EMA/2020/46/TDA, Lot 3 - ROC36 Use of causal inference methods commonly used in non-interventional studies to estimate treatment effects in clinical trials

First published: 21/08/2025

Last updated: 30/07/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000720

Study ID

1000000720

DARWIN EU® study

No

Study countries

Austria

Germany

Sweden

Study description

This project evaluates the use of causal inference methods for estimating treatment effects in randomized controlled trials (RCTs) under the ICH E9(R1) estimand framework.

In a structured review of the scientific and regulatory literature, we will identify causal inference methods used to derive estimators for different estimand strategies to handle intercurrent events such as treatment policy, hypothetical, principal stratum, composite, and while-on-treatment strategies. Estimation methods proposed in this context include inverse probability weighting, g-estimation, g-computation, and targeted minimum loss based estimation. Clinically relevant trial scenarios will be identified where intercurrent events such as treatment switching or use of rescue medication affect outcome interpretation.

The literature review and scenario identification will inform a comprehensive simulation study assessing key statistical properties of the selected estimators including bias, variance, coverage probabilities, type I error rate, and power. A focus of the assessment will be the robustness of methods to model misspecification. Simulations will be conducted using a modular R based framework on high performance computing servers. The results of this project will support the assessment of strategies for handling intercurrent events.

Study status

Ongoing

Research institutions and networks

Institutions

Medical University of Vienna

Austria

First published: 01/02/2024

Last updated: 26/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

Uppsala University

First published: 01/02/2024

Last updated: 01/02/2024

Institution

University Medical Centre Göttingen (UMG)

Germany

First published: 26/11/2025

Last updated: 26/11/2025

Institution | Hospital/Clinic/Other health care facility

Österreichische Agentur für Gesundheit und Ernährungssicherheit

Contact details

Study institution contact

Robin Ristl robin.ristl@meduniwien.ac.at

Study contact

robin.ristl@meduniwien.ac.at

Primary lead investigator

Robin Ristl 0000-0002-4163-9236

Primary lead investigator

ORCID number:

0000-0002-4163-9236

Study timelines

Date when funding contract was signed

Actual: 30/07/2025

Study start date

Actual: 30/07/2025

Date of final study report

Planned: 30/07/2026

Sources of funding

- EMA

Study protocol

ROC36_Simulation_Study_Protocol_v1-2.pdf (383.62 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Other

Study topic, other:

Causal inference methods in randomized controlled trials

Study type:

Not applicable

Scope of the study:

Method development or testing

Scoping review (including literature review)

Study design:

Review of published literature and regulatory documents, simulation study

Main study objective:

(1) To screen the scientific literature and regulatory documents to identify
(a) randomized clinical trials in which causal inference methods have been used to test and estimate treatment effects, and
(b) methodological approaches based on causal inference for testing and estimating treatment effects in randomized clinical trials.
(2) (a) To identify relevant clinical trial scenarios in which the causal pathway from randomized treatment to outcome may be affected by intercurrent events;
(b) To identify causal inference methods suitable for testing and estimating treatment effects within the estimand framework that appropriately account for these intercurrent events.
(3) To assess the statistical properties (including bias, coverage probabilities, type 1 error rate, and power) of the selected methods in a comprehensive simulation study based on clinical trial data generated under varying scenarios.

Documents

Study report

ROC36_Simulation_Study_Report_v1-1.pdf (1.5 MB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Published literature

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No