

Bridging Estimands & Target Trial Emulation

Matt Baldwin & Lauren Dang

March 25, 2026

AMGEN



Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of PHUSE, CDISC or of the author's parent company.*
- *The authors have no real or apparent conflicts of interest to report.*

Agenda

- (10 min) Welcome & Orientation
- (15 min) Part 1 – Causal Thinking w/ TTE + Estimands (ELARA Case)
- (20 min) Part 1 Activity – Emulating the Target Trial
- (15 min) Part 2 – From Concept to Dataset
- (20 min) Part 2 Activity – Implementing Estimands in ADaM
- (10 min) Summary and Final Q&A

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Brief Recap: What's a TTE?

- Target Trial Emulation:
 - Proposed by Hernán & Robins (2016), refined over time (e.g., Cashin et al., 2025)

“a useful [framework] to **clarify the causal question...** that we wish our **observational analysis** to answer”
(Hernán & Robins (2020))

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Protocol Component
Eligibility Criteria
Treatment Strategies
Assignment Procedures
Follow-Up
Outcomes
Causal Contrasts
Identifying Assumptions
Data Analysis Plan

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Protocol Component	Target Trial Specification
Eligibility Criteria	
Treatment Strategies	
Assignment Procedures	e.g., treatment v. comparator randomized at baseline
Follow-Up	
Outcomes	
Causal Contrasts	
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Fill in 2nd column as though you are designing a randomized controlled trial (RCT)

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Protocol Component	Target Trial Specification	Target Trial Emulation
Eligibility Criteria		
Treatment Strategies		
Assignment Procedures	e.g., treatment v. comparator randomized at baseline	e.g., treatment assigned by physician based on XX, randomization mimicked by adjustment for XX
Follow-Up		
Outcomes		
Causal Contrasts		
Identifying Assumptions		
Data Analysis Plan		



Fill in 3rd column to show emulation of target RCT using RWD.

Brief Recap: What's an Estimand?

- **Estimand:** Answer to the **specific causal question** posed by the RCT
- **ICH E9(R1) Addendum on Estimands... In Clinical Trials (ICH, 2021)**
 - Process for defining Estimand similar to TTE

TTE Protocol Component	ICH E9(R1) Estimand Attribute
Eligibility Criteria	Population
Treatment Strategies	Treatment
Assignment Procedures	
Follow-Up	
Outcomes	Variable/Endpoint
Causal Contrasts	Population-Level Summary
Identifying Assumptions	
Data Analysis Plan	
	Handling of Intercurrent Events



Designed for RCTs
(e.g., Assignment by
randomization
unspoken)

Brief Recap: What's an Estimand?

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Emphasizes intercurrent events

Brief Recap: What's an Intercurrent Event?

“events occurring **after treatment initiation** that affect either the **interpretation or the existence** of the measurements associated with the clinical question of interest” (ICH, 2021)

Examples:

- **Existence of Measurements:**

- **Outcome:** Foot ulcer symptoms
- **Intercurrent Event:** Leg amputation



Leg amputation prevents measurement of foot ulcer symptoms

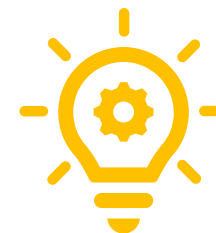
- **Interpretation of Measurements:**

- **Treatment:** Drug A v. B monotherapy
- **Intercurrent Event:** Initiation of Drug C



Rescue medication complicates assessment of Drug A v. B **alone**

What can I do about it?



Stay tuned!

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Part 1 – Causal Thinking with TTE + Estimands (ELARA Case Study)

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March 25, 2026

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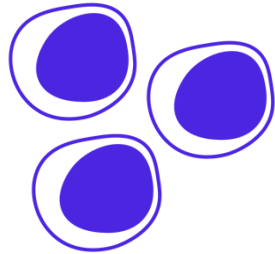


Case Study: ELARA Single-Arm Trial + Real-World External Control

- Case study based on Hampson et al., 2024
- **Context:**
 - Single-arm trial (SAT)

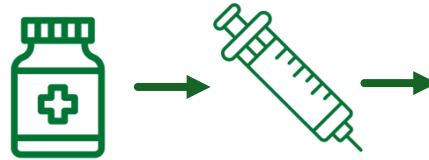
Rare Disease

→ Follicular lymphoma



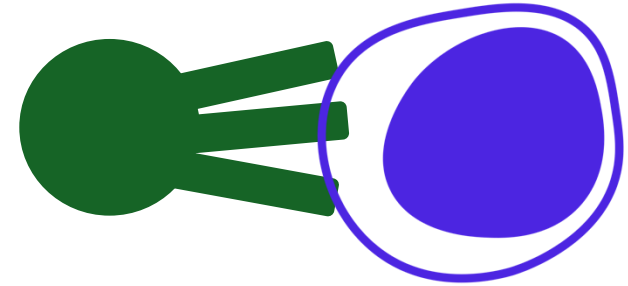
High Unmet Need

→ Relapsed/Refractory



Novel Therapy

→ Tisagenlecleucel (CAR-T)



- "An **EMA rapporteur** highlighted the importance of having an ECA with patient-level data to **support the review of any potential submission** based on the ELARA trial."
- RWD external comparator (standard of care) to "contextualize" results from SAT
 - Flatiron Health Research Database (FHRD) = US EHR from ≈ 280 cancer clinics
- **Target Trial Emulation / Estimand Frameworks**
 - → comparison **as close as possible** to results from RCT

Combine TTE and ICH E9(R1) to Clarify the Causal Estimand

TTE Protocol Component	ICH E9(R1) Estimand Attribute
Eligibility Criteria	Population
Treatment Strategies	Treatment
Assignment Procedures	
Follow-Up	
Outcomes	Variable/Endpoint
Causal Contrasts	Population-Level Summary
Identifying Assumptions	
Data Analysis Plan	
	Handling of Intercurrent Events



Both aim to define a **specific** causal question, promoting alignment and interpretability.

