TARGET- EU: Bridging the Target Trial Emulation and Estimand Frameworks to Strengthen Comparative Effectiveness and Safety Research Using Real-World Data

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Methodological Principles for Non-Interventional Studies with Causal Objectives

For non-interventional studies (NIS) with causal objectives, EMA recommends combining two frameworks:

ICH E9(R1) estimand framework — supplies the precise causal-question specification (estimand attributes and intercurrent event strategies)

Target trial emulation (TTE) — supplies the overall design logic, emulating a hypothetical trial using epidemiological methods

Together, the two frameworks keep the NIS coherent with — and transparent relative to — the hypothetical target trial, from design through statistical analysis

This integration is considered a promising bridge between real-world data and randomized controlled trial evidence

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Source: EMA, 2025c (Reflection paper on RWD in non-interventional studies)

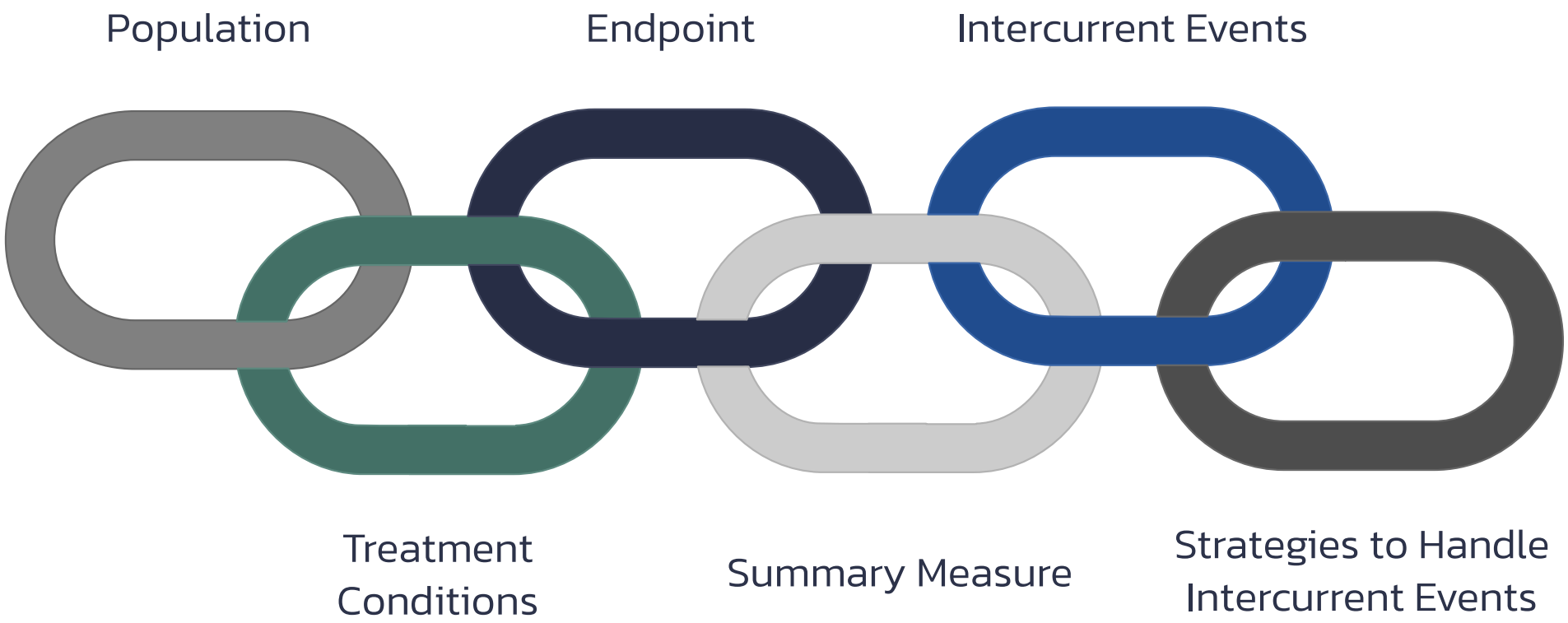
Target Trial Emulation Framework



Estimand

> "a **precise description of the treatment effect** *reflecting the clinical question posed by a given clinical trial objective.*"

