# Bridging the Target Trial Emulation and Estimand Frameworks

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*This study has been registered in the HMA-EMA Catalogue of Real-World Data under the EU PAS numbers: EUPAS1000000539, EUPAS1000000791*

# Background

Questions around comparative safety, efficacy or effectiveness should ideally be studied in a randomised controlled trial (RCT)

Non-interventional studies complement RCTs by providing evidence on safety and effectiveness in settings where RCTs are not possible

Applying the Target Trial Emulation and Estimand Frameworks can help bridge the gap between RCTs and design of non-interventional studies (NIS)

**By applying these frameworks, the hypothetical trial is made explicit.**

In the non-interventional study setting, causal inference can then be approached by emulating this explicit target trial.

# Target Trial Emulation Framework


Hansford HJ, *et al. BMJ Open* 2023;**13**:e074626. doi:10.1136/bmjopen-2023-074626

# Estimand framework useful for NIS with Causal Objectives

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 March 2025
EMA/99865/2025
Committee for Human Medicine Products/Methodology Working Party (CHMP/MWP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes

- *To increase the coherence between definitions of exposures, endpoints and intercurrent events,* ***the estimand framework*** *described in the ICH E9 (R1) Adddendum on Estimands and Sensitivity Analysis in Clinical Trials* ***should be considered in the design of the hypothetical trial****, such as the attributes of the estimand, intercurrent events and strategies to manage them*

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

# ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

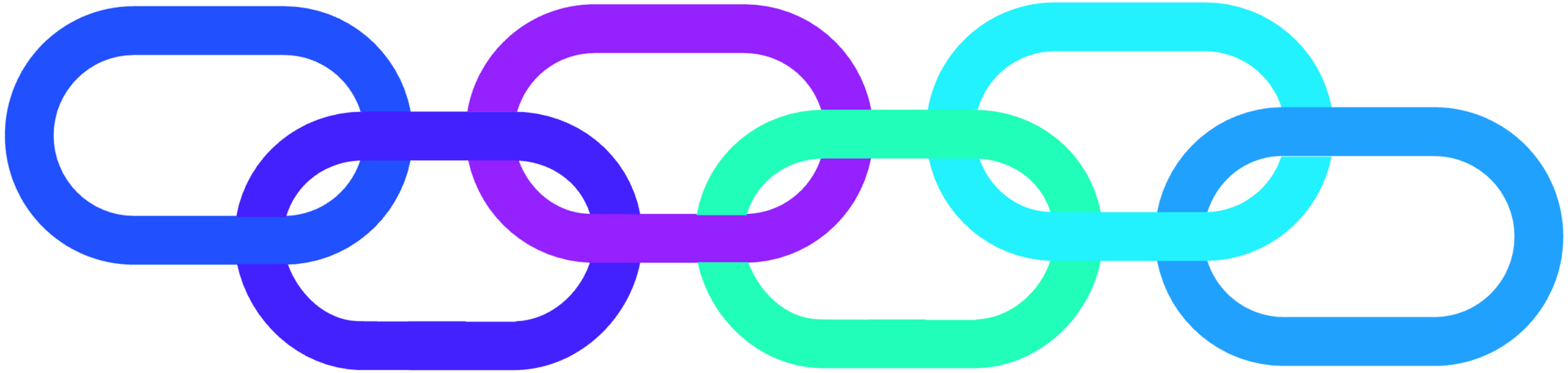
> "An estimand is a **precise description of the treatment effect** *reflecting the clinical question posed by a given clinical trial objective.*"

