

Activity 1: Structure

- Handouts given out upon entry to workshop
- Lauren introduces Activity 1 on last slide of Part 1
- Participants discuss with others at their table for 12 minutes
- Discussion prompts: 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.
 - **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.
 - Choose one ICE strategy you would use in this context, and give one reason why.
- Group sharing: Volunteers share insights and questions from their groups.

Excerpt # 1 from Hampson et al. (2024)

***Note: ReCORD was a 2nd RW cohort used as an external control arm.**

“The right-hand columns of Table 1 summarize the RCT that we *can* emulate given the data available from ELARA and the external controls. Comparing this with our target RCT highlights limitations of the RWD. In particular, while we can emulate the target population based on key ELARA eligibility criteria as envisioned in future drug label criteria, not all criteria were captured in the RWD (e.g. ECOG or lab results were not recorded or incomplete). However, based on clinical assessment it was concluded that the impact of these criteria on the adequacy of the ECA is likely to be limited and does not prevent meaningful comparisons. Another potential limitation is that CR and progression in the RWD were assessed per real-world regular practice and not following the Lugano classification 2014 criteria²⁶ as used in ELARA. Regarding this, a subgroup analysis for patients treated after 01-Jan-2014, to coincide with the introduction of the new Lugano response criteria, was conducted. Moreover, this limitation does not impact OS. A third limitation is that while the date of treatment initiation is available for all patients, the date of prescription is unknown for RW patients. However, in the context of currently available therapies and a serious condition such as follicular lymphoma, the lag between prescription and start of treatment is likely to be short, meaning the date of treatment initiation will be an adequate approximation for the date of prescription. Since the date of initiation of all treatments is recorded for RW patients, the key intercurrent event of initiation of a new anticancer therapy is captured. We can apply the same strategy as would be used in the target RCT to handle this event when comparing the ELARA and external controls with regards to CR and OS. However, progression dates were unavailable for many patients in ReCORD, so the comparison of PFS was performed by considering a new anticancer therapy as an event for patients in both ReCORD and ELARA. If no progression, death or starting a new anticancer therapy occurred, patients are censored at the last contact date. For FHRD, PFS was handled in the same way as the target RCT. If patients have not had disease progression before the start of new anticancer therapy, they were censored at the date of the starting new anticancer therapy, or last clinic note date if the selected LoT was the last LoT [hypothetical strategy].”

Handout # 1

Excerpt from ICH E9(R1)

“A.3.2. Strategies for Addressing Intercurrent Events when Defining the Clinical Question of Interest

Descriptions of various strategies are listed below, each reflecting a different clinical question of interest in respect of a particular intercurrent event...

Treatment policy strategy

The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs. For example, when specifying how to address use of additional medication as an intercurrent event, the values of the variable of interest are used whether or not the patient takes additional medication.

If applied in relation to whether or not a patient continues treatment, and whether or not a patient experiences changes in other treatments (e.g. background or concomitant treatments), the intercurrent event is considered to be part of the treatments being compared. In that case, this reflects the comparison described in the ICH E9 Glossary (under ITT Principle) as the effect of a treatment policy...

Hypothetical strategies

A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.

A wide variety of hypothetical scenarios can be envisaged, but some scenarios are likely to be of more clinical or regulatory interest than others. For example, it may be of clinical or regulatory importance to consider the effect of a treatment under different conditions from those of the trial that can be carried out. Specifically, when additional medication must be made available for ethical reasons, a treatment effect of interest might concern the outcomes if the additional medication was not available. A very different hypothetical scenario might postulate that intercurrent events would not occur, or that different intercurrent events would occur. For example, for a subject that will suffer an adverse event and discontinue treatment, it might be considered whether the same subject would not have the adverse event or could continue treatment in spite of the adverse event. The clinical and regulatory interest of such hypotheticals is limited and would usually depend on a clear understanding of why and how the intercurrent event or its consequences would be expected to be different in clinical practice than in the clinical trial...

Composite variable strategies

This relates to the variable of interest (see A.3.3.). An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable. For example, a patient who discontinues treatment because of toxicity may be considered not to have been successfully treated. If the outcome variable was already success or failure, discontinuation of treatment for toxicity would simply be considered another mode of failure..." (pages 7-8)

Handout # 2: Simplified Table 1 from Hampson et al. (2024)

***Note: ReCORD was a 2nd RW cohort used as an external control arm.**

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
Treatment assignment	Block randomized to either tisagenlecleucel arm or SoC arm.	Tisagenlecleucel infusion after optional bridging therapy and Lymphodepleting therapy	One eligible LoT per patient in the external source was systematically selected based on the highest propensity score to be in ELARA.
Variables	CR and progression are assessed per Lugano classification 2014²⁶ until patient initiates a new anticancer treatment. CR is best overall response. If no response is reported before progression or time of new therapy, patient is regarded as non- responder. PFS is time to the first documented progression or death from any cause... OS is time to death from any cause regardless of treatment	CR and OS as target RCT. For comparison with ReCORD, PFS is performed by considering new anticancer therapy as an event. For comparison with FHRD, PFS is the same as target RCT.	CR and progression were based on real-world response criteria. For FHRD, only abstracted response with non-missing value were considered, and only patients with at least >=1 non-missing value for abstracted response were included for CR analysis. For ReCORD, a subgroup analysis for patients treated after 01-Jan-2014 was conducted as year of introduction of Lugano response criteria. - In ReCORD, progression dates were unavailable for many patients, so consider new anticancer therapy as an event for PFS. - In FHRD, PFS was handled using the same hypothetical strategy as target RCT. OS same as in target RCT.
Start of follow-up	Date of randomization, regarded as date of prescription	Date of enrolment into ELARA, regarded as date of prescription	Start date of SoC
Intercurrent event(s)	Initiation of new anticancer therapy before progression. - CR: ICE reflected in Variable - PFS: Hypothetical strategy - OS: Treatment policy strategy	Same as target RCT for CR and OS PFS comparison with ReCORD: Composite strategy PFS comparison with FHRD: the same as target RCT.	

