Implementing Estimands & Target Trial Emulation (TTE) in Real-World Evidence: Case Studies & Perspectives

Tuesday, February 24th, 2026
11:00 AM - 12:00 PM ET

Co-moderators:

- **Aaron Crowley, Genesis Research Group**
- **Thanh G.N. Ton, F. Hoffmann-La Roche (Genentech)**

PHUSE Estimands for RWD/RWE Project Team

- PHUSE RWE Working Group (link)
  - PHUSE Estimands for RWD/RWE project team (link)
    - Co-Leads
      - Matt Baldwin, Amgen
      - Ksenia Titorenko, ICON
      - Paramita Chakraborty, IQVIA
    - ~20 active project team members
    - Subteam 1 – White Paper Development
    - Subteam 2 – Webinar Series

Subteam 1: White paper development

- Co-leads: Ksenia Titorenko (ICON) and Paramita Chakraborty (IQVIA / Gilead)
- *Establishing Robust Estimands in Real-World Evidence*
  - Literature review
  - Gap analysis
  - Combining frameworks
  - Example use cases
  - Regulatory submission aspects
  - etc
- Preparing for internal PHUSE project team review
- Future public review before published

Subteam 2: At the Intersection of Estimands and Target Trial Emulation (TTE) for RWE webinar series

Project Lead: Matt Baldwin

- **Webinar 1 (22 Apr 2025):** An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks (recording & slides)
- **Webinar 2 (05 Jun 2025):** Estimands in Real-World Evidence Studies (recording & slides)
- **PHUSE Blog:** "*What's the Hype About? PHUSE's Record-Breaking Webinars Explore Estimands and Target Trial Emulation for RWE*"
- **Webinar 3 (24 Feb 2026):** Implementing Estimands & Target Trial Emulation (TTE) in Real-World Evidence: Case Studies & Perspectives
- **Webinar 4 (TBD):** Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment
- **Webinar 5 (TBD):** Q&A Panel

Implementing Estimands & TTE in Real-World Evidence: Case Studies & Perspectives

Today, our speakers will walk through external comparator analyses using real-world data and address common challenges such as data completeness, index date alignment, baseline confounding and treatment switching. A closing commentary will synthesize considerations when jointly applying estimands and TTE in external comparator studies.

- Applying the Estimand and Target Trial frameworks to external control analyses using observational data: a case study in the solid tumor setting.
- Combining the Target Trial and Estimand Frameworks to Define the Causal Estimand: An Application Using Real-World Data to Contextualize a Single-Arm Trial
- External comparator studies and the joint application of the estimand and target trial emulation frameworks.

GUEST SPEAKERS

LETIZIA POLITO
ROCHE

JUFEN CHU
DAIICHI SANKYO

GERD RIPPIN
IQVIA

GUEST SPEAKERS

THANH G.N.TON
ROCHE

AARON CROWLEY
GENESIS RESEARCH

MATT BALDWIN
AMGEN

Implementing Estimands & TTE in Real-World Evidence

Webinar 3 Outline

- (5 min) Introduction
- (10 min) Dr Letizia Polito, *Roche*
- (10 min) Dr Jufen Chu, *Daiichi Sankyo*
- (10 min) Dr Gerd Rippin, *IQVIA*
- (25 min) Presenter Dialogue and Closing

ATTENTION – No live Q&A, any questions submitted via the Zoom chat, Q&A, or workinggroups@phuse.global will be answered in a published Q&A file with the recording and slide decks

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Bridging Estimands & Target Trial Emulation

Matt Baldwin & Lauren Dang

March 25, 2026

AMGEN

Presenter Dialogue

Discussion Topics

1. ICEs and Treatment Switching
2. Making RWD Limitations Explicit
3. Marginal Estimand Choice
4. Time Zero and Follow-Up
5. Stakeholder Communications
6. Standardization and Estimand Quality

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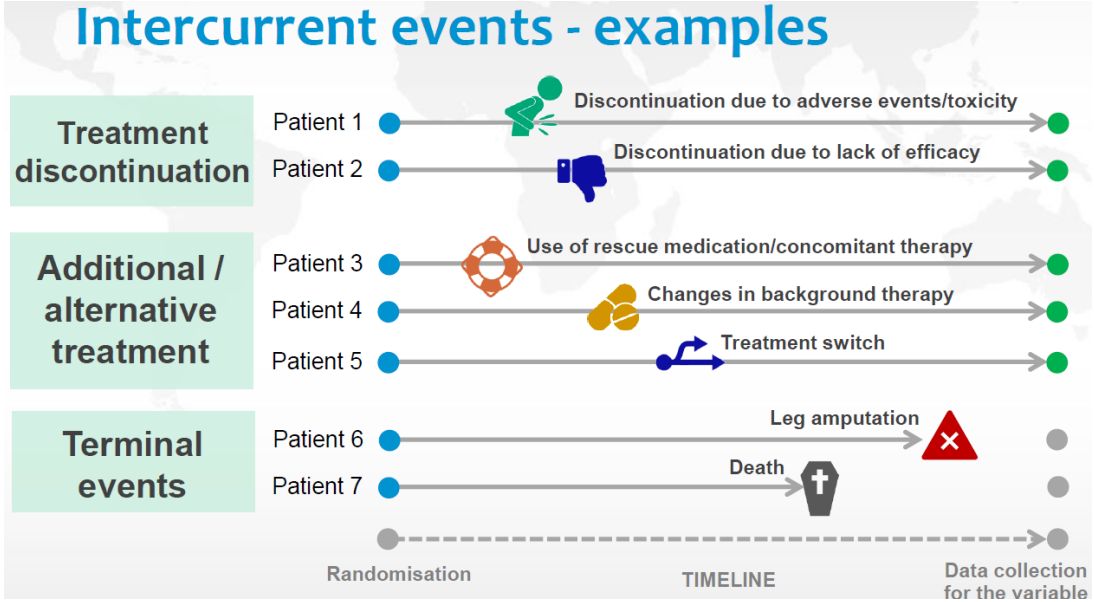
GENESIS RESEARCH

MATT BALDWIN
AMGEN

Presenter Dialogue 1:
ICEs and Treatment Switching

Letizia:

In your external comparator study, what led to the decision to use a hypothetical strategy for treatment switching, and how did that choice shape the estimand, the compatible estimator, the assumptions you relied on, and the sensitivity analyses you pre-specified?



ICH E9(R1) Training Material

Presenter Dialogue 2: Making RWD Limitations Explicit

Jufen:

In your external comparator study, how did jointly applying the estimand and target trial emulation frameworks make RWD limitations explicit, and how did that transparency drive your design and analysis choices?

Table 1: Application of the target trial and estimand frameworks to design an ECA based on the ReCORD study and the comparison of this with the ELARA trial cohort. The same considerations applied when constructing an ECA from the FHRD.

Component	Target RCT to be emulated	RCT that can be emulated using ELARA and external RWD	
		ELARA	RW cohort

Hampson, L. V., et al. (2024). Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial. Statistics in Biopharmaceutical Research, 16(1), 1-10.

Presenter Dialogue 3: Marginal Estimand Choice

Gerd:

- When you design an external comparator analysis, which marginal estimand do you default to, and why?
- Which stakeholder question does it answer best, and which trade-offs do you accept?
- Do you advise including supplementary estimands in protocols?

Table 2. Summary of estimands and methods for estimating them.

Estimand	Target population	Example research question	Matching methods	Weighting methods
ATT	Treated patients	Should medical providers withhold treatment from those currently receiving it?	Pair matching (e.g., nearest neighbor, optimal) without a caliper (10) Full matching (15) Fine stratification (16)	Standardized mortality ratio weights (2)
ATU	Untreated (control) patients	Should medical providers extend treatment to those not currently receiving it?	Same as ATT	Same as ATT
ATE	Full sample/ population	Should a specific policy be applied to all eligible patients?	Full matching (15) Fine stratification (16)	Inverse probability weights (13,17)
ATO	Clinical equipoise	Should those at clinical equipoise receive treatment? Is there an effect of the treatment for some patients?	Caliper matching (10,12) Coarsened exact matching (18,19) Cardinality matching (20)	Overlap weights (21) Matching weights (22) Weight trimming (23)

Notes: ATT - average treatment effect in the treated; ATU - average treatment effect in the untreated; ATE - average treatment effect in the population; ATO - average treatment effect in the overlap

Greifer, N., & Stuart, E. A. (2021). Choosing the causal estimand for propensity score analysis of observational studies. arXiv preprint arXiv:2106.10577.

Presenter Dialogue 4: Time Zero and Follow-Up

Letizia:

- How did you define time zero in each data source, justify any misalignment, and set the follow-up window?
- What are the implications for the estimand's interpretation, and would you change these choices if the disease had different diagnostic or treatment patterns?

Start/end follow-up	Start of follow-up occurs at the time when the treatment is assigned (i.e., when eligibility is met) End of follow-up is reported in Supplementary Table 1	Same as target trial. To emulate the start of follow up for the OC arm, some assumptions are needed. To emulate the end of follow up we truncated the follow-up time at Month 21 because there were few patients remaining in the RCT arm after Month 21	For the OC arm, the actual start of follow-up occurs at the time when the treatment is initiated (dose 1 cycle 1)
			The risk of comparing different time zero is to introduce immortal time bias. This cannot be quantified. The primary estimate is unbiased if the following assumptions are met.
			Assumptions in the OC
			• There are no reasons for a patient to not initiate treatment other than death once assigned to treatment
			• Death is unlikely to have occurred in between assignment and start of treatment because we assume
			○ The time between assignment and start of therapy is short
			○ mNSCLC is a disease with no rapid course in first line
			No assumption for RCT. We verified that
			• All patients assigned to treatment started treatment
			• Median time between assignment and start of therapy was 2 days

Polito, L., et al. (2024). Applying the estimand and target trial frameworks to external control analyses using observational data: a case study in the solid tumor setting. Frontiers in Pharmacology, 15, 1223858.

Presenter Dialogue 5: Stakeholder Communications

Jufen:

- Your work engaged EMA (including a rapporteur's early request for an external comparator), FDA, and HTA bodies.
- How did the joint EF and TTE approach facilitate conversations with clinicians, statisticians, RWE scientists, regulatory affairs, and with regulatory/HTAs, from pre-specification to the final submission?

The above adjusted analyses were supported by unadjusted analyses showing similar results. Analyses restricted to the time point from 2014 and 2020 have also been provided, based on scientific advice, such that the treatment options would be similar to those for the E2202 study, and show similar results. Nevertheless, interpretation of the RWD is complicated by the fact that it was not possible to fully emulate the inclusion criteria in the E2202 study. As such the patient populations were similar but not identical. Important prognostic values were lacking and could not be adjusted for in the analyses. Also, response assessments were lacking in the RWD, necessitating changes to the endpoint definition (ReCORD), or further exclusion of patient that otherwise would qualify (Flatiron). This provides some uncertainty when used to contextualise the pivotal phase 2 clinical study E2202. These studies are despite the remaining uncertainty of the effect estimates nevertheless providing valuable context, and are in general deemed supportive of the pivotal study, due to the clear differences in outcomes they show.