# Attributes of the Estimand

Population

Endpoint

Intercurrent Events



Treatment Conditions

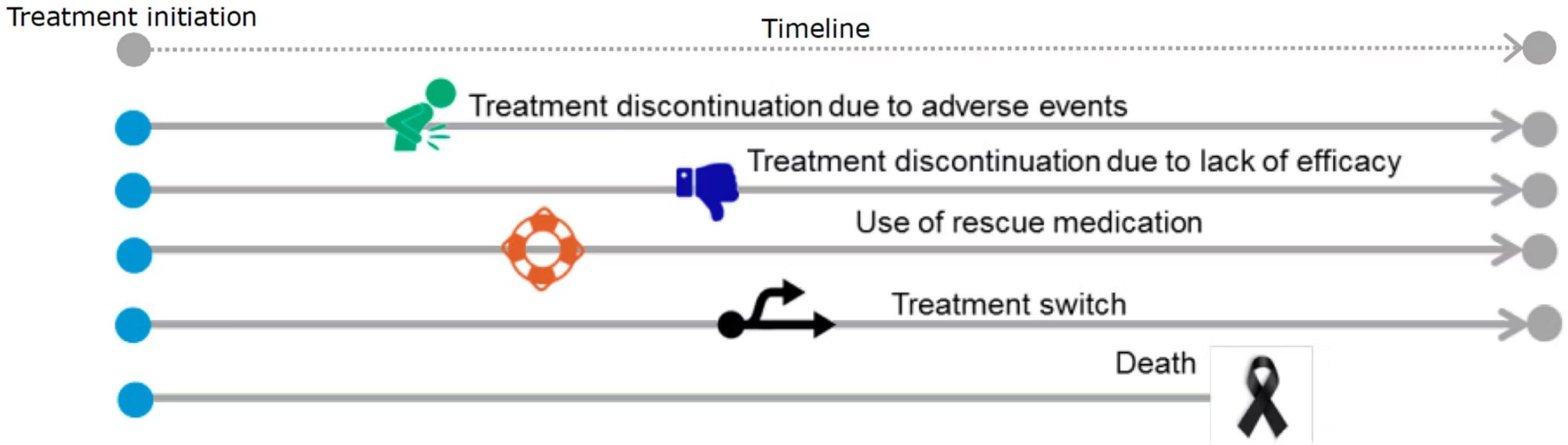
Summary Measure

Strategies to Handle Intercurrent Events

# 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

### 1

#### Treatment policy

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

### 2

#### Hypothetical

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

### 3

#### Composite

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

### 4

#### While-on-treatment/ while alive

Only outcomes observed up until the occurrence of the intercurrent event are considered.

### 5

#### Principal stratum

The effect is estimated within the stratum of patients in whom the intercurrent event would (or would not) occur *under each treatment* but could also be *under the target treatment.*

# TARGET-EU Objectives

To enable better understanding of opportunities, limitations and challenges when conducting TTE for regulatory decision making, using European data sources.

Develop an overview of advantages and challenges of combining target trial emulation with the estimand framework for comparative efficacy and safety studies.

# TARGET-EU Approach

Selection of RCT or NIS as inspiration for case studies

Used as inspiration, not to replicated

Development of protocol for hypothetical target trial

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 Common Data Model and a common analytic approach**

# Criteria for Selection of Use Cases

At least 3 PAEs and at least 2 PASS

Most use cases should preferably be based on RCTs but with NIS design are also possible.

A variety of disease areas, including at least 2 use cases in the area of oncology.

A variety of sample sizes, with at least one use case targeting an orphan medicinal product.

A variety of real world data sources, covering at least 6 European countries across all 10 use cases.

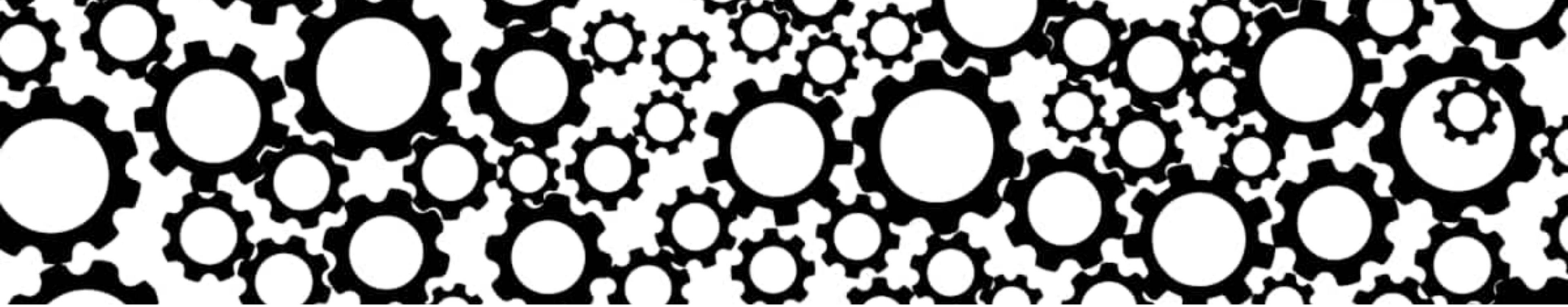
Other aspects to consider: Pregnancy, Elderly

