Real-world evidence in applications to the Danish Medicines Council

1. Introduction

This document is a guideline for the inclusion of real-world evidence (RWE) in applications to the Danish Medicines Council. The guideline is not exhaustive, and the applicant is also referred to the Danish Medicines Council's methods guide (1) and NICE's RWE framework (2).

2. Background

Real-world evidence (RWE) is evidence generated on the basis of real-world data (RWD). RWD may contribute with knowledge, which is not generated or cannot be generated (e.g., due to ethical reasons) in a controlled trial. RWD may be included in applications to the Danish Medicines Council to support the assessment of the effect of a pharmaceutical, for descriptive purposes, e.g., patient characteristics and utilization of pharmaceuticals, and for describing the natural history of a given disease. RWE may furthermore be used in the health economic analysis, e.g., for external validation of extrapolations.

2.1 Descriptive analyses

If RWE is used for descriptive purposes such as characterizing patient populations or utilization of pharmaceuticals, the following points should as minimum be described (also consult sections 3 and 4):

- Data and data sources (see section 4.1)
- Target population (see section 4.2)
- Adjustments, matching and weighting, if the target population deviates from the population in the data sources
- Methods
- Study design and data analysis

2.2 Assessment of the effect of pharmaceuticals

Randomized controlled trials (RCT) are the preferred source of evidence for the assessment of pharmaceutical effects. In RCTs the allocation to receive the intervention and the comparator is randomized, which reduces the risk of systematic bias at baseline. Prior to the initiation of a RCT a protocol should be published. The purpose of the protocol is to define and ensure similar treatment and follow up across participating study sites.

For comparative effect studies based on RWD, i.e., data collected or generated outside a RCT setting, the allocation to the intervention and comparator arm is not random and thus depends potentially on observed and unobserved patient characteristics. If specific patient characteristics influence both the use of the pharmaceutical and the resulting treatment outcome, the comparative effect estimate may be biased if left unadjusted. In addition, the follow-up,

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outcomes etc. are not necessarily subject to the same definitions as in RCTs, which implies that the outcome may be measured differently and thus subject to bias.

RWE studies to be included in the Danish Medicines Council's assessment of the effect of a pharmaceutical, must be included similarly to clinical studies (e.g., RCTs), i.e., the same table templates should be used. In addition, a protocol must be included as a supplement and reporting should comply with sections 3 and 4.

3. Protocol

It is recommended to use templates such as HARPER (3) or STaRT-RWE (4), and include the completed template as a supplement to the application to the Danish Medicines Council.

The protocol must include detailed information about:

1. Background and rationale for the study.
2. Hypotheses and purposes for the study, including PICOT (population, intervention/exposure, comparator, outcome and definition of follow-up (time horizon)).
3. Data sources and argumentation for the choice of these.
4. Methods, including study design, definition of time 0, in- and exclusion criteria, definitions of variables (outcomes, exposures/intervention, confounders).
5. Data analyses, including primary and secondary analyses and potential subgroup and sensitivity analyses. In addition, specification of models, weights, matching and strategies for addressing missing data.

4. Reporting

RWE must be reported transparently and with sufficient detail such that the results can be reproduced.

Sufficient reporting in an application includes description of data relevance and quality, data cleaning, flow diagrams, patient characteristics, information about missing data, information about follow-up and all planned analyses and post-hoc analyses. Sufficient reportion must also include evaluation of risk of bias and generalizability to the relevant Danish population.

Reporting must include the listed items in section 3.

4.1 Data

The choice of data source must be justified, which may be done by "The Structured Process to Identify Fit-For-Purpose Data" (SPIFD,5) framework or with NICE's DataSAT-template (6). It must be clear, which sources of RWD are used in the analyses, how they are generated and for what purpose.

The quality of the data must be described. This includes a description of the proportion of missing data, whether the data source includes the relevant outcomes, interventions, and confounders and how accurate and valid they are. The definitions of variables and outcomes must be given, such that the study is reproducible with access to the same data source.

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4.2 Effect studies

It is recommended to use target trial emulation (7,8), whenever the purpose of a RWE-study is a comparison of effect between 2 or more treatments. Target trial emulation (target trial approach) is a method to emulate a RCT in a RWD-setting, i.e., emulating the ideal study if not limited by time, economy and ethics.

Reporting of RWE effect studies should include description of the following elements of a target trial:

1. Inclusion and exclusion criteria (eligibility)
2. Treatment strategies
3. Allocation
4. Follow up
5. Outcome
6. Causal contrast (e.g., intention-to-treat estimand)
7. Analysis plan

The emulated study is designed and executed such that it matches the above-mentioned elements. It is an advantage to list the inclusion and exclusion criteria in a table for easy comparison. Deviations from the target trial must be clearly marked and the impact on the results evaluated.

4.3 Design diagram

It is an advantage to describe RWE studies with a design diagram (9). For emulating a target trial, time 0 is an anchor in the study diagram and defines the timepoint where the follow up begin. Furthermore, allocation to treatment happens at time 0 for eligible individuals. Time 0 must be clearly defined in the description of the study, since it is pivotal for the evaluation of the validity of the study, including the risk for time related biases, e.g., immortal time bias (10,11).

4.4 Analyses

All analyses must be described in detail, including:

1. Hypothesis, including outcomes and treatments
2. Population
3. Statistical model and/or estimator
4. Methods for reducing bias, e.g., weighting, matching or adjustment.
5. Planned analyses, which cannot be performed and the reason(s)
6. Post-hoc analyses and argumentation for their relevance.

4.5 Results

The reporting of the study must include flow diagrams, patient characteristics, description of follow up (number of events, duration of follow-up, event rates etc.). Comparative studies must also include information about any weights, patient characteristics per treatment before and after any adjustment (matching, weighting or similar).

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5. References

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6. Version log

Version log		
Version	**Date**	**Change**
1.0	6 June 2023	Approved and published.

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