European Public Assessment Report (EPAR): EMA Type II variation II/0044 (follicular lymphoma, FL) for tisagenlecleucel (Kymriah)

Presenter Dialogue 6: Standardization and Estimand Quality

Gerd:

- Looking ahead, how would you formalize the 9 unified elements across sponsors and reviewers, and would you add an estimand quality dimension for RWD?
- What should be the minimum reporting standard for external comparator protocols?

Unifying element #
1 Treatment Conditions and Strategies
2 Population
3 Endpoint and Validation
4 Intercurrent Events (ICEs)
5 Population-level Summary
6 Follow-up Period
7 Baseline
8 Assignment Procedures
9 Marginal Estimator

Rippin, G., & Sanz, H. (2024). External comparator studies and the joint application of the estimand and target trial emulation frameworks. Frontiers in Drug Safety and Regulation, 4, 1409102.

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THANK YOU!

Applying the Estimand and Target Trial frameworks to an external control analysis using observational data: a case study in the solid tumor setting

Letizia Polito, Principal Real World Data Scientist, Roche

PHUSE Webinar Series

Disclosure: this presentation reflects the views of the authors and not necessarily those of Hoffman-La Roche and Flatiron Health

The Value and Challenges of External Control Arms

- There is a rapidly growing necessity for **External Control Arms (ECA) to support Regulatory and HTA decision-making**

  Key use case: contextualizing single-arm trials or updating outdated comparators caused by rapid shifts in Standard of Care.
- Ability to replicate trials' internal control arm using observational data is **challenged by confounding and other operational constraints**

Baseline (Measured) Confounding: patients are different at the start

Intercurrent Events and Post-Baseline (Measured) Confounding

Aligned index dates (randomization date vs. treatment start date) and end of follow-up between trial control arm and ECA

Missing variables/unmeasured confounding and/or missing data/poor data quality

The methodological framework adopted

Estimand Framework (ICH E9 R1):
Clarifies the scientific question in a language familiar to regulators and drug makers (step 1-2)
What to estimate?

Target Trial Emulation (TTE):
Provides the operational blueprint (step 3-4)
How to estimate it?

The evolution of the scientific question

Initial Question

Does OS differ for mNSCLC patients on 1L platinum chemotherapy in trials vs. real-world practice?

The constraint

Routine clinical practice shows much greater diversity in 2L drug use than the highly controlled environment of a clinical trial. This creates spurious survival differences that mask the intrinsic equivalence of the treatment regimens.

Treatment Switching Patterns in Clinical Trials vs. Real-World Settings

Metrics	RCTs Control (N=849)	Observational Control (N=3340)
Switching Frequency to Subsequent Therapy anytime during the follow-up period, %	449 (52.9%)	1881 (56.3%)
Median (IQR) Time to Switch, months (among patients who switched)	6.24 (4.27–9.69)	5.45 (3.12–9.43)

Refined question

"Is there a difference in OS... **had patients not received a subsequent therapy**?"

OS, overall Survival; mNSCLC; metastatic non-small cell lung cancer; 1L, first-line

Scientific Question and Estimand

Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care **had patients not received a subsequent therapy**?

Attribute	Definition for Case Study
Population	Metastatic NSCLC (squamous & non-squamous), ECOG 0-1, >=18 years of age, with adequate hematological and end-organ function.
Treatment	Front-line platinum-based chemotherapy (RCT Protocol vs. Routine Care)
Endpoint	Overall Survival (OS)
Intercurrent Event	**Receipt of a subsequent treatment**: handled using a **Hypothetical Strategy** (instead of Treatment Policy Strategy)
Summary Measure	Hazard Ratio (HR) with 95% CI; Kaplan–Meier estimator

Baseline characteristics

Data sources: IMpower 130, 131, 132 trials (Control Arms) & Flatiron Health electronic health record (EHR)-derived database

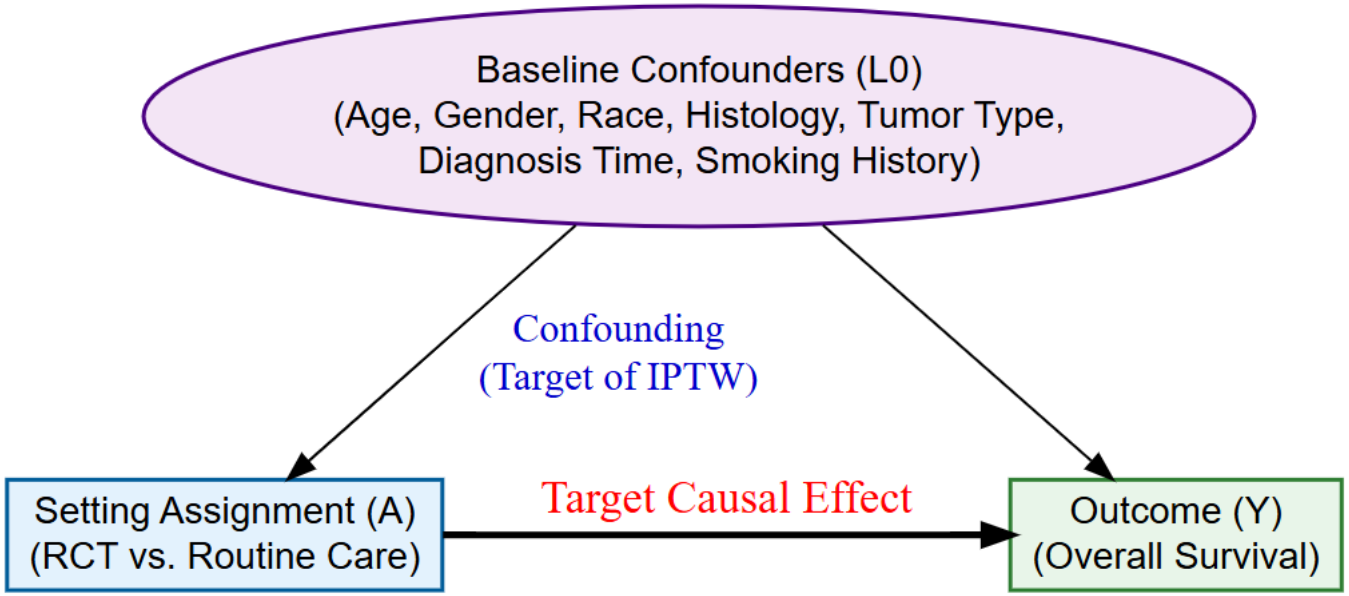
Patients enrolled in the trials were on average younger, more frequently were males, diagnosed as *de novo* stage IV and with squamous histology compared to patients in the real world

Variable	Categories	Pooled_trial control arms N=849	Observational control arm N=3340	SMD Pre-IPTW **	SMD Post-IPTW
Age group (years), n(%)	< 65	435 (51.2)	1222 (36.6)	**0.42**	0.03
	≥65 and <75	322 (37.9)	1268 (38.0)		
	≥75	92 (10.8)	850 (25.4)		
Gender, n(%)	Female	248 (29.2)	1457 (43.6)	**0.3**	0.04
Race, n(%)	Asian	105 (12.4)	46 (1.4)	**0.75**	0.06
	Other	45 (5.3)	921 (27.6)		
	White	699 (82.3)	2373 (71.0)		
ECOG-PS, n(%)	0	314 (37.0)	714 (21.4)	0.05*	
	1	532 (62.7)	1179 (35.3)		
	NA	2 (0.2)	1447 (43.3)		
Metastatic diagnosis, n(%)	De novo Stage IV	706 (83.2)	2118 (63.4)	**0.46**	0.03
	Recurrent disease	143 (16.8)	1221 (36.6)		
Smoking history, n(%)	No	69 (8.1)	257 (7.7)	0.02	0.06
	Yes	780 (91.9)	3070 (91.9)		
	NA	0 (0.0)	13 (0.4)		
Histology, n(%)	Non-squamous	509 (60.0)	2278 (68.2)	**0.17**	0.01
	Squamous	340 (40.0)	1062 (31.8)		
Time from initial diagnosis to index date (months), (median [IQR])		1.41 [0.92, 2.89]	1.25 [0.79, 2.27]	**0.15**	0.01
Treatment, n(%)	Carboplatin+Pacli/Nab-pacli	568 (66.9)	1877 (56.2)	**0.22**	0.04
	Platinum+Pemetrexed	281 (33.1)	1463 (43.8)		

**ECOG-PS variable was not included in the propensity score model because of the high proportion of missing ECOG-PS. Developing an Imputation model to differentiate score 0 vs 1 was considered out of scope for the goal of this presentation.*

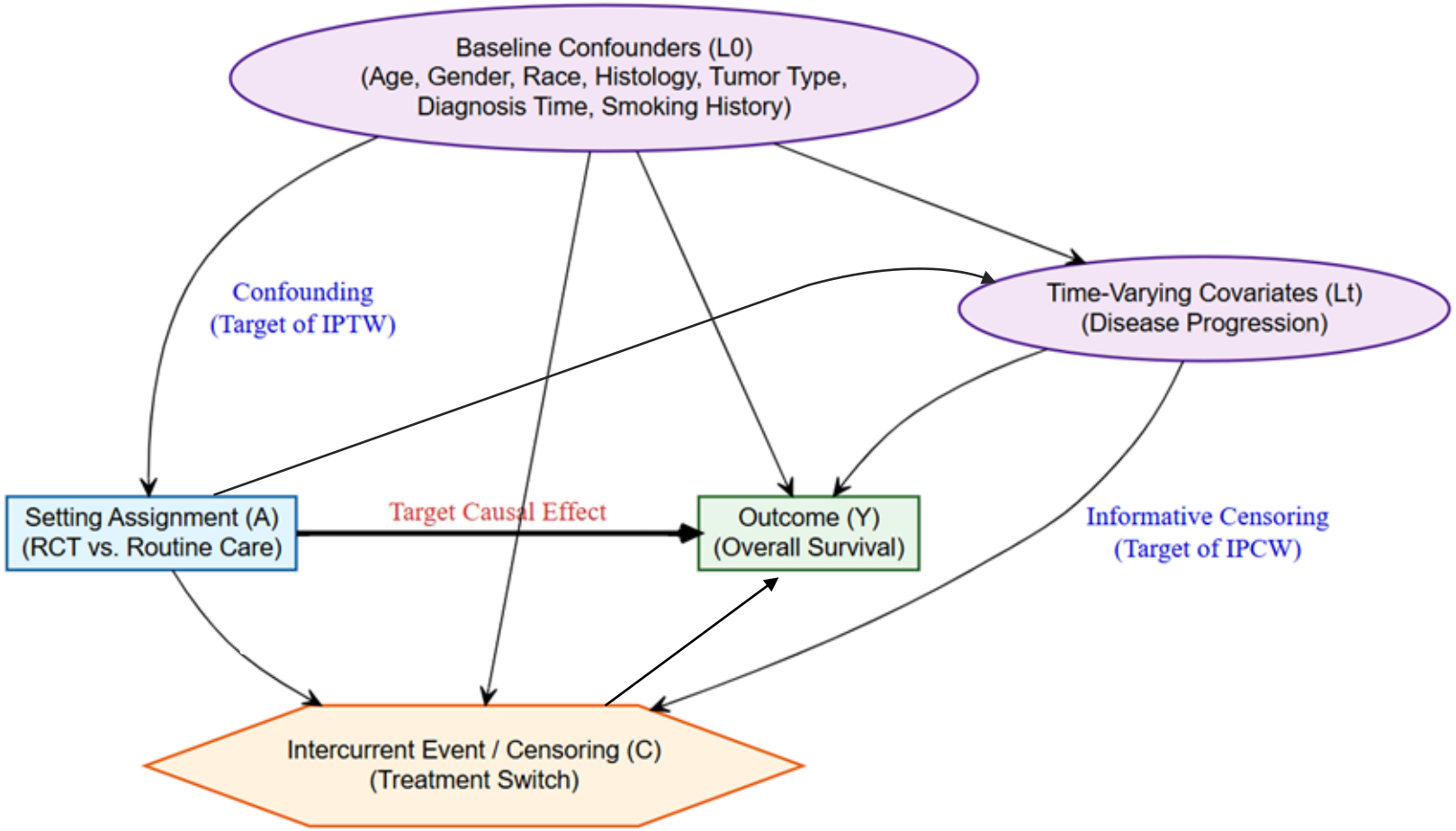
***IPTW$_{ATT}$, Inverse Probability of Treatment Weighting; ATT, Average Treatment Effect on the Treated*
SMD, Standardized Mean Differences

Double Weighting Strategy (IPTW$_{ATT}$ × IPCW$_{(t)}$)



Note: ECOG PS (0 vs 1) was excluded from the model due to high missingness in the RWD.
IPTW, Inverse Probability of Treatment Weighting; ATT, Average Treatment Effect on the Treated; IPCW(t), Inverse Probability of Censoring Weighting (time-dependent).