# Ten Selected Case Studies

| Exposure | Comparator | Indication | Population | Outcome |
|---|---|---|---|---|
| SARSCoV-2 mRNA vaccine | No vaccination | NA | Adult | COVID-19 infection |
| Nivolumab + ipilimumab | Pembrolizumab | Non-small-cell lung cancer | Adult | Overall survival |
| Dapagliflozin | DPP4-i | Type II Diabetes Mellitus | With or at high risk of atherosclerotic cardiovascular disease | Major Adverse Cardiovascular Event |
| Rivaroxaban | Apixaban | Atrial fibrillation | Elderly | Major GI Bleed |
| Vilanterol- fluticasone furoate | Other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate) | Asthma | Adolescents | Pneumonia |
| Sacubitril/valsartan | Angiotensine converting enzyme inhibitors | Heart failure | Adult | Angioedema |

# Ten Selected Case Studies (cont.)

| Exposure | Comparator | Indication | Population | Outcome |
|---|---|---|---|---|
| Valproate (paternal exposure) | Levetiracetam (paternal exposure) | Epilepsy | Adult males | Adverse pregnancy outcomes, death of offspring after birth, and diagnosis of autism or ADHD in offspring |
| Nirsevimab | No treatment | Prevention of lower respiratory tract disease caused by RSV | Infants | Hospitalization for RSV-associated with Lower Respiratory Tract Infection |
| Tolvaptan | Unexposed | Autosomal Dominant Polycystic Kidney Disease | Adult | Hepatotoxicity |
| CapOx chemotherapy in combination with bevacizumab | CapOx chemotherapy alone | Metastatic colon cancer | Adult | Progression free survival |



# Core Estimand, Design, and Estimation Tables

## Target Trial vs. Emulation

# Core Estimand Table

| Attribute | Target Trial | Target Trial Emulation | Comments |
|---|---|---|---|
| **Population** | | | |
| **Treatment Conditions** | | | |
| **Endpoint** | | | |
| **Summary Measure** | | | |
| **Intercurrent Events and Strategies to Handle them** | | | |

# Core Design Table

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Inclusion criteria** | | | |
| **Exclusion criteria** | | | |
| **Setting** | | | |
| **Method of assignment to trial intervention** | | | |
| **Study treatment conditions** | | | |
| **Time (when follow-up begins and ends)** | | | |
| **Outcome** | | | |
| **Intercurrent Events and strategies to handle them** | | | |
| **Loss to follow-up** | | | |

# Core Estimation Table

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Analysis Method** | | | |
| **Missing Data Assumptions and Methods** | | | |
| **Statistical Model Assumptions** | | | |
| **Sensitivity Analyses** | | | |

# Case Study inspired by DECLARE-TIMI 58 Trial

Randomized, double-blind, multinational, placebo-controlled, phase 3 trial of dapagliflozin

Patients with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease

Non-inferiority study design

Included two co-primary outcomes:

- Time to first occurrence of Major Adverse Cardiovascular Events (MACE), a composite of cardiovascular death, myocardial infarction or stroke
- Time to first occurrence of cardiovascular death or hospitalization for heart failure (also a composite)