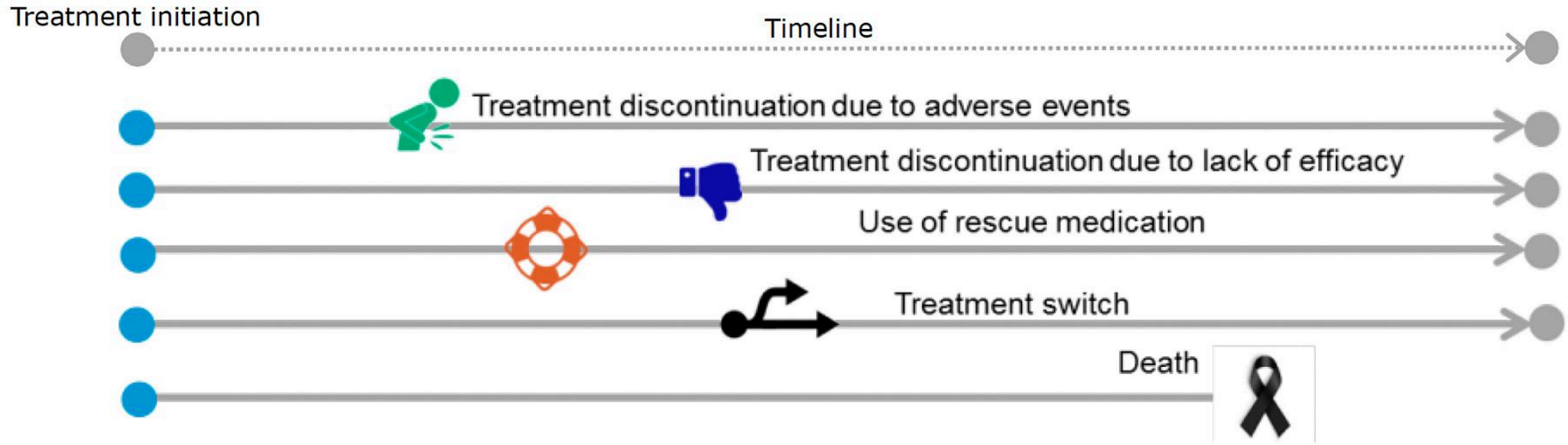
Elements of the Estimand



Intercurrent events

Definition: *"Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest"*

Examples of intercurrent events:



Strategies to Handle Intercurrent Events

Definition: *A pre-specified rule that determines how the effect of treatment is defined and estimated when events occurring after treatment initiation affect the interpretation or measurement of the outcome.*

Five Main Strategies

Treatment policy
The occurrence of the intercurrent event is considered irrelevant; all outcomes are analyzed regardless of the event.

Hypothetical
The treatment effect is defined in a scenario where the intercurrent event would not occur (e.g., “what if no patient discontinued?”).

Composite
The intercurrent event is incorporated into the outcome definition itself (e.g., treatment failure includes both relapse and use of rescue medication).

While-on-treatment/ while alive
Only outcomes observed up until the occurrence of the intercurrent event are considered.

Principal stratum
The effect is estimated within the subgroup of patients in whom the intercurrent event would (or would not) occur under each treatment.



Challenges

Translating the combined estimand + target trial emulation approach into practice introduces methodological and operational challenges that remained unresolved prior to this project, pending further work to determine how they could be addressed

TARGET–EU

TARGET-EU is an EMA-sponsored methodological research initiative examining the opportunities, limitations, and challenges of conducting non-interventional studies with causal objectives for regulatory decision-making using European data sources with a particular focus on integrating target trial emulation with the estimand framework.

The aim is to support the uptake of these frameworks for causal questions in regulatory decision-making, increasing the reliability of real-world findings within the European regulatory network.