Combine TTE and ICH E9(R1) to Clarify the Causal Estimand

TTE Protocol Component	ICH E9(R1) Estimand Attribute
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	Handling of Intercurrent Events (ICEs)

TTE: Avoid methodologic pitfalls with RWD analyses

E.g., How do I define time 0 in a retrospective dataset?

Combine TTE and ICH E9(R1) to Clarify the Causal Estimand

TTE Protocol Component	ICH E9(R1) Estimand Attribute
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	Handling of Intercurrent Events (ICEs)

Both: Improve Transparency

Is it plausible that bias (e.g., due to confounding), is minimal?

Does my ICE handling strategy answer a question of clinical/regulatory importance?

Combine TTE and ICH E9(R1) to Clarify the Causal Estimand

TTE Protocol Component	ICH E9(R1) Estimand Attribute
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**Simplified Table 1
Hampson et al. (2024)**

Component
Patient Population
Treatment
Treatment Assignment
Start of follow-up
Variables
Performed Comparison, Causal Effect, Causal Contrast
Analysis
Intercurrent Event(s)

Target Trial / Estimands Framework for ELARA

Simplified Table 1 from Hampson et al. (2024)

Component	Target RCT to be emulated
Patient Population / Eligibility Criteria	"Eligibility criteria of ELARA" Adult patients with relapsed or refractory (r/r) follicular lymphoma who were r/r to second or later line therapy. (https://clinicaltrials.gov/study/NCT03568461)
Treatment / Treatment Strategies	Tisagenlecleucel vs standard of care
Treatment Assignment	Randomization
Variables / Outcomes	•Complete Response (CR) •Progression free survival (PFS) •Overall survival (OS)
Start of follow-up	Randomization
Intercurrent event(s)	To be discussed next
Causal Effect / Contrasts	"Effect of prescribing tisagenlecleucel vs SoC [on CR, PFS, OS] in patients meeting ELARA inclusion/exclusion criteria"



How can we best emulate the target trial using ELARA and the FHRD comparator arm?

Target Trial / Estimands Framework for ELARA

Simplified Table 1 from Hampson et al. (2024)

Component	Target RCT to be emulated	RCT that can be emulated using ELARA and external RWD
		ELARA
Patient Population / Eligibility Criteria	"Eligibility criteria of ELARA"	"Same as target RCT"
Treatment / Treatment Strategies	Tisagenlecleucel vs standard of care	Tisagenlecleucel
Treatment Assignment	Randomization	All enrolled patients receive Tisagenlecleucel
Variables / Outcomes	• Complete Response (CR) • Progression free survival (PFS) • Overall survival (OS)	Assessed as in RCT: • CR, progression: Lugano classification • Progression & death monitored as in RCT
Start of follow-up	Randomization	Date of enrollment
Intercurrent event(s)	To be discussed next	"Same as target RCT"



ELARA conduct similar to RCT (enrollment, monitoring, outcome assessment)

Target Trial / Estimands Framework for ELARA

- FHRD non-interventional, retrospective, EHR dataset
- → More challenges for emulating trial control arm
- → Potential differences in patient characteristics v. ELARA enrollees

Component	Target RCT to be emulated	RCT that can be emulated using ELARA and external RWD	
		ELARA	RW Cohort (FHRD)
Treatment Assignment	Randomization	All enrolled patients receive Tisagenlecleucel	"One eligible [line of therapy] LoT per patient in the external source was systematically selected based on the highest propensity score to be in ELARA. See Section 4 for details."



Lack of randomization → classic Epi challenge: **confounding!**

Brief Review: Confounding



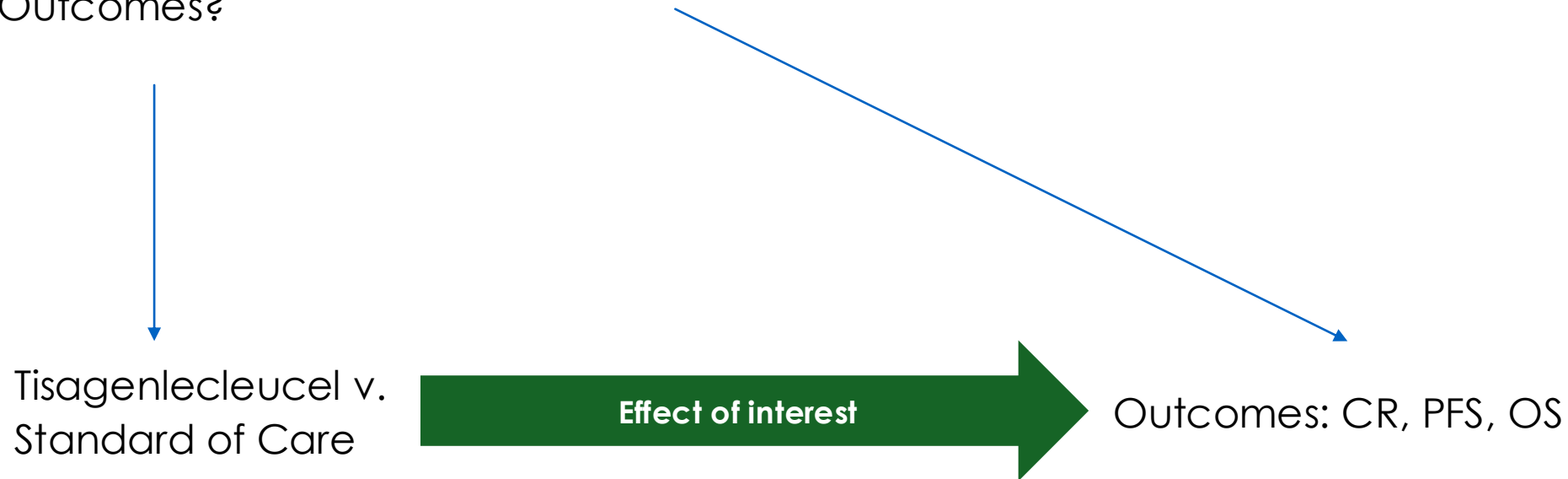
Note: Discussion not addressing time-dependent confounding, other post-baseline differences between ELARA and RW cohort

