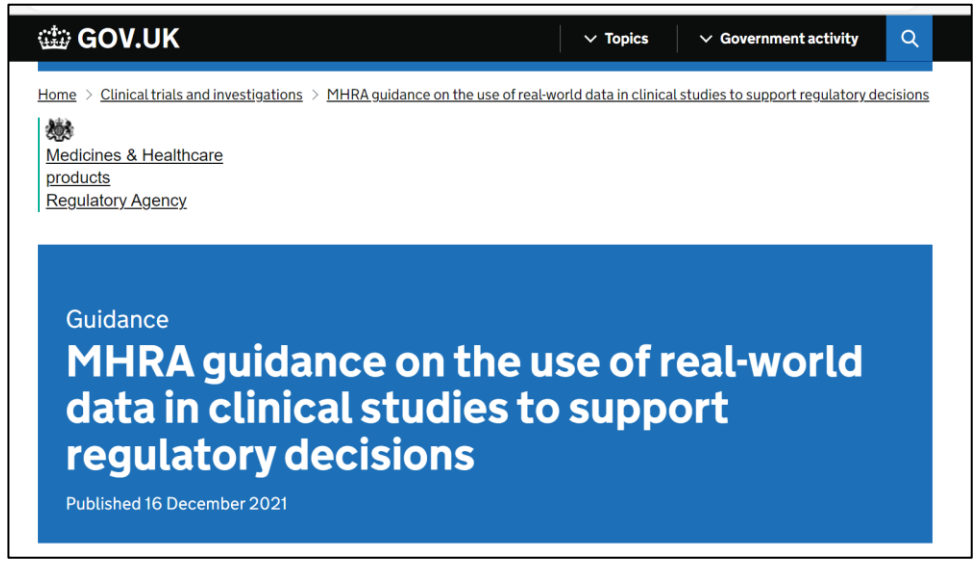
Sherman RE, et al. *NEJM* 2016; **375**: 2293-2297.

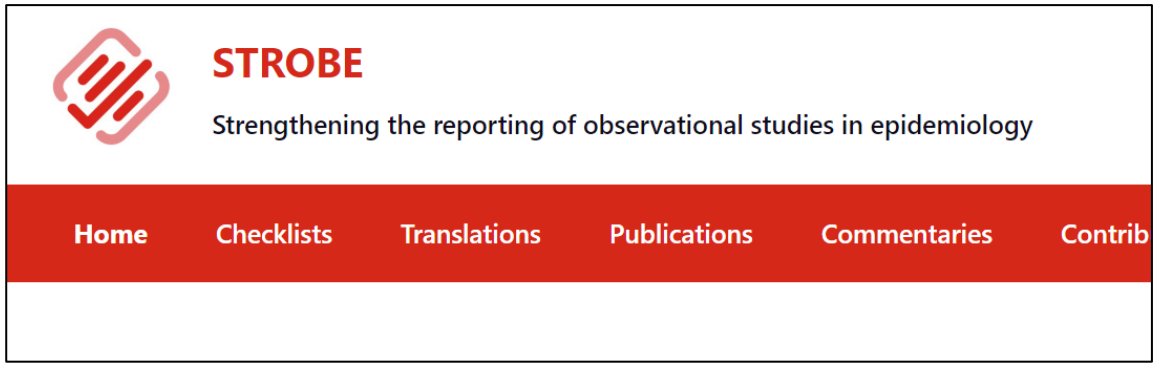
Are RWE studies any different to cohorts?

- No - RWE studies are observational studies with branding!

Are RWE studies any different to cohorts?

- No - RWE studies are observational studies with branding!
- Need to apply the same epidemiological rigor to them as for cohort studies
- Guidance exists……





Summary

- RWE studies are increasingly being published – evidence from these studies is often promoted with the same strength as that from RCTs
- RWE studies have the potential to be of huge value for understanding how drugs work in a real-life setting when used for the treatment of people who are more representative of those seen for clinical care
- Can also suggest unexpected yet important adverse events that may have been missed in RCTs
- However, these studies have the potential to be affected by several major biases, and thus results should always be treated cautiously

Summary – top tips for reviewing RWE studies

- What is the **SOURCE** of the data and what impact could this have?
  - Single clinic, multi-clinic, multi-country?
  - Electronic health record data, patient notes or specific prospective data collection?
- How are people **FOLLOWED UP**?
  - Do endpoint definitions allow for different follow-up patterns?
  - How do the authors deal with any missing outcomes?
- Are any **COMPARISONS** being made?
  - Are comparison groups similar and if not, could this introduce confounding?
  - If so, how was confounding addressed in analyses?
- Are the results **UNEXPECTED** or are they supported by other evidence?