TARGET-EU Study Team

Co-Leads : Olaf Klungel & Daniala Weir (UU)

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Project Management: Teamit

WP2 leads: Linda Nab, Oisín Ryan, Miriam Sturkenboom (UMCU)

WP3 leads: Ian Douglas (LSHTM), Olaf Klungel, Daniala Weir

ARS Toscana Programming Team, UMCU programming team, 10 case study leads + teams, DEAPS

EMA Study Team



TARGET-EU Overall Approach

Selection of RCT or NIS as inspiration for case studies

Used as inspiration, not to replicated

Development of protocol for hypothetical target trial

Estimand using ICH (E9) R1

Modified template based on ICH-11

Feasibility assessment

Applied EMA Data Quality Framework

Development of protocol for target trial emulation

HARPER template

Complete analyses of 10 NIS using the Conception/OMOP Common Data Model and a common analytic approach

CASE STUDY EXAMPLE

TARGET-EU: Clinical benefit of bevacizumab in metastatic colorectal cancer

Identifier: EUPAS1000000539

Primary investigator

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CORE EMULATION TABLE

Estimand 1

Attribute	Target Trial	Target Trial Emulation	Comment
Population	Patients with mCRC	Patients with mCRC	-
Treatment Conditions	CapOx-B regimen vs CapOx regimen alone	CapOx-B regimen vs CapOx regimen alone, identified using administration data	Exposure defined based on first observed administration within first-line treatment regimen (new-user design)
Endpoint	Time to first occurrence of disease progression or death	Time to first occurrence of disease progression or death. Disease progression is marked by the end of an "episode" in the NCR.	The measure used is ***validated*** and routinely applied in NCR-based observational studies PFS measurement differs slightly from the target trial, but limited expected impact. Observational PFS ***less frequently*** assessed than in trial and more ***heterogeneous*** (no central review) Progression is assessed identically across both treatment groups, this is not expected to bias results.

CORE EMULATION TABLE

Estimand 1

Attribute	Target Trial	Target Trial Emulation	Comment
Summary Measure	Hazard ratio	Hazard ratio	Target trial and emulation are identical.
Intercurrent Events and Strategies to Handle Them	**Treatment discontinuation (bevacizumab):** treatment policy **Partial/full discontinuation:** treatment policy **Treatment switch (i.e. use of new anticancer therapy):** treatment policy **Local treatment:** treatment policy	**Treatment discontinuation (bevacizumab):** stop date of individual drugs is registered **Partial/full discontinuation:** stop date of individual drugs is registered **Treatment switch:** stop date and start date of individual drugs is registered. If the treatment is switched due to toxicity, this is registered within the same "episode". Treatment switching due to disease progression is not an intercurrent event. **Local treatment, registration of codes and dates for:** - Surgery - Radiotherapy - Ablation - Other local treatment: e.g. hyperthermic intraperitoneal chemotherapy (HIPEC) or embolization	Target trial and emulation are identical. Treatment policy implies using all available data regardless of the occurrence of the intercurrent events. ***Issues with the identification of the corresponding intercurrent events in real-world data will bear no consequences for the estimand as long as relevant post-intercurrent event data are available in the data source.***

RESEARCH QUESTION TARGETED BY ESTIMAND 1

> What is the HR of disease progression or death for CapOx–B vs CapOx alone in patients with mCRC, regardless of treatment discontinuation, treatment switch or local treatment?