Brief Review: Confounding

Confounders

What factors affect

1. Who receives Tisagenlecleucel v. SOC
2. Outcomes?



Note: Presentation not addressing time-dependent confounding, other post-baseline differences between ELARA and RW cohort

Brief Review: Confounding

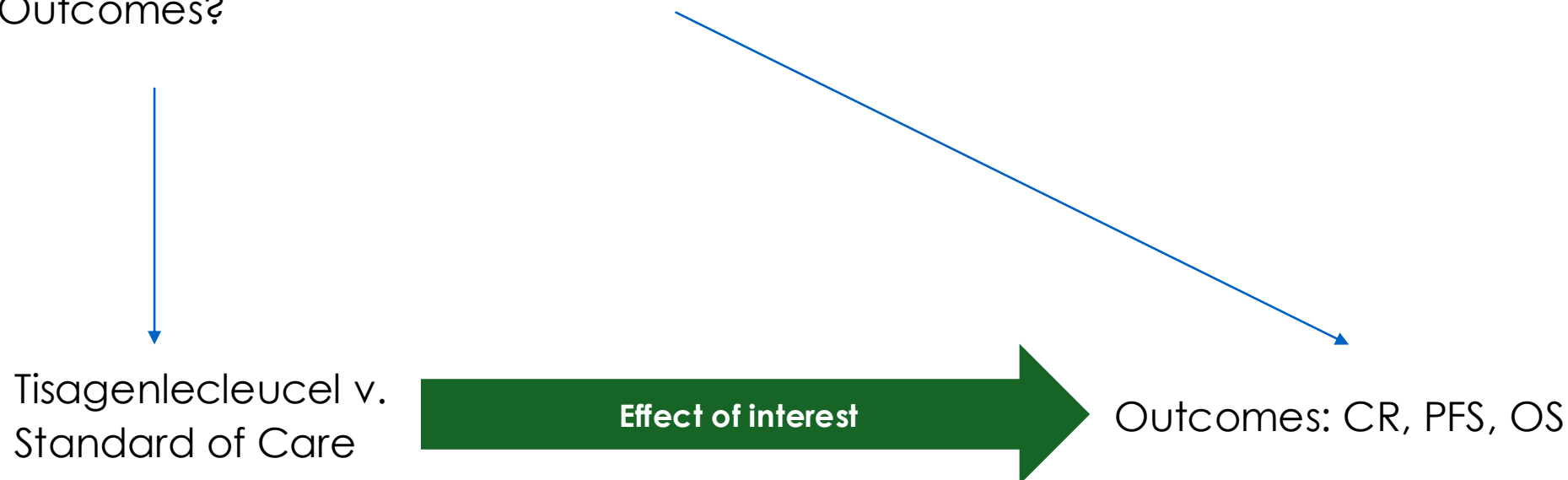
Confounders

What factors affect

1. Who receives Tisagenlecleucel v. SOC
2. Outcomes?



Unmeasured confounders →
biased results



Note: Presentation not addressing time-dependent confounding, other post-baseline differences between ELARA and RW cohort