# Estimand Table (Estimand 1)

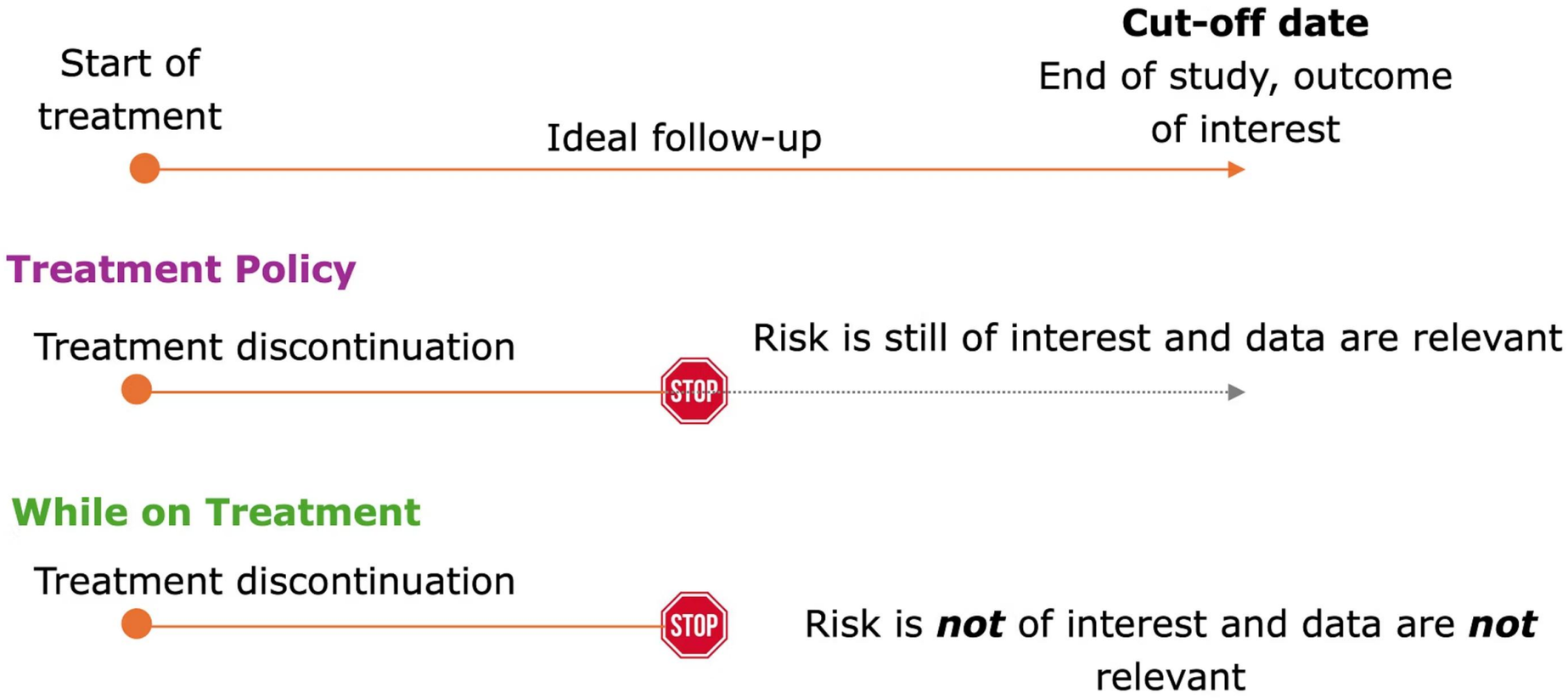
| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Population** | Patients with type 2 diabetes who have or are at risk for ASCVD | Same, but population identified using RWD (primary care, hospital records, prescription records). | Potential for mismeasurement of tobacco use within the past year (under-reporting) |
| **Treatment Conditions** | Dapagliflozin vs. DPP-4i inhibitor | Initiation of Dapagliflozin vs. DPP-4i | Intention to initiate the study treatments (i.e., treatment allocation) will be emulated using the first observed prescription |
| **Endpoint** | Time to first MACE (non-fatal MI, stroke, cardiovascular or non-CV death) | Same: time to first MACE, defined using diagnostic codes in primary and secondary care and death registry data | Emulated using validated code lists |
| **Summary Measure** | Hazard Ratio | Hazard Ratio | |