Double Weighting Strategy (IPTW$_{ATT}$ × IPCW$_{(t)}$)



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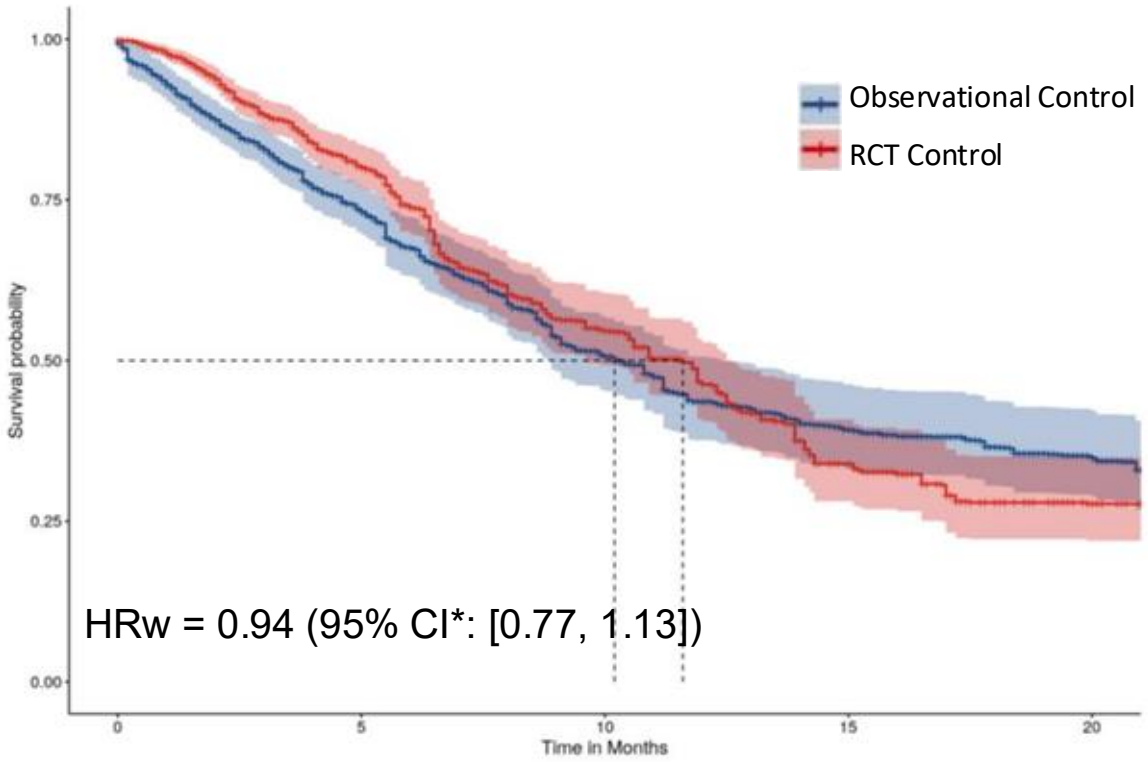
IPTW, Inverse Probability of Treatment Weighting; ATT, Average Treatment Effect on the Treated; IPCW(t), Inverse Probability of Censoring Weighting (time-dependent).

Primary vs. Supplementary Analysis: different estimands

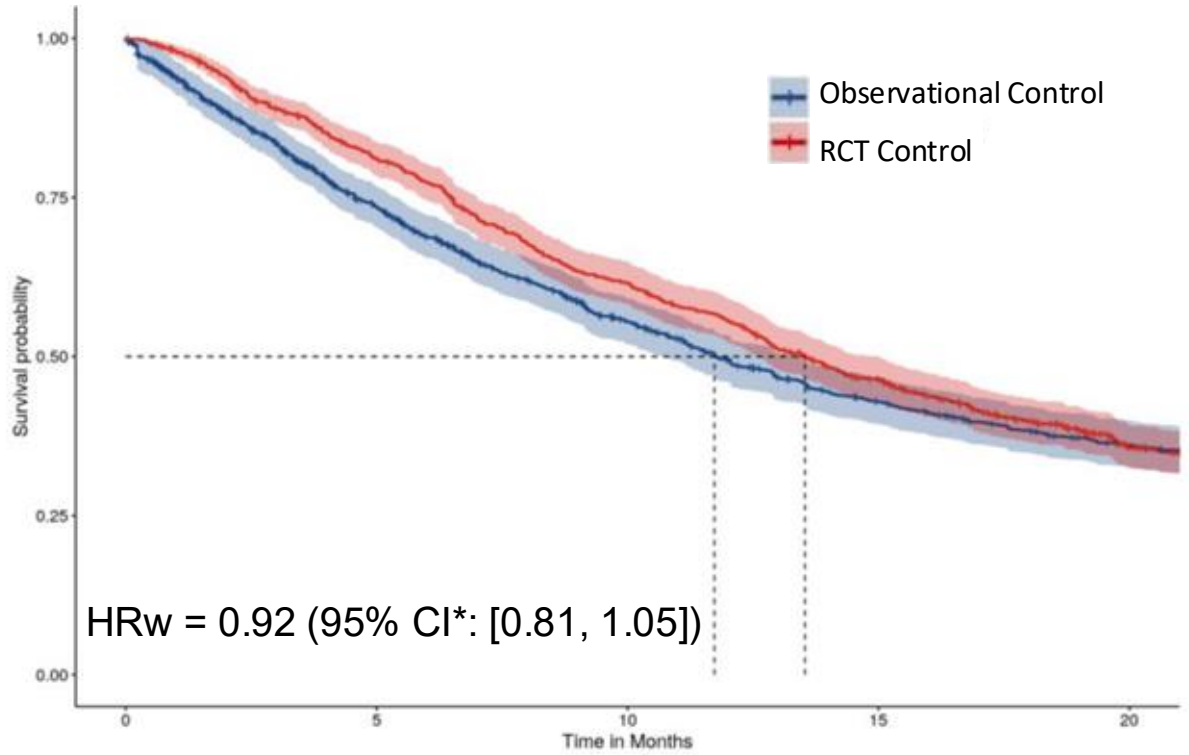
Primary analysis

IPTW-ATT*IPCW(t)
Hypothetical strategy



Supplementary analysis

IPTW-ATT
Treatment policy strategy

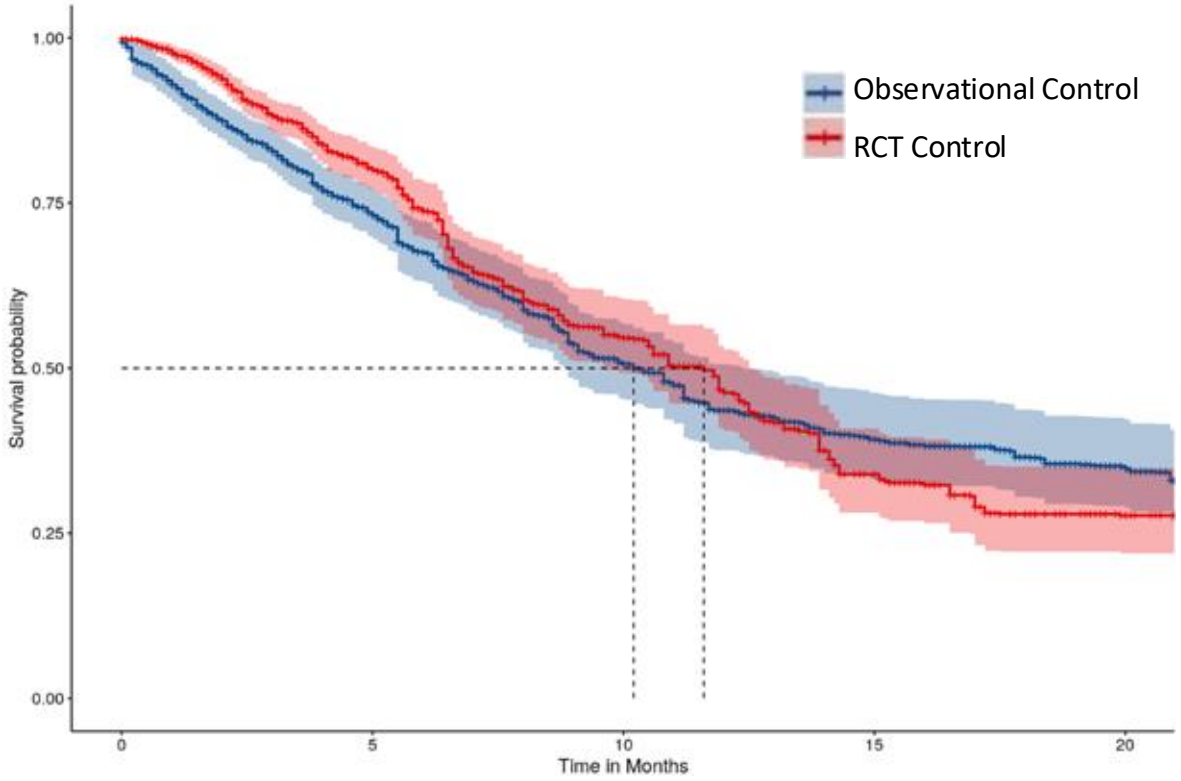


95% CIs calculated using non-parametric bootstrapping. IPCW calculated as stabilized weights.