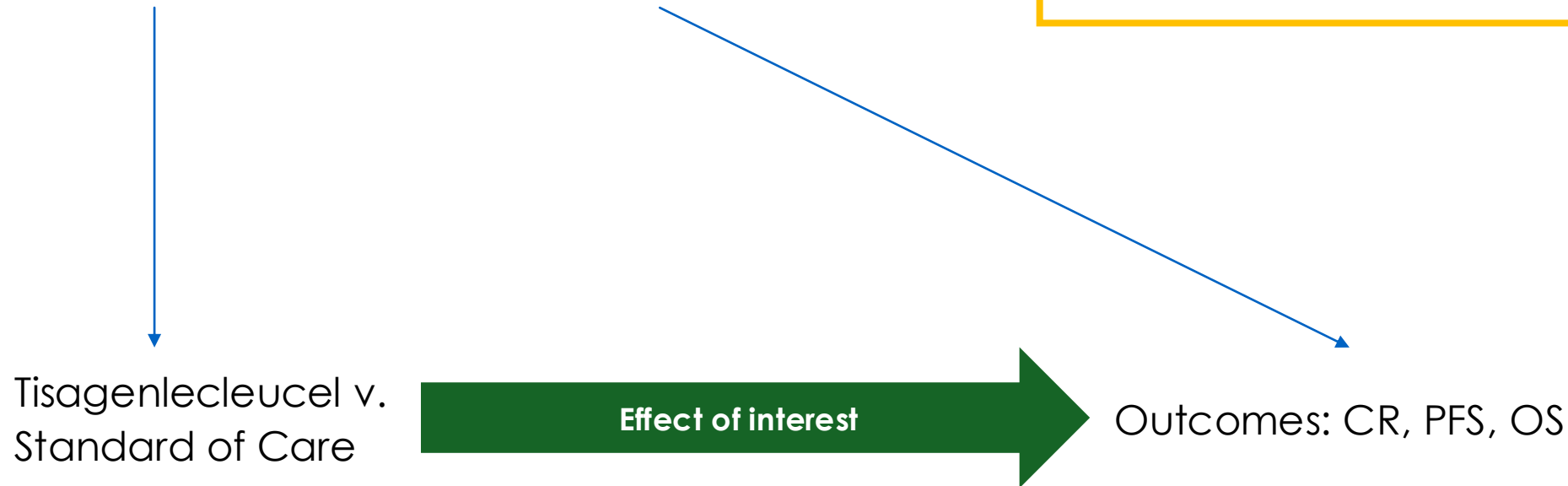
Brief Review: Confounding

Line of Therapy

- Number of anticancer therapies a patient has tried
- **Strong** predictor of progression and survival



Balance as closely as possible
between ELARA and RW cohort



Note: Presentation not addressing time-dependent confounding, other post-baseline differences between ELARA and RW cohort

Brief Review: Confounding

Other Confounders

- Demographic and clinical characteristics



Balance using **Propensity Score**

Tisagenlecleucel v.
Standard of Care

Effect of interest

Outcomes: CR, PFS, OS

Note: Presentation not addressing time-dependent confounding, other post-baseline differences between ELARA and RW cohort

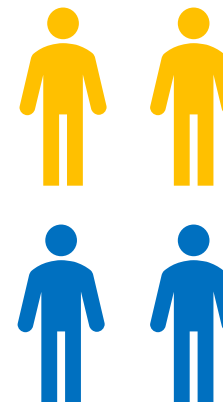
Brief Review: Confounding



Balance using **Propensity Score**

1. Predict probability of ELARA v. RWD using measured confounders
2. Create weighted pseudo-population to balance measured confounders

ELARA



RWD



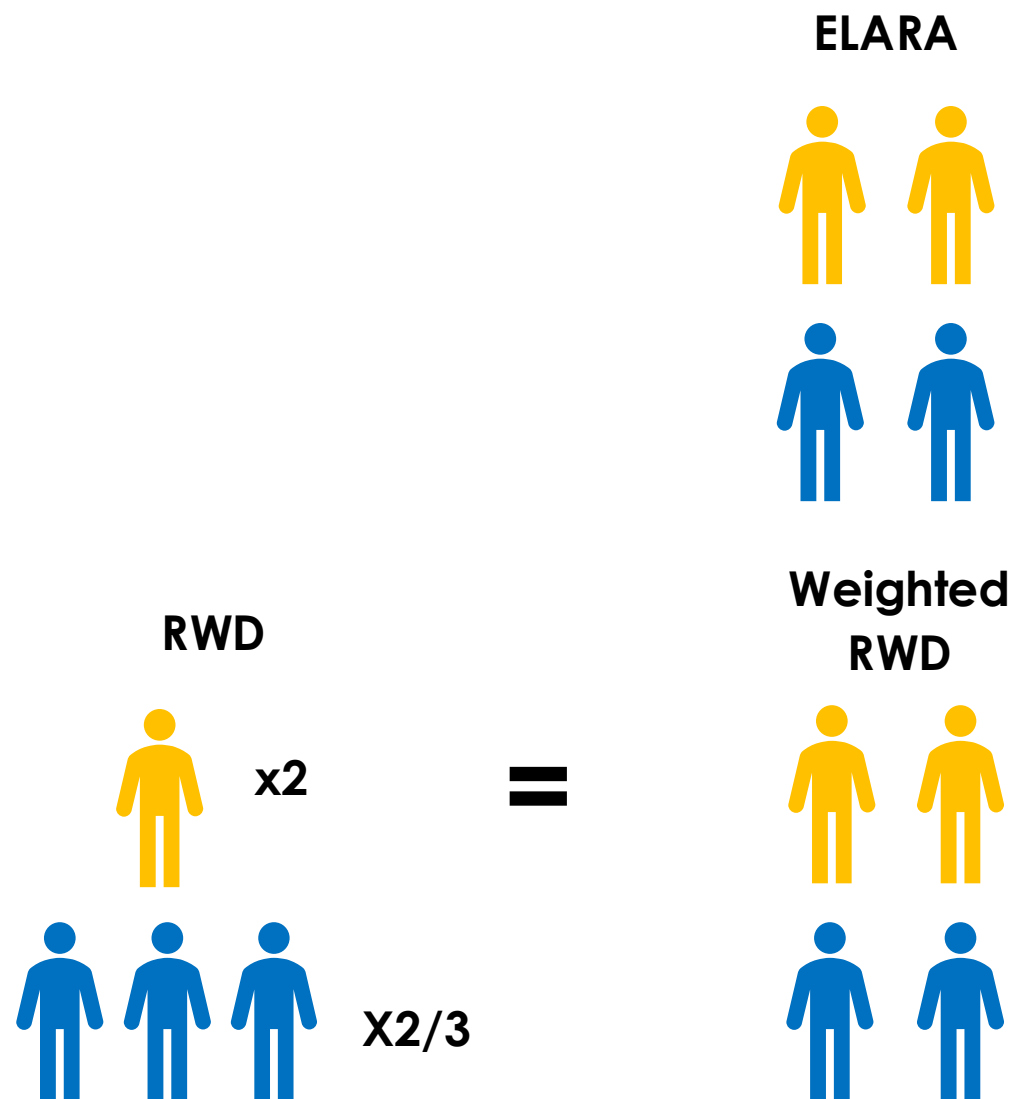
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Brief Review: Confounding