# Estimand Table Cont.

| Attribute | Target Trial | Target Trial Emulation | Comment |
| --- | --- | --- | --- |
| **Intercurrent Events and Strategies to Handle Them** | ***Treatment discontinuation***: treatment policy<br><br>***Treatment switching***: treatment policy<br><br>***Addition of another antihyperglycemic agent:*** treatment policy<br><br>***All-cause death:*** composite strategy (included in endpoint) | **Same**: intercurrent events handled according to pre-specified strategies of the hypothetical target trial | |

# Estimand 2

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| Intercurrent Events and Strategies to Handle Them | ***Treatment discontinuation:*** while on treatment<br>***Treatment switching:*** while on treatment<br>***Addition of another antihyperglycemic agent***: while on treatment<br>***All-cause death:*** composite strategy (included in endpoint) | **Same:** intercurrent events handled according to pre-specified strategies of the hypothetical target trial | For while on treatment approach, mismeasurement of treatment discontinuation, switching or additional of another anti-hyperglycaemic events is an issue for the analysis since we are not interested in data after the occurrence of the IE. |




# Implications of strategies to handle intercurrent events

# Research questions targeted by estimands

### *Research question targeted by Estimand 1 (Primary Estimand)*

What is the HR of MACE for Dapa vs DPP-4i in patients with type 2 diabetes with or at risk for ASCVD regardless of treatment discontinuation, switching or new add-on antihyperglycemic therapy?

### *Research question targeted by Estimand 2 (Supplemental Estimand)*

What is the HR of MACE for Dapa vs DPP-4i in patients with type 2 diabetes with or at risk for ASCVD while on treatment (i.e., before treatment discontinuation, switching or new add-on antihyperglycemic therapy)?

# Design and Estimation Highlights

## Estimand 1

# Treatment Assignment

| Target Trial | Target Trial Emulation | Comment |
| --- | --- | --- |
| Simple 1:1 randomisation | Assignment reflects clinical need. Inverse probability of treatment weighting (IPTW) will be used to adjust for baseline confounders. | Randomisation cannot be directly emulated. IPTW will be used in the statistical analysis to balance confounders in absence of randomisation. |

# Loss to follow-up

| Target Trial | Target Trial Emulation | Comment |
| --- | --- | --- |
| Patients who fail to return for the required study visits and their health condition and vital status remains unknown despite multiple attempts to contact them. | Patients with known deregistration date, practice withdrawal or database end. This is directly measured in RWD source. | Loss to follow-up will be defined using real-world proxies, recognizing that in some cases patients may appear to remain under follow-up despite having effectively left (e.g., if they do not formally de-register from their GP). This risk is expected to be low, where unique patient identifiers ensure automatic de-registration upon re-registration at a new practice. |

# Analysis Method

| Target Trial | Target Trial Emulation | Comment |
| --- | --- | --- |
| Cox proportional hazards model to estimate HR for time to first MACE. Randomization ensures balance in measured and unmeasured confounders | Cox proportional hazards model weighted by IPTW | IPTW used to emulate randomization in observational data |
| | The analysis is conducted in in the trimmed population | Trimming of observations based on PS distribution represents a departure from the original target trial. By removing patients in regions of non-overlap, the analysis is restricted to a population where treatment assignment is more comparable across groups. As a result, the estimated effect no longer applies to the entire eligible population but to this more comparable subset. |

# Model Assumptions

| Target Trial | Target Trial Emulation | Comment |
| --- | --- | --- |
| Proportional hazards assumption for Cox model. Censoring is non-informative (conditional on treatment, and survival time) | Same<br><br>**IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency | Some assumptions for IPTW difficult to verify (e.g., unmeasured confounding). Can argue consistency may be violated as a result of allowing variables doses and medications as part of treatment arm. Correct model specification checked by evaluating SMD in baseline characteristics after weighting. |