Sensitivity Analysis: naïve estimator

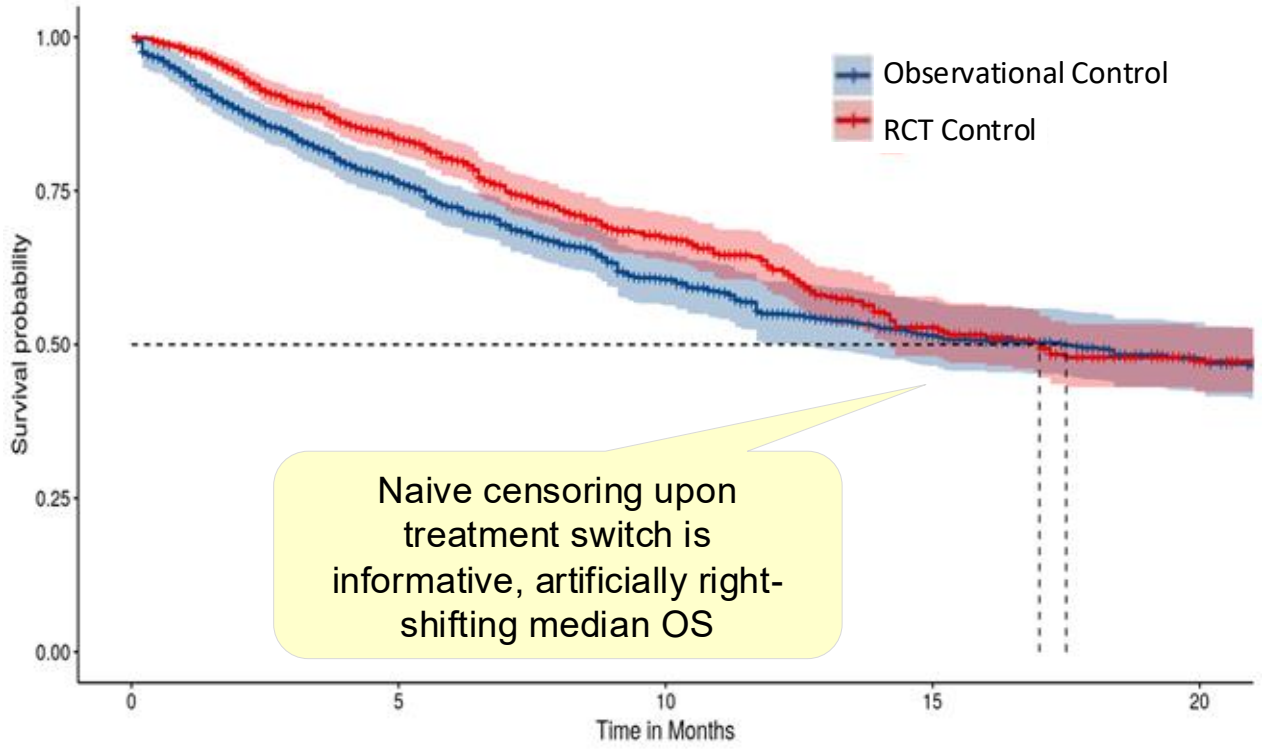
Primary analysis

Hypothetical strategy
IPTW-ATT*IPCW(t)



Sensitivity analysis

Hypothetical strategy
IPTW-ATT with naïve censoring



Key Takeaways

Integration

Combining Estimand Framework (ICH E9 R1) with Target Trial Emulation (TTE) ensures the scientific question aligns with the estimand and study design

Validity

Under study specific assumptions, observational data can act as a valid comparator using the right estimator - in this case via Double Weighting

Transparency

Explicit definition of the causal model and assumptions is a prerequisite for acceptance and alignment across all stakeholders

Acknowledged limitations: results may be subject to unmeasured confounding, time-zero mismatches, and geographic heterogeneity

Acknowledgements

Roche/Genentech Team
Navdeep Pal, Kaspar Rufibach[1], Dominik Heinzmann

Flatiron Team
Qixing Liang[1], Philani Mpofu[1], Ahmed Sawas, Olivier Humblet[1]

[1]Affiliations at the time the study was conducted

> Front Pharmacol. 2024 Jan 26:15:1223858. doi: 10.3389/fphar.2024.1223858. eCollection 2024.

Applying the estimand and target trial frameworks to external control analyses using observational data: a case study in the solid tumor setting

Letizia Polito [# 1], Qixing Liang [# 2], Navdeep Pal [3], Philani Mpofu [2], Ahmed Sawas [2], Olivier Humblet [2], Kaspar Rufibach [1], Dominik Heinzmann [1]

Affiliations + expand

PMID: 38344177 PMCID: PMC10853363 DOI: 10.3389/fphar.2024.1223858

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Implementing Estimand and Target Trial Emulation Frameworks: A Practical Case Study

Presenter: Jufen Chu

PHUSE Real-World Evidence Working Group

Feb 24th, 2026

External control requested for single arm trial

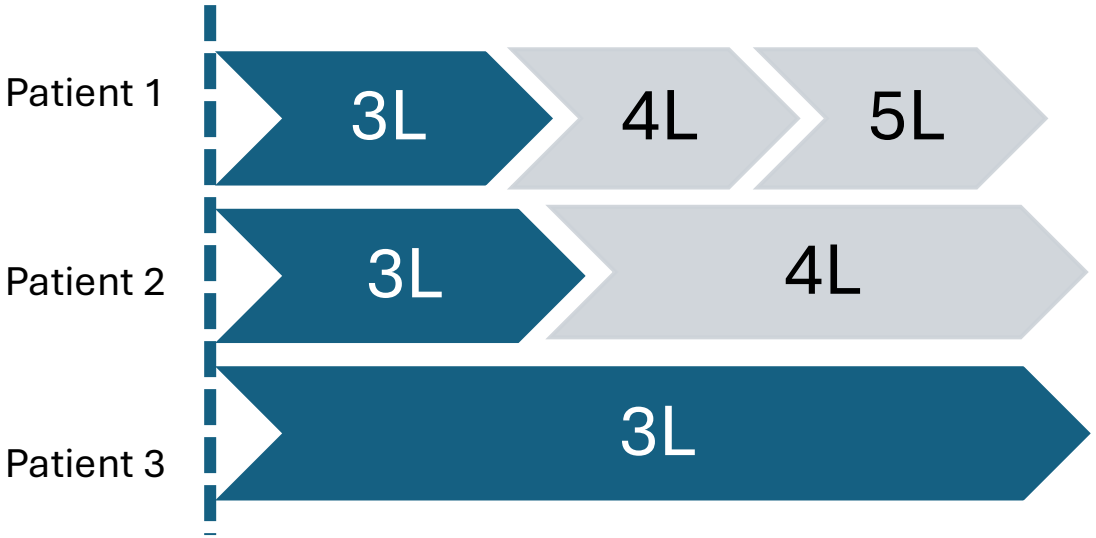
- **ELARA:** A single arm, multi-center, phase II study to determine the efficacy and safety of tisa-cel in adult patients with Follicular Lymphoma after ≥2 lines of prior therapy
- Need for external control with **patient-level data** highlighted by the Norwegian Health Authority (Tisa-cel rapporteur country) during protocol review :

3 Question #2

Being a single-arm trial, we assume that, prior to any comparative analyses, the external control will be pre-specified and consist of a population (e.g. from registries or historical trials) where there is access to individual patient-level data. Furthermore, the selection criteria of the external control should match with the selection criteria for the patient population proposed in this trial, to make the two populations as similar as possible. If matching on patient characteristics to the

Selection of index line

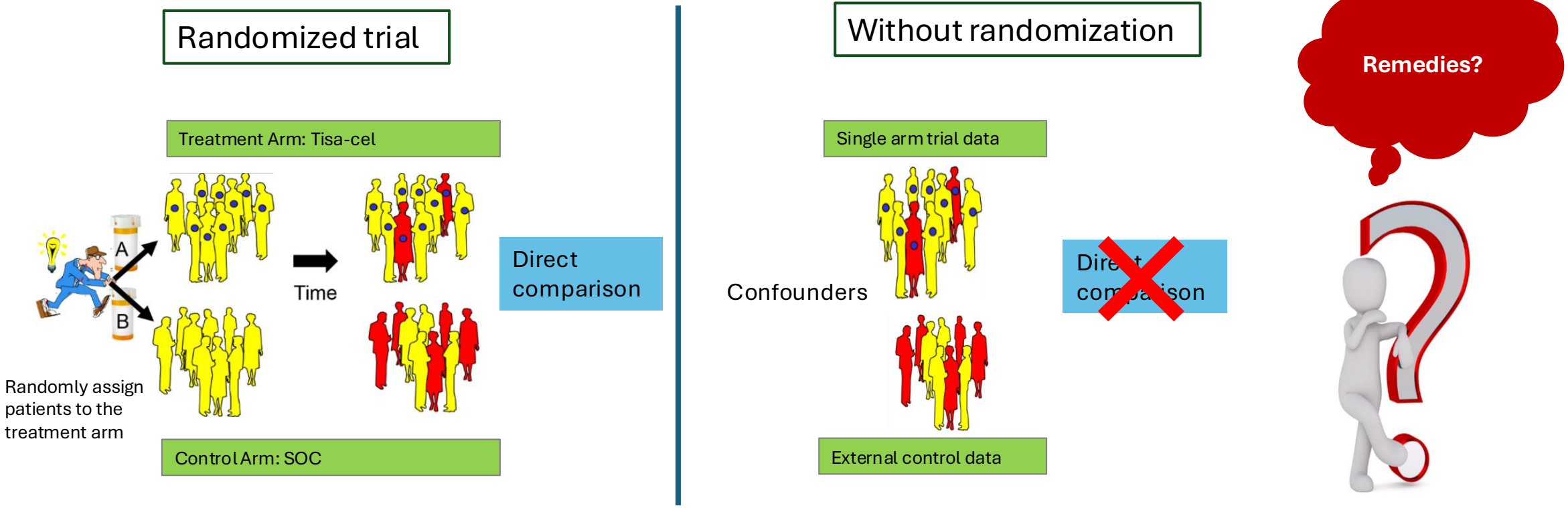
- Longitudinal data across several lines of therapies available in RWD sources
- Patients in RWD can meet the eligibility criteria of ELARA at multiple lines of therapy



- Use data from all lines?
- Use earliest/latest lines ?
- Randomly select one line?

Bias due to baseline confounding

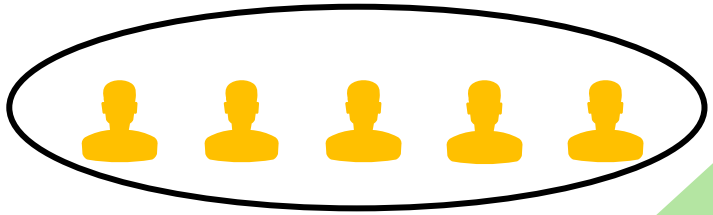
- One *fundamental problem* is that patients treatment assignment is not random, but dependent on baseline covariates → unbalanced baseline covariates



Other design-associated biases

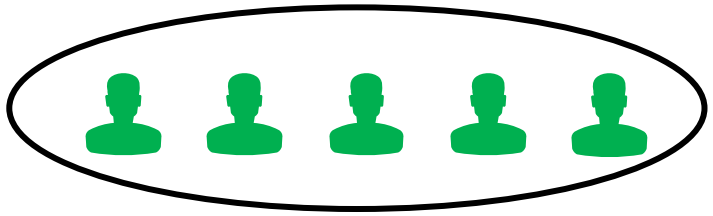
Single arm trial data

Observed outcomes on drug



External control RWD

Observed outcomes on control



Other biases could impact our causal inference. *± E.g.