Balance using **Propensity Score**

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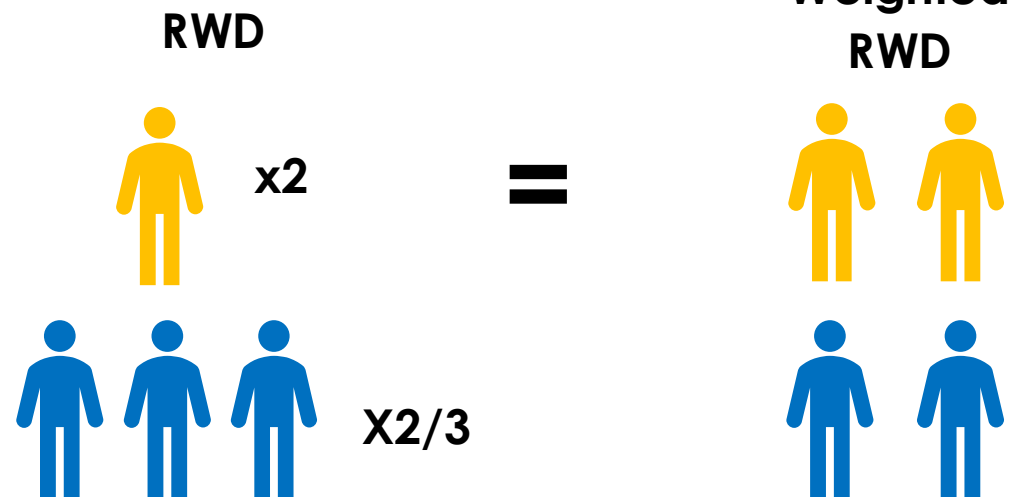
Note: Illustration only, weights determined based on propensity score.

Brief Review: Confounding



Balance using **Propensity Score** → **Mimic Randomization**

1. Predict probability of ELARA v. RWD using measured confounders
2. Create weighted pseudo-population to balance measured confounders



Note: Presentation not addressing time-dependent confounding, other post-baseline differences between ELARA and RW cohort

ICH E9(R1) Strategies for Handling Intercurrent Events (ICEs)

ICE: Initiation of new anticancer therapy



Overall Survival

1. Treatment Policy:

- ICE irrelevant for defining treatment effect
- Intention-to-treat
- No changes to Target Trial Components



Follow-Up

**Outcome:
Death**

ICH E9(R1) Strategies for Handling Intercurrent Events (ICEs)

ICE: Initiation of new anticancer therapy



Complete Response

2. Composite Variable:

- ICE included in composite outcome

**Outcome:
Non-Response**



Component
Patient Population / Eligibility Criteria
Treatment / Treatment Strategies
Treatment Assignment
Variables / Outcomes
Start of follow-up
Intercurrent event(s)
Causal Effect / Contrasts



ICH E9(R1) Strategies for Handling Intercurrent Events (ICEs)

ICE: Initiation of new anticancer therapy



Progression Free Survival

Censor at new
anticancer therapy



3. Hypothetical Strategy:

- Effect if the ICE did not occur?
- E.g. If no additional therapies available
- Modify treatment strategies

Component

Patient Population / Eligibility Criteria

Treatment / Treatment Strategies

- Initiate Tisagenlecleucel & **do not start additional therapy** v.
- Initiate SOC & **do not start additional therapy**

Treatment Assignment

Variables / Outcomes

Start of follow-up

Intercurrent event(s)

Causal Effect / Contrasts



Additional challenge: Post-baseline confounding?

ICH E9(R1) Strategies for Handling Intercurrent Events

1. Treatment Policy:
 - ICE irrelevant for defining treatment effect
 - Intention-to-treat
2. Composite Variable:
 - ICE included in composite outcome
3. Hypothetical Strategy:
 - What would be the effect if the ICE did not occur?

4. While on Treatment
 - Effect before intercurrent event
 - e.g., “while alive”
5. Principal stratum
 - E.g., effect for population who **would not** have ICE if assigned treatment 1



- • Different ICE rates by arm → compare outcomes for different durations of treatment
- • Hard to identify principal stratum (not = observed subset without ICE)

ICH E9(R1) Strategies for Handling Intercurrent Events

1. Treatment Policy:
 - ICE irrelevant for defining treatment effect
 - Intention-to-treat
2. Composite Variable:
 - ICE included in composite outcome
3. Hypothetical Strategy:
 - What would be the effect if the ICE did not occur?
4. While on Treatment
 - Effect before intercurrent event
 - e.g., “while alive”
5. Principal stratum
 - E.g., effect for population who **would not** have ICE if assigned treatment 1



- May only be appropriate for sensitivity analyses

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Target Trial / Estimands Framework for ELARA



- FHRD non-interventional, retrospective, EHR dataset
- → More challenges for emulating trial control arm

Activity 1: Practice describing trial emulation from RWD

- ☐ Read **Excerpt # 1 from Hampson et al. (2024)**. Use **Handout #1** (ICH E9(R1) ICE Strategies) & **Handout #2** (Simplified Table 1 from Hampson et al. (2024)) as references.
- ☐ **Discussion Prompts:**
 1. **No target trial can be replicated exactly using RWD.** Identify one aspect of the emulation that is particularly well-aligned with the target trial, and one aspect where the investigators faced the toughest design trade-off given RWD limitations.
 2. Choose one ICE strategy you would use in this context, and give one reason why.