CORE EMULATION TABLE

Comparison of Target Trial and Proposed Target Trial Emulation Design Elements

Attribute	Target Trial	Target Trial Emulation	Comment
Eligibility	***Inclusion criteria***		
	Histologically confirmed mCRC	Have a record of histologically confirmed mCRC based on the registration in the Dutch pathology database PALGA or a cancer diagnosis in the national registration of hospital care (LBZ)	Eligibility applied using structured electronic health records (HER) data.
	Age 18 and over at the time of eligibility screening	Age 18 and over at time 0	n/a
	Not felt to be amenable to curative resection	Missing	No information is available on amenability for curative resection. It should be possible to identify which patients underwent (curative) resection, but we cannot identify the patients who intended to undergo curative resection before initiation of systemic treatment.
	ECOG PS ≤ 1	ECOG PS ≤ 1 at the time of recorded diagnosis	If missing, patient excluded
	Life expectancy ≥ 3	Missing	Life expectancy at baseline is not recorded.
	No prior systemic therapy for mCRC or previous treatment with oxaliplatin and/or bevacizumab	No prior systemic therapy for mCRC ***or previous malignancy that could potentially have been treated with oxaliplatin and/ or bevacizumab*** (as a proxy for previous treatment with oxaliplatin and/ or bevacizumab)	Deviation regarding the previous treatment with oxaliplatin and/ or bevacizumab. ***The NCR only contains information on the first-line treatment of previous malignancies, even though oxaliplatin and/ or bevacizumab could have also been applied in later line treatment of previous malignancies.*** It is more conservative if patients with any relevant previous malignancy, that could potentially have been treated with oxaliplatin and/ or bevacizumab, are ineligible for inclusion.
	Radiotherapy or surgery for mCRC was permitted if completed ≥ 4 weeks before random assignment	Radiotherapy or surgery for mCRC was permitted if completed ≥ 4 weeks before treatment assignment	n/a
	Adequate hematologic/clotting, hepatic and renal function		We do not have any information on adequate hematologic/clotting, hepatic and renal function.
		Treatment initiation with either CapOx-B or CapOx using administration records	Because of the new user active comparator study design, the study population will be restricted to study drug initiators. Patients who receive treatment or comparator in clinical practice reflect the target population. Hence, no relevant differences are expected between patients eligible to initiate treatments approved within the same indication. Moreover, using the first administration record can be interpreted as an emulation of intention-to-treat, which is based on eligibility in RCTs.

CORE EMULATION TABLE

Comparison of Target Trial and Proposed Target Trial Emulation Design Elements

Attribute	Target Trial	Target Trial Emulation	Comment
Eligibility	***Exclusion criteria***		
	Pregnant or breastfeeding women	***Missing***	Pregnancy, breastfeeding, and comorbidities at diagnosis are only registered in some Dutch regions, and data on breastfeeding or serious nonhealing wounds/ulcers is unavailable , despite these being contraindications for capecitabine, oxaliplatin, and/or bevacizumab (guidelines also recommend a 5-week gap between chemotherapy/bevacizumab and resection). This gap is not expected to have a large impact, since these drugs are unlikely to be used in such patients in clinical practice.
	Serious nonhealing would or ulcer	***Missing***	
Setting	Multicentre, parallel-group, randomised controlled open-label trial	Routine care data from NCR database; capturing patient and disease characteristics, prescriptions, outcomes and covariates from the in- and outpatient hospital setting	Real-world data (RWD) captures care as delivered; pragmatic design supports effectiveness focus.
Treatment conditions	CapOx-B regimen vs. CapOx regimen alone Discontinuation of oxaliplatin is a part of the standard treatment protocol as are adjustments to the dose and dosing interval	Initiation of first-line CapOx-B regimen or CapOx regimen alone (no prior use), identified using administration data The CapOx(-B) regimen consists of repetitively administered 21-day cycles. Within a cycle, oxaliplatin (and bevacizumab) are administered intravenously on day 1. Capecitabine is administered orally, twice daily, on day 1-14 Discontinuation of oxaliplatin (after 6 cycles) is part of the standard treatment protocol	
Treatment Assignment	1:1 randomisation, stratified by ECOG PS and liver as a metastatic site	***Stratified randomisation will be emulated through 1:1 matching (without replacement) by ECOG PS and liver as a metastatic site.*** ***IPTW will be used to account for baseline differences between treatment groups.***	1:1 matching without replacement & PS methods used to balance confounders in absence of randomisation; design emulates stratified, randomised treatment assignment. *If matching excludes many patients, include ECOG +liver met in prop score model