- Selection bias
- Assessment bias
- Different endpoint bias
- Immortal time bias
- Efficacy / effectiveness gap
- Drift in SoC over time

Take steps to eliminate or mitigate potential biases through the careful design *and* analysis of the effectiveness comparison between single arm trial data and its external control data

* Burger et al. *Pharmaceutical Statistics*, 2021

± Catalogue of Bias Link

Target trial & Estimand frameworks

- ICH E9(R1) estimand provides a structured framework to clinical trial design, conduct, analysis and interpretation
- Target trial emulation framework can be used to extend the ICH E9(R1) estimand thinking process to studies using RWD, but doesn't include intercurrent events

- Provides formal frameworks to identify and avoid common methodological pitfalls of study design and statistical analysis
- Facilitates transparent communication about potential limitations

Applying target trial & estimand frameworks

Question: ***What's the treatment effect of prescribing tisa-cel vs SoC in the patient population who participated in the ELARA trial?*** – average treatment effect on treated (ATT)

Attribute	Target RCT	Emulated trial		Our strategy
		ELARA	RWD	
Population /Eligibility criteria	ELARA inclusion/exclusion (I/E) criteria	Same as target RCT	ELARA I/E criteria that are feasible to apply retrospectively	Be transparent and summarize all criteria that were not feasible to apply in RWD
Treatment/ Treatment strategy	**CAR-T treatment strategy** vs **Current SoC**	CAR-T treatment strategy as target RCT	Current SoC	
Treatment assignment	Block randomized to either CAR-T arm or SoC arm	Emulate simple randomization		Propose statistical methods to emulate randomization
Variables	OS is time to death from any cause	Same as in target RCT		
	CR best overall response of complete remission per Lugano criteria	Same as target RCT	CR and progression based on real-world response criteria	Subgroup analysis ≥ 2014 was conducted as year of introduction of Lugano response criteria
	PFS is time to first progression or death from any cause	Same as target RCT	Progression dates unavailable for many patients	To consider new anticancer therapy as PFS event and pre-specify in SAP

Applying target trial & estimand frameworks

Attribute	Target RCT	Emulated trial		Our strategy
		ELARA	RWD	
Start of follow-up	Start: date of randomization	Start: enrollment, regarded as prescription date	Start: start date of SoC treatment • Multiple line of therapy	Propose statistical method to select index line
Intercurrent event(s)	**IE: new anti-cancer therapy** OS: Treatment policy strategy CR: ICE reflected in Variable PFS: Hypothetical strategy	Same as target RCT for OS and CR PFS: Composite strategy		
Causal effect	**ATT:** Effect of prescribing tisagenlecleucel vs SoC in patients meeting ELARA inclusion/exclusion criteria	Same as in target RCT		
Summary measure	Binary endpoints: Difference in marginal response probabilities on CAR-T vs SoC Time-to-event (TTE) endpoints: Marginal HR	Same as in target RCT		
Analysis	Binary: Difference in response rates TTE: Cox regression	Binary: Difference in weighted proportions of responders TTE: HR obtained from a weighted Cox regression		

Novel approach to select line of therapy

<u>Step1</u>. Estimation of propensity scores per patient per line
(as each patient has new set of 'baseline' covariates at start of each line)

<u>Step 2</u>. Selection of one eligible line per patient in external cohort
- The **highest** propensity score per patient is chosen, i.e. line where the patient is mostly closely aligned with that ELARA population.

External Cohort

Real-world patient ID	LoT where SOC is given	Propensity score
1	3	0.67
1	4	0.49
1	5	0.68
2	4	0.56
2	5	0.75
3	3	0.77
....	....	....

Propensity score = probability a patient would have been enrolled in ELARA

External Cohort

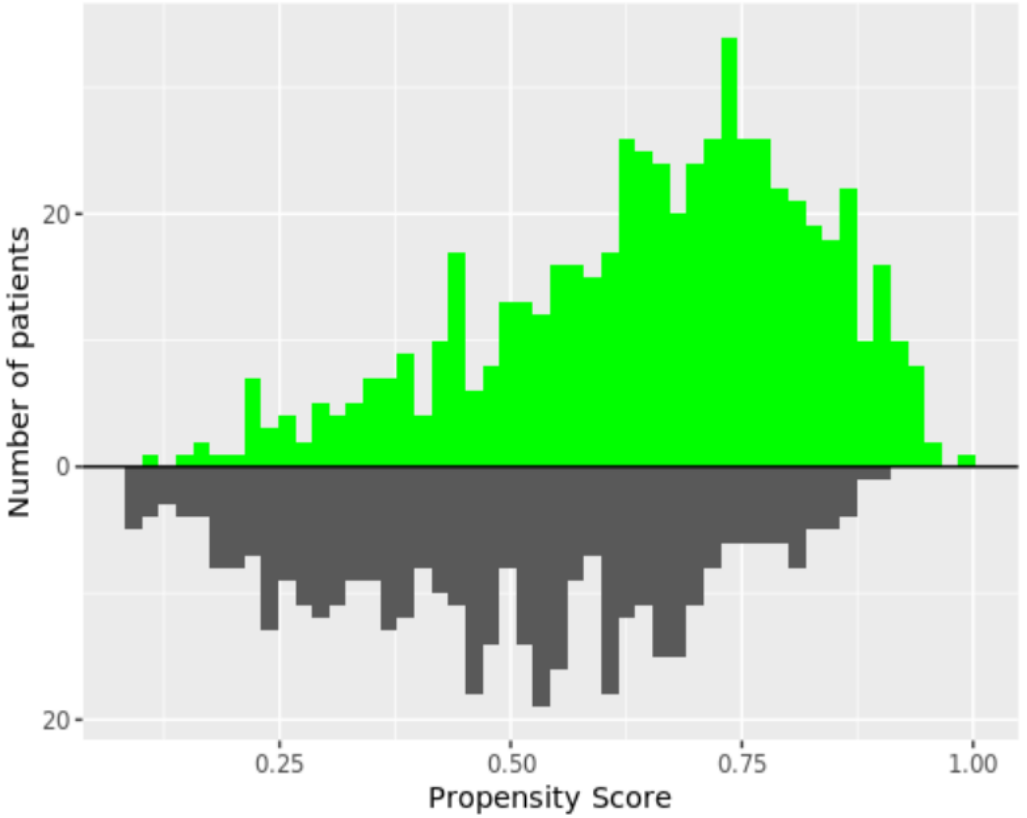
Real-world patient ID	LoT where SOC is given	Propensity score
1	3	0.67
1	4	0.49
1	5	0.68
2	4	0.56
2	5	0.75
3	3	0.77
....	....	....

Higher propensity score = more similar to ELARA patients

Utilizing PS to mitigate confounding bias

- **ATT: "What is the effect of prescribing tisa-cel (vs SoC) on efficacy in the population who participated in ELARA?"**

→Weight each patient in the external cohort based on their odds of being in ELARA



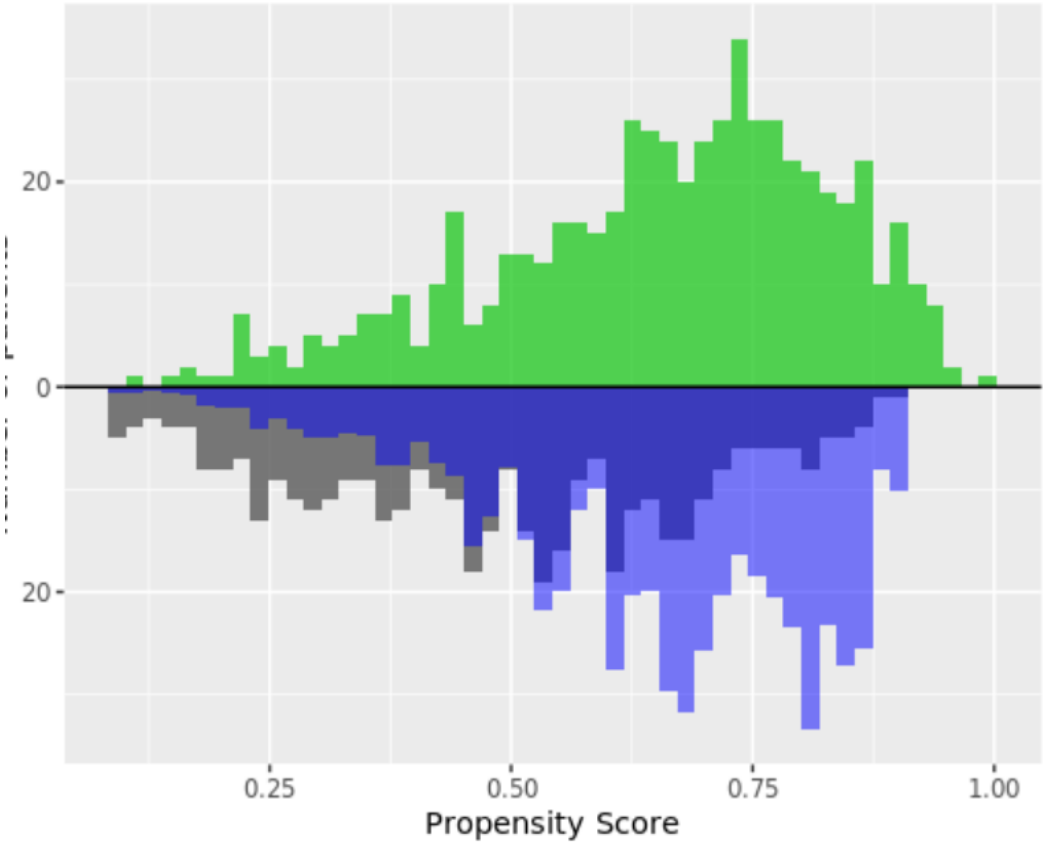


Illustration purpose only not from real data

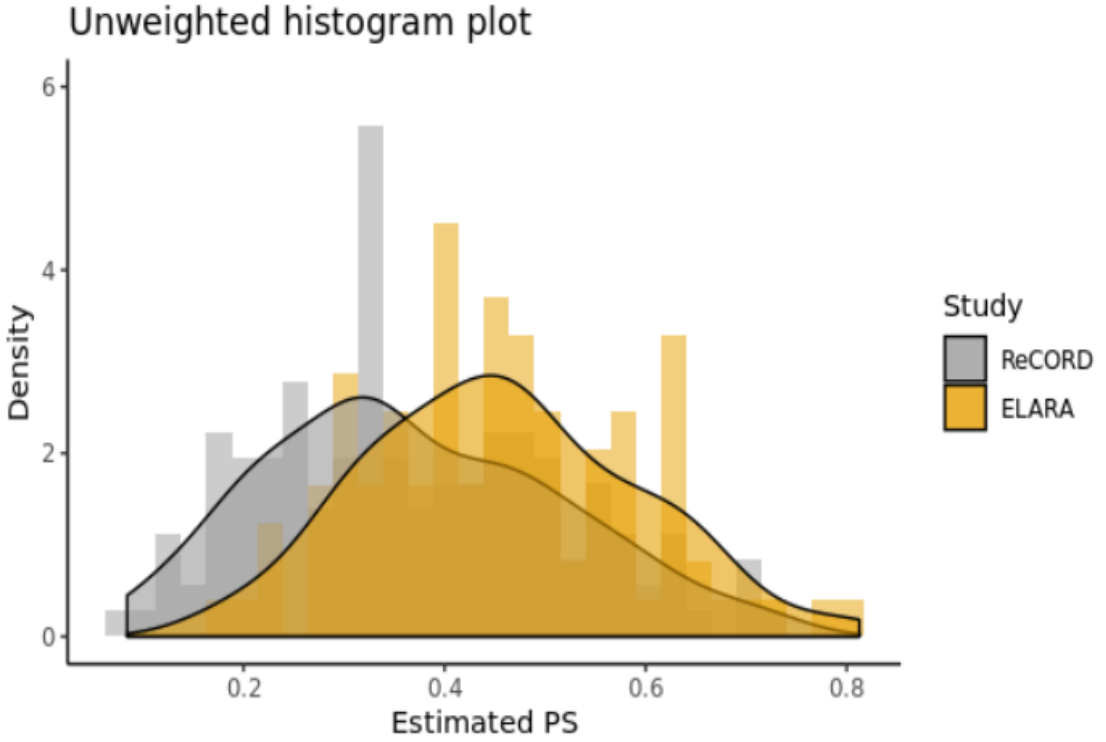
Treatment arm (original)