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Part 2 – CDISC ADaM Implementation, from Concept to Dataset

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Biomedical Data Stewardship Senior Manager,
Center for Design & Analysis (CfDA), Amgen

March 25, 2026

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Part 2 – From Concept to Dataset

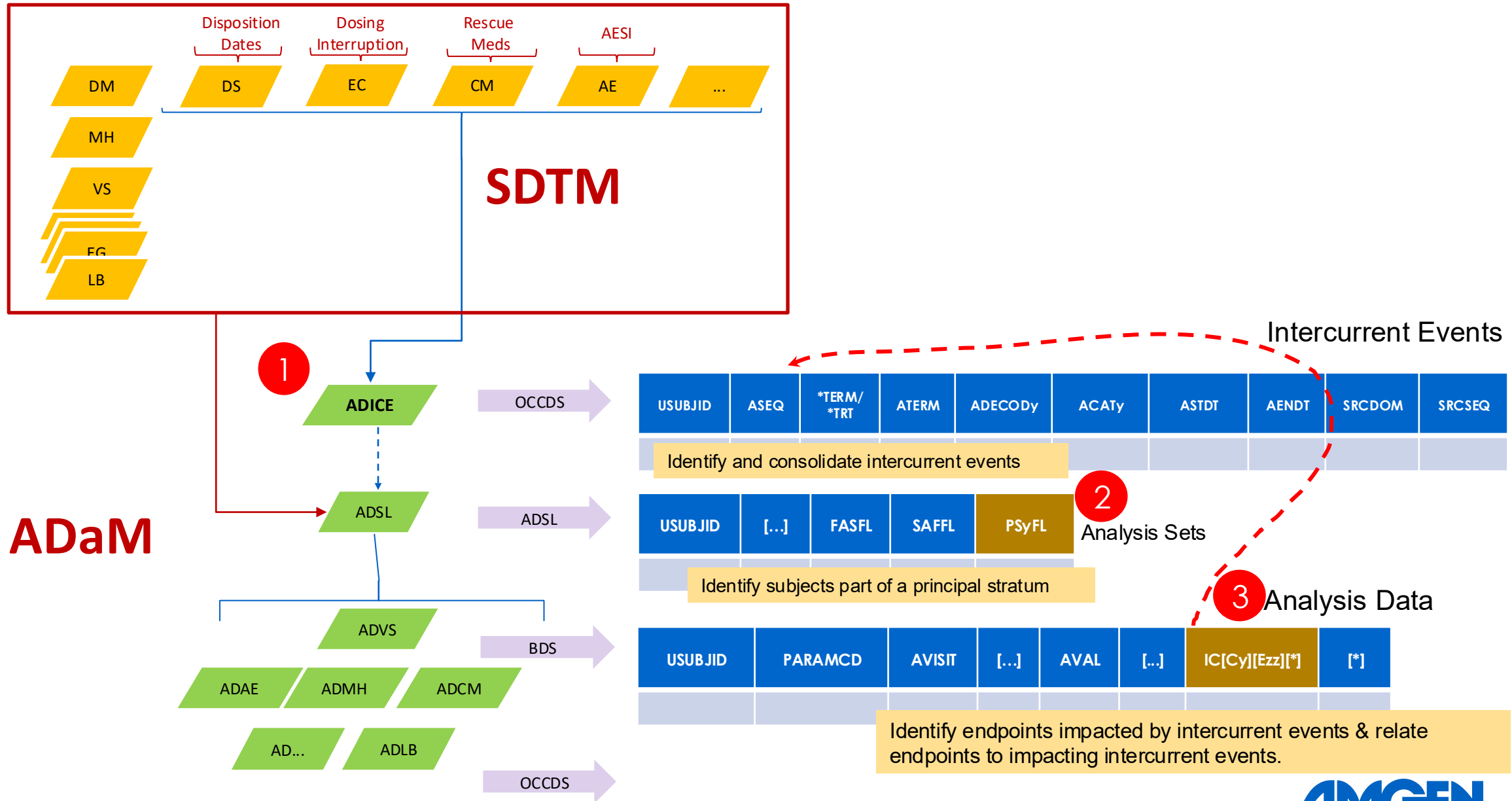
- PHUSE Estimands Implementation white paper and appendix/example (developed 2022-2025; published on May 19, 2025)
 - [Main white paper](#)
 - [appendix/example](#)
- Borrowing conventions from RCT context and applying to RWD/RWE context

