

# 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:** 02/07/2024

Study

Finalised

## Administrative details

### EU PAS number

EUPAS46420

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### Study ID

49976

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### DARWIN EU® study

No

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### Study countries

☐ Austria

☐ Germany

☐ Sweden

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## 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.

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## Study status

Finalised

## Research institutions and networks

### Institutions

Medical University of Vienna

☐ Austria

**First published:** 01/02/2024

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**Institution**

**Educational Institution**

**Hospital/Clinic/Other health care facility**

Universitätsmedizin Göttingen Robert-Koch-Str.

40, 37075 Göttingen, Germany, 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

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**Study contact**

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### Primary lead investigator

Martin Posch

**Primary lead investigator**

## Study timelines

**Date when funding contract was signed**

Planned: 10/12/2021

Actual: 10/12/2021

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**Study start date**

Planned: 24/03/2022

Actual: 24/03/2022

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**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

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

Not applicable

## Methodological aspects

### Study type

### Study type list

**Study topic:**

Other

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**Study topic, other:**

Disease/Epidemiology study

**Study type:**

Not applicable

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**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 of 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

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**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)

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## **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)

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### **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, Fellingner T, Galaune V, Heinz J, Heinzl H...](#)

[F Klinglmüller, T Fellingner, F König, T Friede, AC Hooker, H Heinzl, M Mittlböc...](#)

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## Data management

## Data sources

## Data sources (types)

Other

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### 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

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### Check completeness

Unknown

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### Check stability

Unknown

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### Check logical consistency

Unknown

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## Data characterisation

**Data characterisation conducted**

No