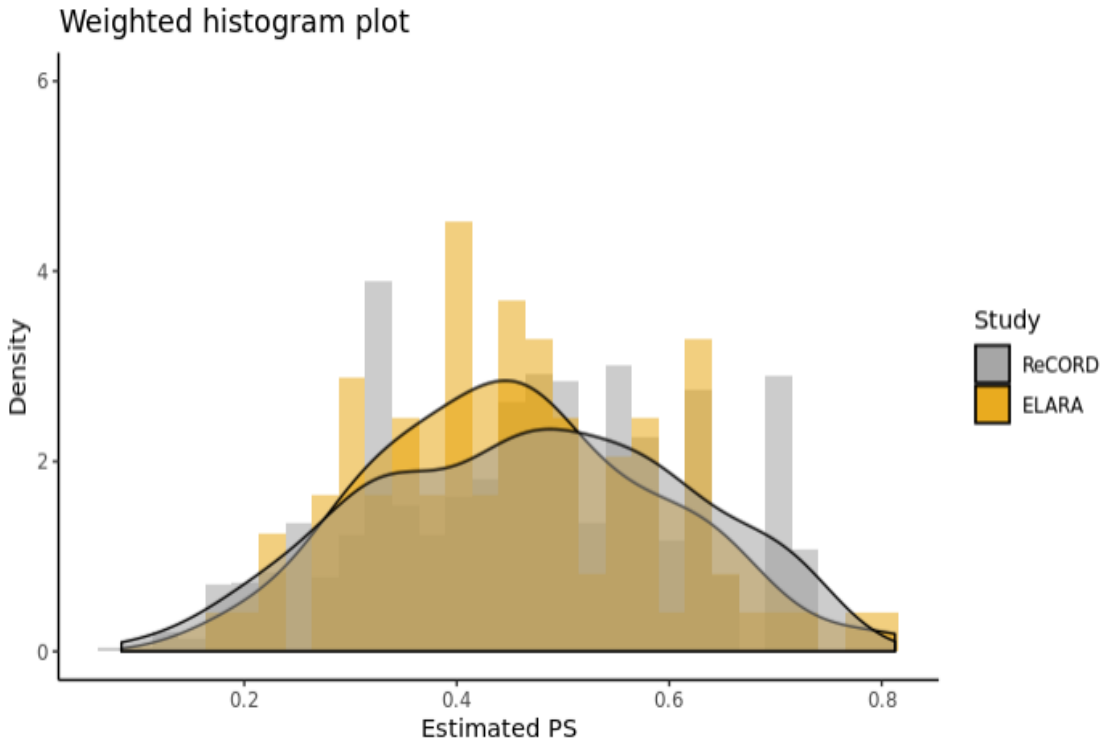
Control arm (original)

Control arm (weighted)

Diagnostics: how successful were we at emulating randomization?

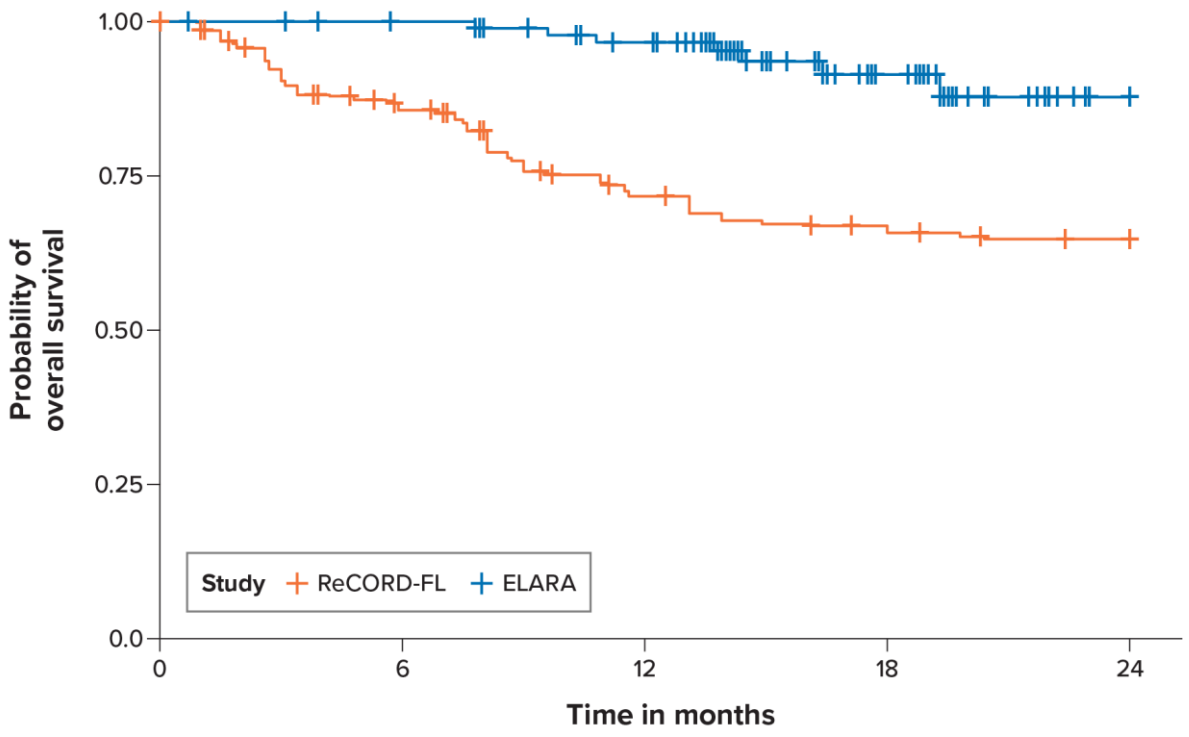
Figures compare the empirical distributions of propensity score estimates in ELARA vs ReCORD before and after weighting (similar results for Flatiron cohort)





Kaplan-Meier plots for ELARA vs ReCORD after weighting

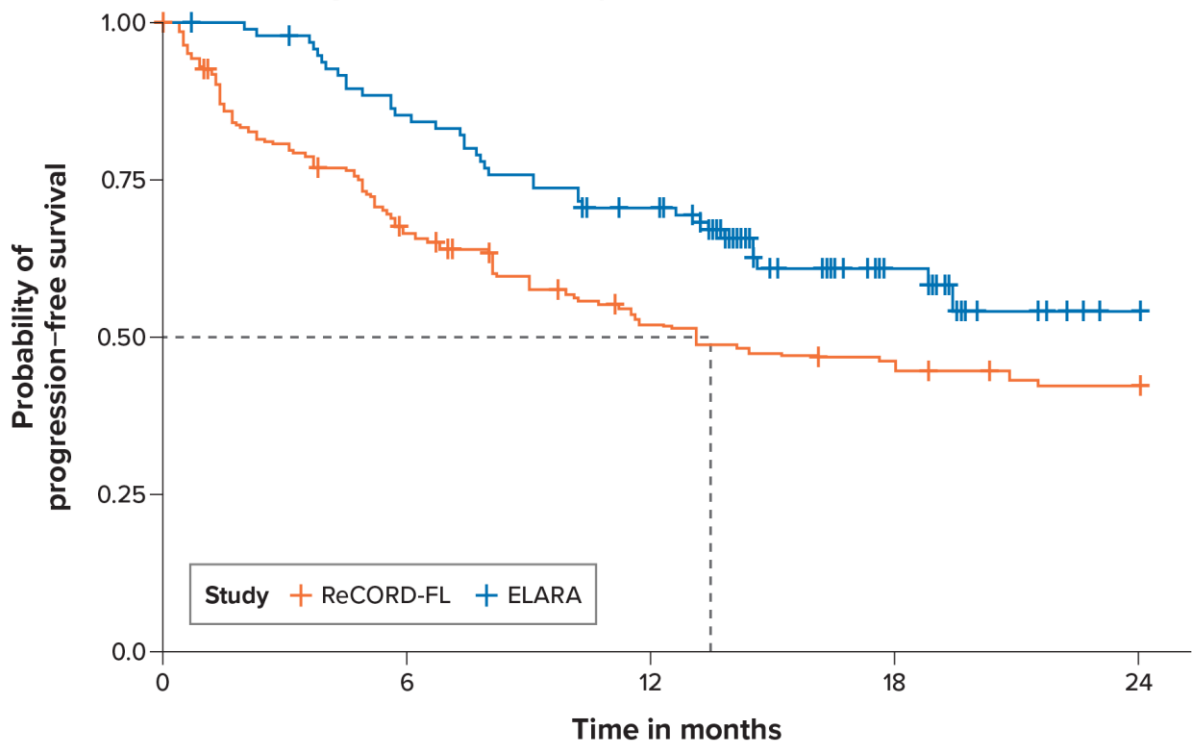
Overall survival



Number at risk

ReCORD-FL	99	79	60	54	50
ELARA	97	93	83	34	2

PFS considering new anticancer therapy as event



Number at risk

ReCORD-FL	99	64	46	40	35
ELARA	97	81	64	23	1

Regulatory interactions and outcome

HA	Interactions/ Outcome
EMA	• EMA Rapporteur asked for external comparator during the protocol review in 2018 • Scientific Advice received on proposed analysis plan and target • Positive CHMP opinion in March 2022, RWE contributed to contextualization of results • Tisageneleucel approved in r/r Follicular Lymphoma in April 2022 – RWE data not accepted for inclusion in the EU label – RWE data is reflected in EPAR after approval • Target trial and estimand frameworks facilitated the transparent and constructed discussions
FDA	• Tisageneleucel approved in r/r Follicular Lymphoma based on ELARA trial • Considered SAT alone sufficient for benefit-risk assessment in this setting and did not indicate any potential value of RWE submission
HTA	• Submitted to HTA to support the evaluation of final pricing and reimbursement decision