**Implementation of ICH E9(R1) Estimands Framework
using Data Standards**

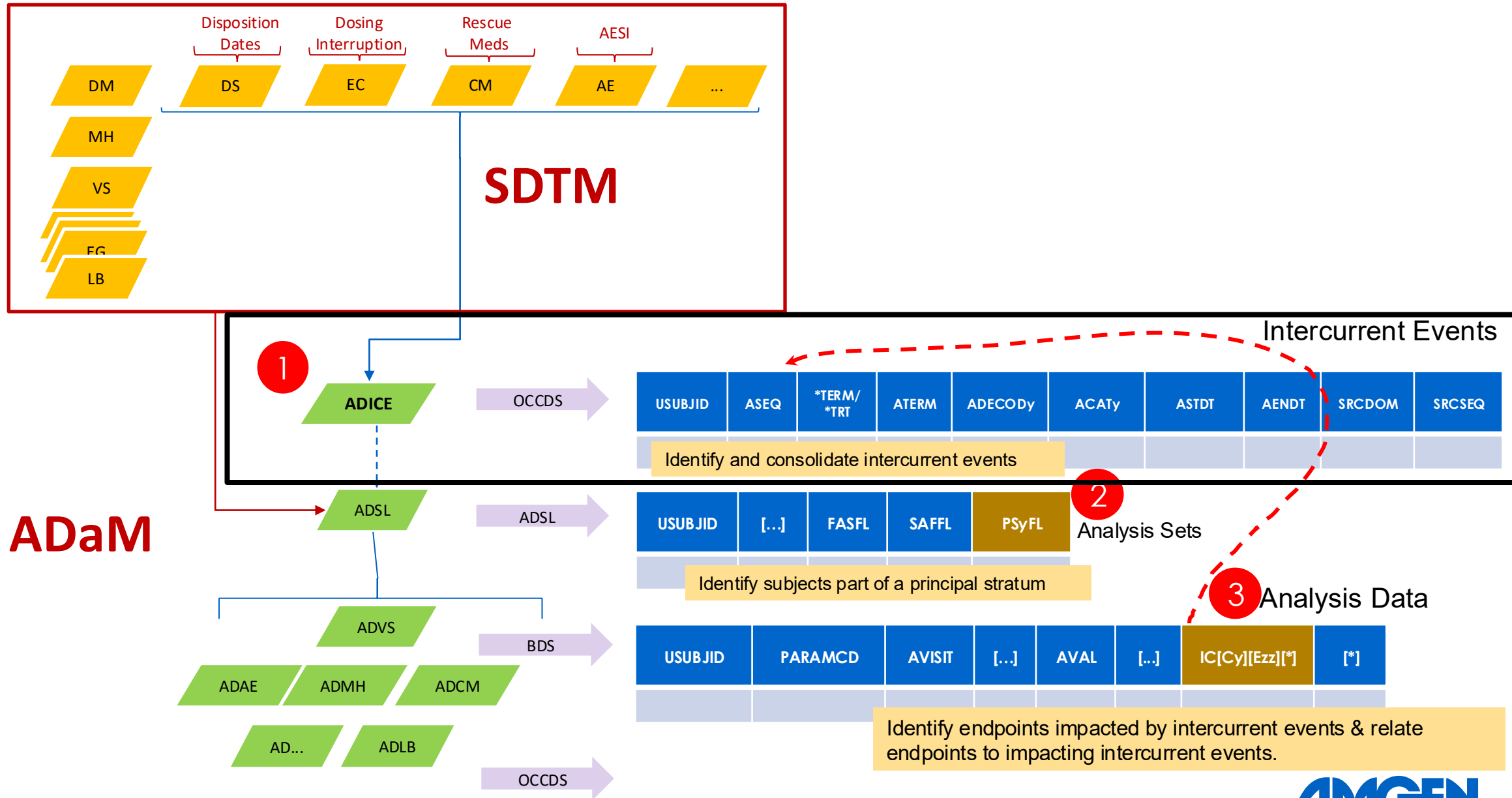


**Implementation of ICH E9(R1) Estimands Framework
using Data Standards - Example Document**

ADaM Implementation – Overview



ADaM Implementation – Overview

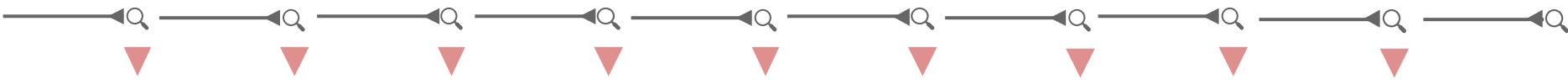


Workshop Supportive example - question

Question of interest from workshop part 1:

What would the hazard ratio for progression free survival by 24 months be if all patients with refractory or relapsed Follicular Lymphoma (Grade 1, 2, 3A) and meeting the additional ELARA eligibility criteria were prescribed optional bridging therapy and lymphodepleting therapy followed by tisagenlecleucel infusion compared to if they were prescribed standard of care, if patients were not able to initiate a new anticancer therapy before progression, but regardless of treatment discontinuation.

PHUSE Paper Example data – patient journeys



Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SOx			
ABC002	R/TI		TD LOG	SOx						
ABC003	R/TI			---	SOx			TD LOG		
ABC004	R/TI			---			TD AE/LoE		SOx	
ABC005	R/TI			---		TD AE/LoE				

R/TI Randomisation/Treatment initiation

 Hamilton Questionnaire at visit (retrospective on the week)

 Treatment administration at visit (end of week)

 Start other medications for MDD

 Treatment discontinuation due to Adverse Event or Lack of efficacy

 Treatment discontinuation due to geopolitical logistical restrictions

 Outcome collected

PHUSE Paper Example data – patient journeys



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ABC003	R/TI			---	SOx			TD LOG		
ABC004	R/TI			---			TD AE/LoE		SOx	
ABC005	R/TI			---		TD AE/LoE				

R/TI Randomisation/Treatment initiation

—🔍 Hamilton Questionnaire at visit (retrospective on the week)

▼ Treatment administration at visit (end of week)