CORE EMULATION TABLE

Comparison of Target Trial and Proposed Target Trial Emulation Design Elements

Attribute	Target Trial	Target Trial Emulation	Comment
Follow-up	Begins at the time of randomisation; ends at the first occurrence of the outcome (disease progression or death), loss to follow-up, study withdrawal or after a maximum follow up period of 104 weeks	***Begins at treatment initiation (index date) and ends at outcome (disease progression or death), loss to follow-up or after a maximum follow-up time of 104 weeks.*** ***In estimand 2, the occurrence of some intercurrent events will inform the end of follow-up. This is the case for the intercurrent events partial/full discontinuation and treatment switch, under the hypothetical strategy. For local treatment, under the composite strategy, patients are assumed to have completed the intended follow up and will be administratively censored at 104 weeks.*** Follow-up is continued regardless of the occurrence of intercurrent events when the treatment policy strategy is applied, which is the case in estimand 1 and 3.	Aligns start of follow-up with treatment initiation to mimic randomisation. From the NCR, disease progression will be identified through the end of an "episode". This identification from the NCR is validated and regularly used in observational studies using NCR data. With little expected impact, it differs from the target trial measurement, in which disease progression is identified through medical imaging. The hypothetically handled intercurrent events from estimand 2 can be identified from the NCR reliably due to the availability of start and stop dates of SACT.
Outcome	Time to first occurrence of disease progression, based on abdominal CT scans and/or MRI, or death In estimand 2, local treatment (surgery, radiotherapy, ablation, or other local treatments) will be added as a composite outcome	Time to first occurrence of disease progression, based on end of "episodes" in NCR database, or mortality records (in linked databases) In estimand 2, local treatment (surgery, radiotherapy, ablation, or other local treatments) will be added as a composite outcome	PFS measurement differs between target trial and emulation. A new "episode" in the NCR database is only made if the reason for treatment switch is disease progression. A new "episode" indicates disease progression and thus the end of PFS. PFS is assessed locally instead of centrally, which may introduce some heterogeneity in the outcome assessment. If treatment is switched due to toxicity, this is added to the same "episode". Outcome measurement is validated and regularly used in observational studies using NCR data. Date of death is always available through linkage with the municipal basic administration (GBA), also if the patient is transferred to another (Dutch) hospital.

CORE EMULATION TABLE

Comparison of Target Trial and Proposed Target Trial Emulation Design Elements

Attribute	Target Trial	Target Trial Emulation	Comment
Intercurrent Events and Strategies to Handle Them	Estimand 1 and 3: treatment policy for all intercurrent events Estimand 2: treatment policy for the treatment discontinuation intercurrent event, hypothetical for partial/full discontinuation or treatment switch, composite for local treatment	Same strategies implemented using censoring and creating a composite outcome including local treatment Intercurrent events will be measured in NCR as follows: Treatment discontinuation (bevacizumab): stop date of individual drugs is registered Partial/full discontinuation: stop date of individual drugs is registered Treatment switch: stop date and start date of individual drugs is registered. A treatment switch due to toxicity is registered within the same “episode”. Local treatment: Surgery: the performance of surgery for metastases is registered, alongside the specific codes and dates Radiotherapy: the performance of radiotherapy for metastases is registered, alongside the specific codes and dates Ablation: the performance of ablation for (liver) metastases is registered, alongside the specific codes and dates Other local treatment: the performance of other local treatments is registered alongside the specific codes and dates	Estimand-aligned censoring rules and use of a composite outcome. A treatment switch due to toxicity is registered within the same “episode” and can be identified correctly.
Loss to follow-up	A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits, they cannot be contacted by the study staff and their health condition and vital status remains unknown despite attempts to contact them.	***Moving to another country.*** ***De-registration from the data source upon request from the patient.***	Loss to follow-up in the target trial emulation could happen if the patient moved to another country or de-registered from the data source. Both are assumed to be very rare in this populationn

