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

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Study | Finalised

Administrative details

PURI
https://redirect.ema.europa.eu/resource/49976

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 institution and networks

Institutions

Medical University of Vienna
Austria
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26/02/2024

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

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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

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