EPAR: European Public Assessment report, HTA: Health Technology Assessment

Thank you

Standardizing the joint application of the estimand and the target trial emulation frameworks

PHUSE Real World Evidence Webinar:
Implementing Estimands & Target Trial Emulation (TTE) in Real-World Evidence: Case Studies & Perspectives

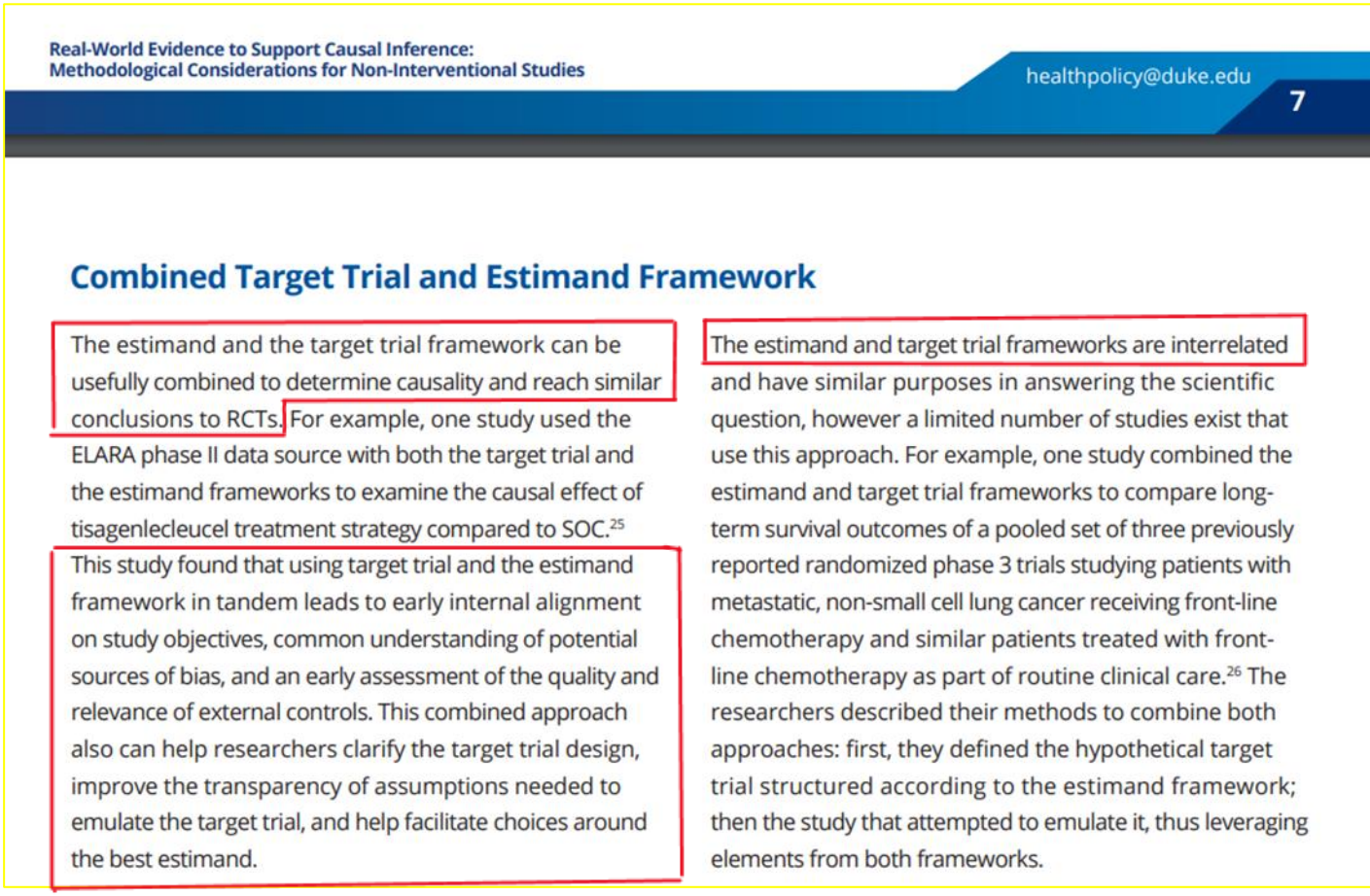
Dr. Gerd Rippin, Senior Director Biostatistics, Real World Solutions, IQVIA, 24th of February 2026

Both the EF & TTEF frameworks should be considered for observational studies

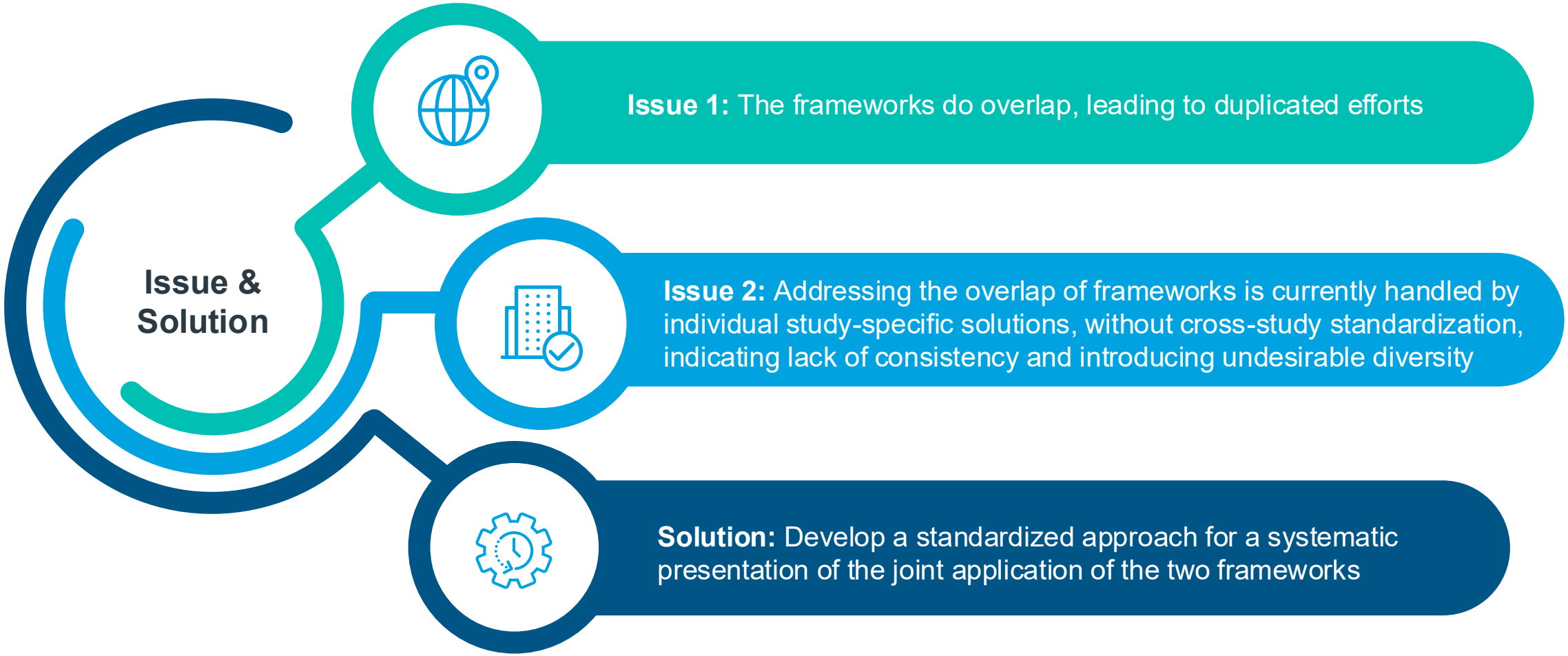
Both frameworks should be applied for EC studies and non-interventional studies in general. The European Medicines Agency (EMA) states that, "The target trial emulation (TTE) framework should be considered …", and "…the estimand framework described in the ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials should be considered …" (European Medicines Agency, 2024). Similarly, the US Food and Drug Administration (FDA) states that the chosen analytical approach should include information about the estimand, and the TTEF is also mentioned as an option to support defining causal contrasts (U.S. Food and Drug Administration, 2024). This is further supported by the Duke Margolis Institute for Health Policy White Paper, stating that "The estimand and the target trial framework can be usefully combined to determine

Snippet from Rippin & Sanz (2024)

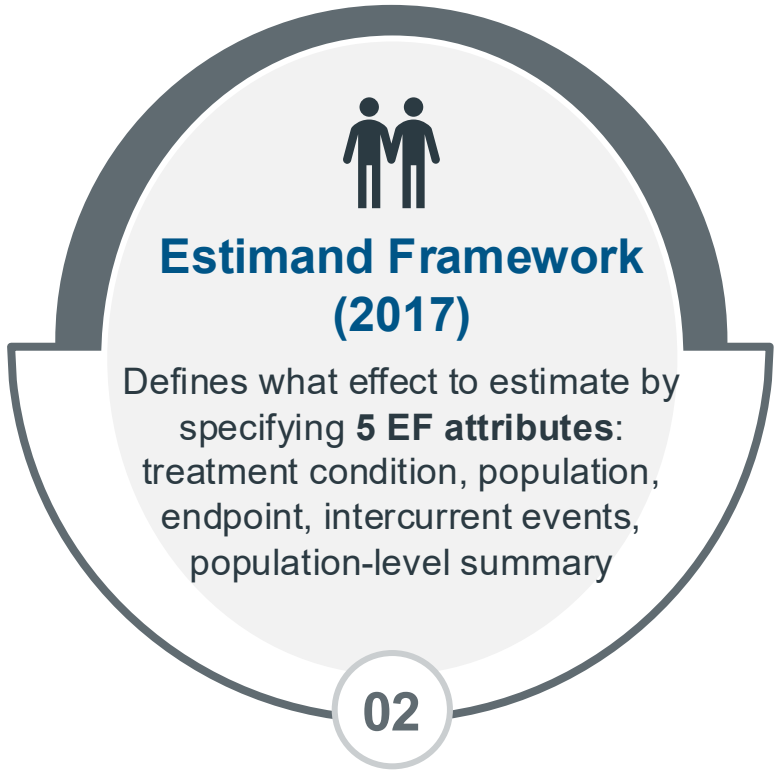
Snippet from Duke Margolis Center for Health Policy White Paper: Real-world evidence to support causal inference: methodological considerations for non-interventional studies (2024)

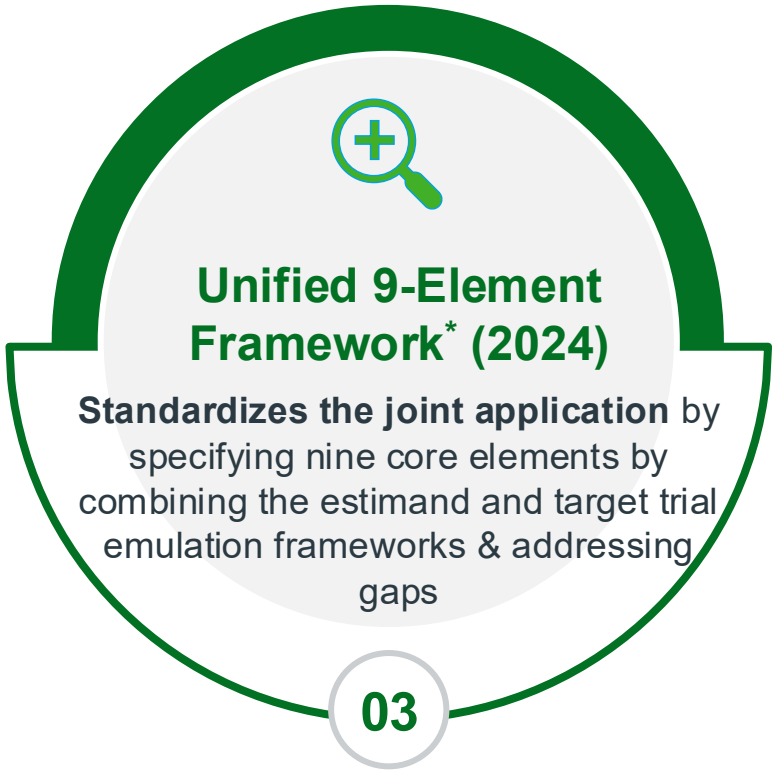


Why should the joint application of both frameworks be standardized?