# Sensitivity Analyses

| Target Trial | Target Trial Emulation | Comment |
| --- | --- | --- |
| None | **IPCW:** Varies conditions of the censoring at random assumption<br><br>**Tipping Point Analysis:** Conducted under the missing not at random assumption<br><br>**Probabilistic Bias Analysis:** Monte Carlo simulation to assess impact of non-differential exposure misclassification | Potential for exposure mismeasurement only present in emulation since exposure based on prescription records and assume adherence to prescribed treatment. |


# Many Thanks to our EU PE & PV Partners and EMA!

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SoSeTe/Pedianet
DUTh
UEF
RSU
NIPH

UCPH
UGENT
Teamit
IDIAPJGol
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# Design Summary Estimand 1

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Eligibility** | **Inclusion**:<br>- Age ≥ 40<br>- Diagnosed with type 2 diabetes<br>- Established ASCVD or high ASCVD risk (age ≥55 (men) or ≥60 (women) plus at least one cardiovascular risk factor(e.g., hypertension, dyslipidemia, tobacco use)<br>**Exclusion**:<br>- Prior use of SGLT2i or DPP-4i within the last year prior to randomisation<br>- Acute cardiovascular event in past 12 months<br>- Type 1 diabetes | **Inclusion:**<br>Same:<br>- Diagnosis codes for type 2 diabetes<br>- Recorded ASCVD or ≥1 CV risk factors in baseline data<br>- Treatment initiation with either dapa or Dpp-4i using prescription records<br>All measured in the one year prior to the first prescription for either dapagliflozin or DPP4-i<br>**Exclusion:**<br>- Same:<br>-Prior prescription of SGLT2i or DPP-4i based on prescription records<br>- Type 1 diabetes identified from diagnostic codes<br>- Acute cardiovascular events measured using diagnostic codes<br>– Medications are measured in the one year prior to the first prescription for either dapagliflozin or DPP4-I; Chronic conditions are measured at any point prior to this index date. | Emulation restricts to new users in routine care<br>Eligibility applied using structured EHR data; may require proxy measures for ASCVD or risk factors<br>Exposure and comorbidity definitions will be operationalized using prescription and diagnostic codes. We will apply lookback windows (e.g., one year to define incident use), while recognizing that accuracy may also depend on factors such as the choice of phenotyping algorithm, the placement of the lookback period, and the availability and reliability of underlying data. |
| **Setting** | Multicentre | Recruitment of patients for a multicentre study will be emulated by selecting patients who are seen in several primary care clinics | Reflects the setting from which patients are most likely to be recruited from. Will be missing hospital setting for recruitment, but T2DM patients are most likely to be managed in primary care. Although measurement of characteristics (comorbidities) can be conducted using both inpatient and outpatient information, the study setting still reflects those seen in primary care since the represents the base study population in RWD sources. |

# Design Summary Estimand 1 (II)

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Treatment conditions** | Dapagliflozin and DPP-4 inhibitors, each potentially added to usual care, reflecting real-world use without restrictions on dose or treatment duration. | Initiation of dapagliflozin or DPP-4i measured using first prescription of each medication. Added to usual care, meaning in addition to any other antihyperglycemic therapy the patient may already be prescribed. | Dose or duration flexibility mirrors routine care, as does being added to background therapy, although this introduces some uncertainty since the intervention may take several forms. However, these variations can be considered largely exchangeable within the treatment strategies.<br>Potential mismeasurement of treatment initiation may also occur due to non-adherence. |
| **Treatment Assignment** | Simple 1:1 randomisation | Assignment reflects clinical need. Inverse probability of treatment weighting (IPTW) will be used to adjust for baseline confounders. | Randomisation cannot be directly emulated. IPTW will be used in the statistical analysis to balance confounders in absence of randomisation. |
| **Follow-up** | Begins at randomisation; ends at first occurrence of outcome, study withdrawal, loss to follow-up, or at 5 years after randomisation | Begins at treatment initiation which is first prescription of dapagliflozin or DPP-4i; ends at outcome, loss to follow-up or at 5 years after treatment initiation. | Aligns start of follow-up with treatment initiation to mimic start of trial; loss to follow-up can be identified in data sources as de-registration from general practices, migration |
| **Outcome** | Time to first MACE: composite of non-fatal MI, stroke, CV or non-CV death | Same composite outcome identified using diagnostic and mortality records in linked databases | Code lists and outcome definitions validated or informed by prior CVOT emulations |

