Statistical methods for time-to-event endpoints with non-proportional hazards in clinical trials pivotal for benefit risk decision making

First published: 29/03/2022

Last updated: 26/11/2025

Study Finalised

Administrative details

EU PAS number

EUPAS46420

Study ID

49976

DARWIN EU® study

No

Study countries

Austria

Germany

Sweden

Study description

While well-established methods for time-to-event data are available when the proportional hazards assumption holds, there is no consensus on the best approach under non-proportional hazards. However, a wide range of parametric and non-parametric methods for testing and estimation in this scenario have been proposed. The main objective of this work is to provide recommendations on the statistical analysis and reporting of clinical trials where non proportional hazards are expected, e.g. when treatments have a delayed onset of the treatment effect, if efficacy of the treatment wanes over time, or if the treatment effect is not homogeneous in the population. To this end, we will first perform a literature review on the available methods, review the availability of statistical software that implement these methods, and review scientific advice and marketing authorization procedures to identify relevant scenarios where non-proportional hazards occur. Based on this review, a set of methods will be selected for further assessment. Furthermore, their theoretical properties will be reviewed and operating characteristics will be investigated in an extensive simulation study under a wide range of scenarios considering different trial designs, recruitment and censoring patterns as well as different shapes of the hazard functions.

Study status

Finalised

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

University Medical Centre Göttingen (UMG)

Germany

First published: 26/11/2025

Last updated: 26/11/2025

Institution | Hospital/Clinic/Other health care facility

Uppsala Universitet Von Kraemers Allé 4, 751 05 Uppsala, Sweden, Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH Spargelfeldstraße 191, 1220 Wien, Austria

Contact details

Study institution contact

Martin Posch martin.posch@meduniwien.ac.at

Study contact

martin.posch@meduniwien.ac.at

Primary lead investigator

Martin Posch

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 10/12/2021

Actual: 10/12/2021

Study start date

Planned: 24/03/2022

Actual: 24/03/2022

Date of final study report

Planned: 31/01/2023

Actual: 26/06/2023

Sources of funding

- EMA

Study protocol

2022-10-14 CONFIRMS Simulation Study Protocol rev2.pdf (267.37 KB)

Regulatory

Was the study required by a regulatory body?

Yes

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:

Disease/Epidemiology study

Study type:

Not applicable

If ‘other’, further details on the scope of the study

Assessment of statistical methods

Main study objective:

(1) To identify available statistical methods for the analysis of time-to-event endpoints in the presence on non-proportional hazards. (2) to assess the statistical properties of these methods (3) to assess the regulatory acceptability of these methods for clinical trials that are pivotal for drug development and

benefit-risk assessment and derive recommendations

Population studied

Short description of the study population

N/A

Age groups

- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)
- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

0

Study design details

Data analysis plan

Not applicable

Documents

Study results

Summary.pdf (37.51 KB)

Summary V1.1.pdf (43.63 KB)

Study, other information

Literature Review Rev. 2.pdf (1.49 MB)

Summary NPH.pdf (43.63 KB)

Study publications

Bardo M, Huber C, Benda N, Brugger J, Fellinger T, Galaune V, Heinz J, Heinzl H...

F Klinglmüller, T Fellinger, F König, T Friede, AC Hooker, H Heinzl, M Mittlböc...

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)

Other

Data sources (types), other

Literature Review: MEDLINE, EMBASE. Review of EMA EPARS: paediatricdata.eu. Review of EMA Scientific Advice letters: AGES internal database. Simulation Study

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