Core Design Framework for Observational Studies





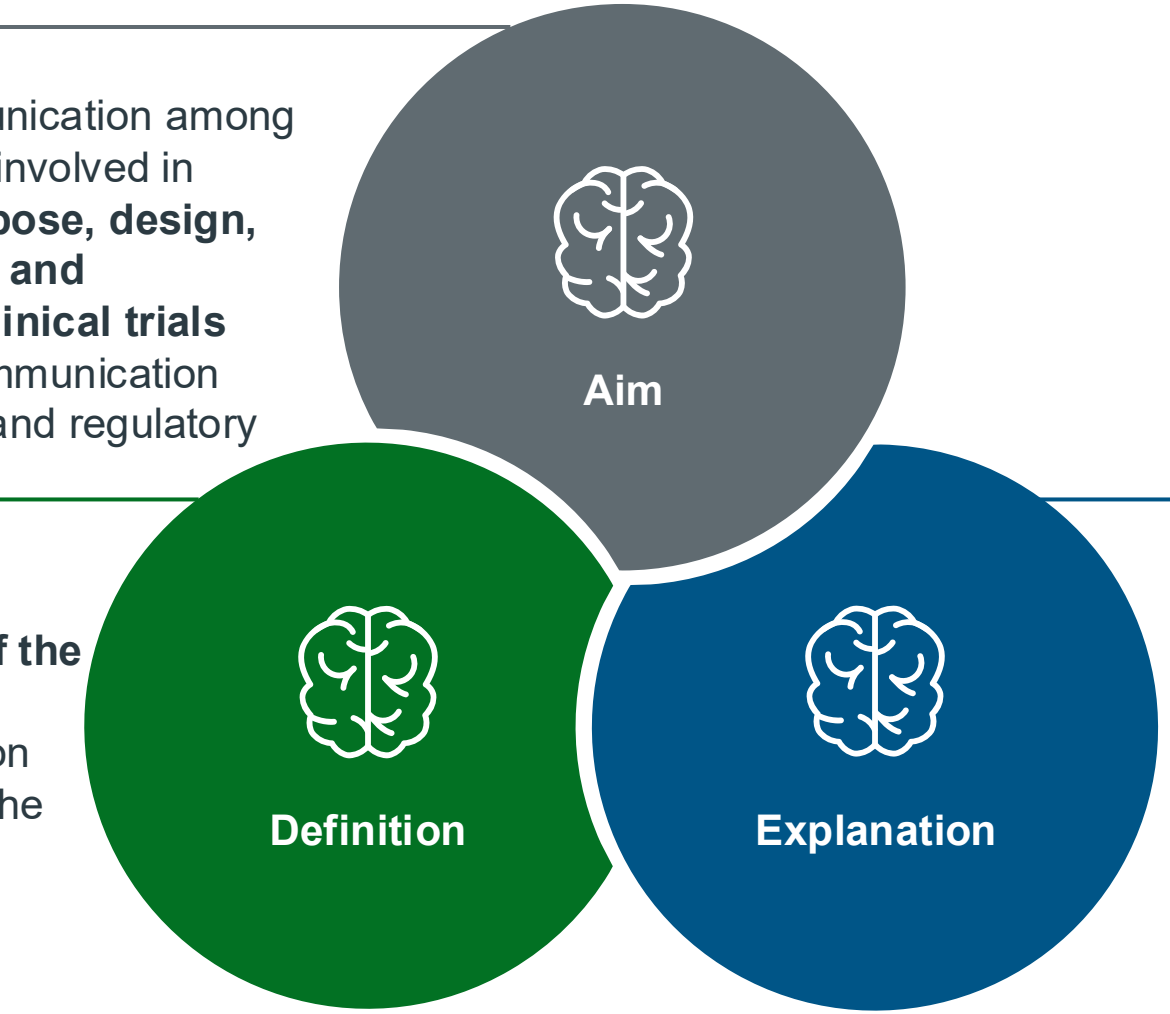
*: Rippin G, Sanz H. External comparator studies and the joint application of the estimand and target trial emulation frameworks. Front Drug Saf Regul. 2024;4:1409102. https://doi.org/10.3389/fdsfr.2024.1409102. **Open-access!**

The EF according to ICH E9(R1), 2017

Aim

A structured framework

- "to enhance communication among multiple disciplines involved in developing the **purpose, design, conduct, analysis, and interpretation of clinical trials**
- and to enhance communication between sponsors and regulatory agencies."



Definition

- "A **precise description of the effect** of a treatment that reflects the clinical question posed for the purpose of the clinical trial."

Explanation

- An estimand is an **estimating target** defined in terms of a specific trial objective.
- Derived from the latin word aestimandum: "which is being estimated".

The EF according to ICH E9(R1), 2017

Study Types

Applicable both for **confirmatory clinical trials** and **observational research**

Scope

Concept of Intercurrent Events (ICEs)

The ICH E9(R1) addendum is aligned with **causal inference thinking** due to the need to address post-baseline intercurrent events

Causal Inference

Trials & Studies

The EF offers a unifying language for clinical trials and observational studies

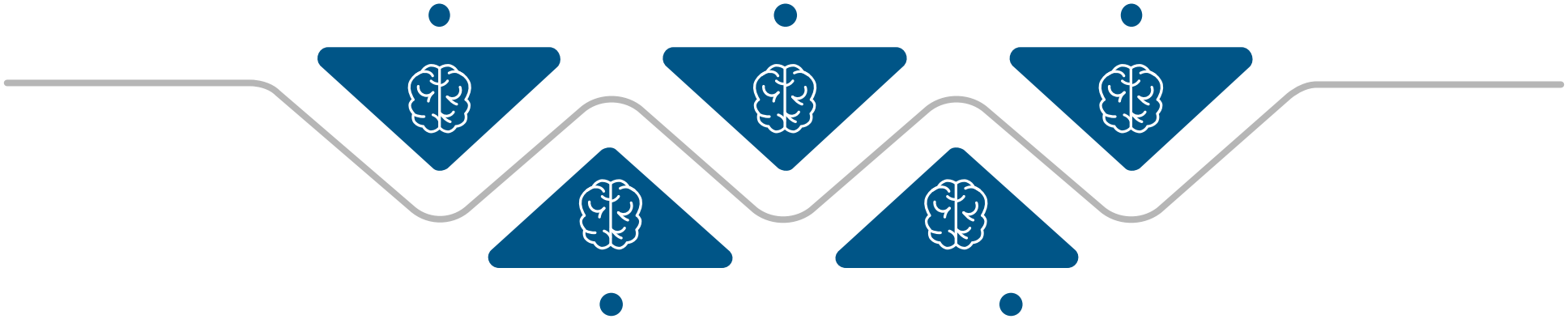
Unifying Language

The 5 Attributes of an Estimand

Treatment conditions
Dosage, route, frequency, …

Population
As per in- and exclusion criteria

Endpoint
E.g., overall response, overall survival, …



Intercurrent Events
E.g., starting a subsequent therapy, additional therapy post-baseline, treatment modification post-baseline, premature end of treatment, experiencing an AE, …

Population-level Summary
E.g., Hazard Ratio, Relative Risk, Restricted Mean Survival Time, …

The 7 Components of the TTEF (Hernán & Robins, 2016)

Component 1
Eligibility criteria

Component 2
Treatment strategies

Component 3
Assignment procedures

Component 4
Follow-up period

Component 5
Outcome

Component 6
Causal contrasts of interest

Component 7
Defining time zero and specifying a grace period for treatment initiation

The EF is a statistical framework while the TTEF is mainly an epidemiological framework, acting mostly (but not completely) on the design level.
It had the specific case of large databases in mind, but other observational study settings benefit from the framework as well.

TABLE 1 Unifying elements of the estimand and target trial emulation frameworks.

Unifying element #	EF attribute #	TTEF component #	Comments
1 Treatment Conditions and Strategies	1. Treatment	2. Treatment strategies	EF focuses on treatment conditions while the TTEF emphases design considerations
2 Population	2. Population	1. Eligibility criteria	The TTEF adds the point of RCT patients engaged in the trial may be approximated by __ patients having regular healthcare contacts prior to baseline (dependent on data availability)
3 Endpoint and Validation	3. Endpoint	5. Outcome	TTEF adds misclassification and validation as further points of consideration
4 Intercurrent Events (ICEs)	4. Intercurrent events	6. Causal contrasts of interest	The EF terminology is a complete guide to how to handle ICEs, while the TTEF addresses treatment-related ICEs only
5 Population-level Summary	5. Population-level summary	*Not mentioned*	Not mentioned in the TTEF
6 Follow-up Period	*Not mentioned*	4. Follow-up period	Not mentioned in the EF
7 Baseline	*Not mentioned*	7a. Analysis Plan: Defining Time Zero 7b. Analysis Plan: Specifying a Grace Period for Treatment Initiation	Typically trivial for trials, so missing in the EF
8 Assignment Procedures	*Not mentioned*	3. Assignment procedures	Specifies whether the study is randomized . If not, includes a data quality assessment regarding the ability to emulate randomization Randomization is discussed in the EF but does not constitute a formal EF attribute
9 Marginal Estimator	*Not mentioned*	*Not mentioned*	Trivial for trials, so missing in the EF. This is not mentioned in the TTEF as well

Note that the elements in the same rows do not have to be identical but can be considered to have sufficient overlap to form a basis for a new unifying element.

Conclusion

Background

- Both frameworks do exhibit **gaps** when being applied on their own.
- Hence, both **should be applied jointly**, as also clearly recommended by regulatory guidance documents.

Recommendation

The joint application should be implemented in a **standardized format** to increase transparency, efficiency and consistency.

Use a set of unifying elements

Such a standardized format was made available by successfully **deriving a tangible set of 9 unifying framework elements** with clear rationale and terminology.

Thank you!

Dr. Gerd Rippin, *Senior Director Biostatistics, Real World Solutions, IQVIA*