CORE EMULATION TABLE

Comparison of Target Trial and Proposed Target Trial Emulation Analysis Elements

Attribute	Target Trial	Target Trial Emulation	Comment
Analysis Method	Cox Proportional Hazards model to estimate the hazard ratio for time to first disease progression or death. Randomisation ensures balance in measured and unmeasured confounders.	Cox proportional hazards model to estimate marginal HR 1:1 matching (without replacement) by ECOG PS and liver as a metastatic site ensures comparability at treatment initiation. IPTW based on propensity score estimation applied after matching	1:1 matching without replacement and IPTW, used to emulate randomisation in observational data. Need for trimming of PS represents a potential departure from the original target trial population. As a result, the estimated effect no longer applies to the entire population but to the overlap population. *If matching excludes many patients, include ECOG +liver met in prop score model
Missing Data Assumptions and Methods	**Outcome**: assumes non informative censoring conditional on treatment, and survival time; censored participants contribute partial information. **Exposure**: N/A (trial monitoring ensures exposure data completeness) **Covariates**: minimized through trial data collection.	**Outcome**: same assumption, covariates included in condition are different (1:1 matching without replacement or alternatively PS matching, included). **Exposure**: missing administration data for CapOx(-B) reflect true treatment discontinuation. **Covariates**: absence of a diagnosis code will be interpreted as absence of the condition. Missingness for disease related variables will be imputed using multiple imputation by chained equations (MICE) under the MAR assumption.	Mechanisms of missing exposure, covariate and outcome data differ between target trial and target trial emulation. Multiple imputation would not occur for missing covariate data in target trial.
Statistical Model Assumptions	Proportional hazards assumption for Cox model. Censoring is non-informative (given assumption re: missing outcome data)	Same: proportional hazards assumption assessed with Schoenfeld residuals and log(log) plots. IPTW assumptions: no unmeasured confounding, positivity, correct model specification, consistency.	Diagnostics confirm appropriateness of Cox model; violations addressed in supplemental estimands and analyses (RMST). Some assumptions for IPTW are difficult to verify (e.g. unmeasured confounding).
Sensitivity Analyses	None	***IPCW: varies conditions of the CAR assumption.*** ***Tipping Point Analysis: conducted under the missing not at random (MNAR) assumption.*** ***Probabilistic Bias Analysis: Monte Carlo simulation to assess impact of non differential exposure misclassification.***	Potential for outcome misclassification only present in emulation since disease progression is assessed differently.

Results

Primary Estimand



Crude and adjusted hazard ratio (95% CI) for the effect of CapOx–B vs CapOx on disease progression or death (Estimand 1)

	Crude (unmatched and unweighted)		Adjusted (matched and ATT-weighted)	
	HR	95% CI	HR	95% CI
CapOx-B vs CapOx	0.98	(0.81-1.18)	0.86	(0.70-1.06)

95% CI: 95% confidence interval, CapOx: capecitabine-oxaliplatin, CapOx-B: capecitabine-oxaliplatin-bevacizumab, HR: hazard ratio

Crude and adjusted hazard ratios (95% CI) for disease progression or death comparing CapOx–B with CapOx across primary and sensitivity analyses

Cohort	Main analysis (Estimand 1) HR (95% CI)	HR adjusted for outcome misclassification (PBA) (95% simulation interval)
Unmatched + unweighted cohort **CapOx-B vs CapOx**	0.98 (0.81-1.18)	1.02 (1.02-1.02)
Matched + weighted cohort **CapOx-B vs CapOx**	0.86 (0.70-1.06)	0.98 (0.98-0.98)

95% CI: 95% confidence interval, CapOx: capecitabine-oxaliplatin, CapOx-B: capecitabine-oxaliplatin-bevacizumab, HR: hazard ratio, IPCW: inverse probability of censoring weighting; PBA: probabilistic bias analysis

Interpretation

The primary analysis found no evidence of a difference in progression-free survival between CapOx-B and CapOx.

The sensitivity analysis was consistent with this finding.



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