# Design Summary Estimand 1 (III)

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Intercurrent Events and Strategies to Handle Them** | ***Treatment discontinuation***: treatment policy<br>***Treatment switching***: treatment policy<br>***Addition of another antihyperglycemic agent:*** treatment policy<br>***All-cause death:*** composite strategy (included in endpoint) | Same but measured based on prescribing data and mortality data<br>**Operational definitions:**<br>· Treatment discontinuation is identified using prescription refill data, where a gap of more than 90 days between refills is considered a discontinuation.<br>· Treatment switching is similarly measured using prescription records, with a gap of more than 90 days and receipt of a new antihyperglycemic indicating a switch to a new therapy.<br>· All cause death determined using death registry data | Accurately identifying treatment discontinuation and switching will not be a limitation since they are ignored under the treatment policy approach |
| **Loss to follow-up** | Patients who fail to return for the required study visits and their health condition and vital status remains unknown despite multiple attempts to contact them. | Patients with known deregistration date, practice withdrawal or database end. This is directly measured in RWD source. | Loss to follow-up will be defined using real-world proxies, recognizing that in some cases patients may appear to remain under follow-up despite having effectively left (e.g., if they do not formally de-register from their GP). This risk is expected to be low, where unique patient identifiers ensure automatic de-registration upon re-registration at a new practice. |

# Estimation Summary Estimand 1 (I)

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Analysis Method** | Cox proportional hazards model to estimate HR for time to first MACE. Randomization ensures balance in measured and unmeasured confounders | Cox proportional hazards model weighted by stabilized IPTW, estimated separately in each data source (CPRD and BIFAP); pooled using random-effects meta-analysis.<br>The analysis is conducted in in the trimmed population | IPTW used to emulate randomization in observational data<br>Trimming of observations based on PS distribution represents a departure from the original target trial. By removing patients in regions of non-overlap, the analysis is restricted to a population where treatment assignment is more comparable across groups. As a result, the estimated effect no longer applies to the entire eligible population but to this more comparable subset. |
| **Missing Data Assumptions and Methods** | **Outcome**: Assumes non-informative censoring conditional on treatment, and survival time; censored participants contribute partial information.<br>**Exposure**: N/A (trial monitoring ensures exposure data completeness)<br>**Covariates**: Minimized through trial data collection | **Outcome**: Same, covariates included in condition the same as those included in IPTW model)<br>**Exposure:** For missing exposure data, assume absence of refill or prescription records for dapagliflozin or DPP-4 inhibitors indicates true treatment discontinuation after 90 days.<br>**Covariates:** absence of a diagnosis code will be interpreted as absence of the condition, while missing lifestyle and laboratory variables will be imputed using multiple imputation by chained equations (MICE) under the missing at random assumption. | Mechanisms of missing exposure, covariate and outcome data differs between target trial and emulation (e.g., rather than leaving study, patients could be part of GP practice that no longer contributes data). Missing exposure data not possible in target trial but could be as a result of missing or incomplete prescription records in emulation. Multiple imputation would not occur for missing covariate data in target trial. |

# Estimation Summary Estimand 1 (II)

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **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.<br><br>**IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency | Some assumptions for IPTW difficult to verify (e.g., unmeasured confounding). Can argue consistency may be violated as a result of allowing variables doses and medications as part of treatment arm. Correct model specification checked by evaluating SMD in baseline characteristics after weighting. |
| **Sensitivity Analyses** | None | **IPCW:** Varies conditions of the censoring at random assumption<br><br>**Tipping Point Analysis:** Conducted under the missing not at random assumption<br><br>**Probabilistic Bias Analysis:** Monte Carlo simulation to assess impact of non-differential exposure misclassification | Potential for exposure mismeasurement only present in emulation since exposure based on prescription records and assume adherence to prescribed treatment. |