💊 Start other medications for MDD

⚠️ Treatment discontinuation due to Adverse Event or Lack of efficacy

✖️ Treatment discontinuation due to geopolitical logistical restrictions

Outcome collected

Intercurrent events structure (OCCDS-ICE) – Needs & solution

Needs

- **Gather intercurrent events from different sources** – direct or derived events – such as disposition, adverse events, lab findings in a structure, facilitating :
 - **reporting**: e.g. frequencies on type of intercurrent events by treatment groups ...
 - **traceability**: relating endpoints to intercurrent events affecting them.
 - **programming** when all intercurrent events are organised in a single dataset

Solution

- ADaM **occurrence** (OCCDS), **subclass for intercurrent events** (ICE) -> **OCCDS-ICE**
- **One record per subject, per intercurrent event**
- Records can originate in SDTM/ADaM sources as direct or derived events
- Dataset name: *recommend* **ADICE** with label "Inter^current ^Events Analysis Dataset"

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ICH E9(R1) Strategies for Handling Intercurrent Events

Component	Target RCT to be emulated	RCT that can be emulated using ELARA and external RWD	
		ELARA	RW cohort
Patient Population	Eligibility criteria of ELARA	Same as target RCT	Eligibility criteria of ELARA that are feasible to implement in a retrospective assessment of the RWD
Intercurrent event(s)	Initiation of new anticancer therapy before progression. • CR: ICE reflected in Variable (Composite; Estimand 01) • PFS: Hypothetical strategy (Estimand 02) • OS: Treatment policy strategy (Estimand 03)	Same as target RCT for CR and OS PFS comparison with FHRD: the same as target RCT.	

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
ABC001	1	ELARA (single arm)	Breyanzi	Initiating a new anticancer therapy before progression	2018-04-20		COMPOSITE	HYPOTHETICAL	TREATMENT POLICY	CM	1
ABC002	1	RW Cohort (FHRD)	Yescarta	Initiating a new anticancer therapy before progression	2019-04-03		COMPOSITE	HYPOTHETICAL	TREATMENT POLICY	CM	1

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID											
ABC001											
ABC002											

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID	ASEQ										
ABC001	1										
ABC002	1										
Origind											

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID	ASEQ	TRTA									
ABC001	1	ELARA (single arm)									
ABC002	1	RW Cohort (FHRD)									

Original name of the event

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID	ASEQ	TRTA	ATERM								
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Original name of the event

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
-------	-------	-------	-------	-------	-------	-------	-------	-------	--------	--------	--------

USUBJID	ASEQ	TRTA	ATERM	ADECOD1
ABC001	1	ELARA (single arm)	Breyanzi	Initiating a new anticancer therapy before progression
ABC002	1	RW Cohort (FHRD)	Yescarta	Initiating a new anticancer therapy before progression

Original name of the event

Standardised name of the intercurrent event, per protocol/SAP wording

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
-------	-------	-------	-------	-------	-------	-------	-------	-------	--------	--------	--------

USUBJID	ASEQ	TRTA	ATERM	ADECOD1	ASTDT
ABC001	1	ELARA (single arm)	Breyanzi	Initiating a new anticancer therapy before progression	2018-04-20
ABC002	1	RW Cohort (FHRD)	Yescarta	Initiating a new anticancer therapy before progression	2019-04-03

Original name of the event

Standardised name of the intercurrent event, per protocol/SAP wording

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID	ASEQ	TRTA	ATERM	ADECOD1	ASTDT	AENDT					
ABC001	1	ELARA (single arm)	Breyanzi	Initiating a new anticancer therapy before progression	2018-04-20						
ABC002	1	RW Cohort (FHRD)	Yescarta	Initiating a new anticancer therapy before progression	2019-04-03						

Original name of the event

Standardised name of the intercurrent event, per protocol/SAP wording

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID	ASEQ	TRTA	ATERM	ADECOD1	ASTDT	AENDT	EST01STP	EST02STP	EST03STP		
ABC001	1	ELARA (single arm)	Breyanzi	Initiating a new anticancer therapy before progression	2018-04-20		COMPOSITE	HYPOTHETICAL	TREATMENT POLICY		
ABC002	1	RW Cohort (FHRD)	Yescarta	Initiating a new anticancer therapy before progression	2019-04-03		COMPOSITE	HYPOTHETICAL	TREATMENT POLICY		

Original name of the event

Standardised name of the intercurrent event, per protocol/SAP wording

Planned strategy, per protocol/SAP

Intercurrent events structure (OCCDS-ICE) – Workshop Example

ADICE

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10	Col 11	Col 12
USUBJID	ASEQ	TRTA	ATERM	ADECOD1	ASTDT	AENDT	EST01STP	EST02STP	EST03STP	SRCDOM	SRCSEQ
ABC001	1	ELARA (single arm)	Breyanzi	Initiating a new anticancer therapy before progression	2018-04-20		COMPOSITE	HYPOTHETICAL	TREATMENT POLICY	CM	1
ABC002	1	RW Cohort (FHRD)	Yescarta	Initiating a new anticancer therapy before progression	2019-04-03		COMPOSITE	HYPOTHETICAL	TREATMENT POLICY	CM	1

Original name of the event

Standardised name of the intercurrent event, per protocol/SAP wording

Planned strategy, per protocol/SAP

Source of intercurrent event

List pros and cons of creating an Intercurrent Events Analysis Dataset (ADICE)

Agenda

- (10 min) Welcome & Orientation
- (15 min) Part 1 – Causal Thinking w/ TTE + Estimands (ELARA Case)
- (20 min) Part 1 Activity – Emulating the Target Trial
- (15 min) Part 2 – From Concept to Dataset
- (20 min) Part 2 Activity – Implementing Estimands in ADaM
- **(10 min) Summary and Final Q&A**

References

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