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Best-practices and guidance on the communication of RWE

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Why MW for RWE is Special

Writing for RWE results needs to be differnt from those of randomized controlled trials (RCTs) because…

- The methodology of the RWE research is different
- Even within the RWE world, verfy different methodologies are used
- The goals of the research are different
- The target audience may be different
- Benefits of RWE methodology need to be explained to „RCT readers and reviewers“

Scientific Value of RWE

In the public domain, the reputation of NIS has been pretty low:

- “Bad conduct”

- “Buying prescriptions”

- “No objective efficacy, safety assessments”

- “Laboratory values are missing”

- “Low data quality”

- “Results over-interpreted”

Scientific Value of RWE

NIS and database studies have big problems with the **confounding bias** (no randomization) and **information bias** (no blinding possible) and this is the reason for the weak link between the treatment and the outcome.

- Therefore, if you want to establish/compare efficacy or safety of a treatment, NIS are clearly **less valid** than RCTs

Scientific Value of RWE

RCTs have big problems with the **selection bias** (inclusion and exclusion criteria) and to some extent with the **confounding bias** (effect through study procedures). Therefore, there is a weak link between the outcome in the study population and that in clinical practice.

• If you want to describe how patients receiving a treatment fare in clinical practice, NIS and in particular database studies are clearly **more valid** than RCTs.

RCTs have high internal validity but low external validity.

NIS/Database studies have high external validity but low internal validity

Scientific Value of RWE – Database Studies

Compared to stand alone NIS studies, database studies have slightly different biases:

- The selection bias is even lower in most databases as sometimes the data collection is mandatory in certain healthcare systems.
- The confounding bias (no randomization) might be less than in a company sponsored NIS as the purpose/company is not known to physicians/patients at the time of data collection.
- The data quality and specificity might be even lower than in prospective NIS as the database is not specific to the questions.

Scientific Value of RWE

Therefore, it is often difficult to present results from NIS in high- to medium- ranked scientific journals.

This happens although results from a carefully conducted and well analyzed and presented NIS may be more interesting and valid as those from some small, open CTs.

And that is where the specific knowledge of Medical Writing for NIS is crucial.

Document Types for RWE/NIS

NIS are **not covered by** Good Clinical Practice (**GCP**) or the International Conference on Harmonization (**ICH**).

Therefore, a lot of documents mandatory for Clinical Trials are **not mandatory** for NIS e.g.:

Full protocol according to ICH,

Statistical Analysis Plan (SAP),

Study report according to ICH-E3.

Document Types for RWE/NIS

Ethics committee approval is not required in all countries. In particular not needed for databases that are used unmodified.

Patient consent (either to participation and/or to data privacy) not required in all countries. Has usually (but not always) already been given for databases.

Therefore, informed consent forms and ethics committee submissions are not **necessarily** required.

Document Types for RWE/NIS

However, to perform a high quality NIS, these or similar documents **should** be in place:

An NIS protocol ideally not based on the CTR protocol, but tailored to the NIS/Database Study requirements.

A **statistical analysis plan** can be handled more flexible but should still be in place.

Patient **informed consent** (to release data) and ethics committee involvement are highly advisable (except for certain database studies).

Document Types for RWE/NIS

A study report is required by the EMEA if the NIS is part of a risk management plan as a post approval safety study (PASS).

All NIS required by regulators as post approval commitments including comparative effectiveness studies need to be reported to the FDA.

Study results can be posted on clinicaltrials.gov but this is not mandatory and the HTML forms provided by the NIH do not fit well for non-interventional studies.

Writing Style for RWE/NIS: Study Protocol

Study Protocol:

Does not need to follow ICH structure and should not use clinical trial language:

- Observation or documentation instead of “Visit”,
- Suggested observation intervals instead of fixed required times,
- Objectives need not necessarily be divided into primary and secondary.
- Objectives need to be formulated in a way that can be achieved in OS.
- Sample size calculation can be less formal but should provide a rationale for the number of patients observed.

Writing Style for RWE/NIS: Study Protocol

- Do not use “efficacy” but effectiveness or patient outcomes in clinical practice

- Do not say “to compare efficacy of WONDERDRUG with STANDARD drug” but “to compare the outcome in patients treated with WONDERDRUG with those treated with STANDARDDRUG”.

- Preferably use objectives not directly related to the drug: e.g. “Effect of disease insight on the effectiveness of treatment with WONDERDRUG in patients with Hypercholesterolemia”

Writing Style for RWE/NIS: Study Protocol

- Do not put too much detail on the description of statistical analyses (unless required for sample size) at study start as you never know what exactly comes out of an NIS.

- This is particularly important in comparative studies.

- When talking about anything similar to an intervention (e.g. definition of cohort sizes, requiring blood draws or non-routine clinical assessments) be sure to formulate clearly that this is non-interventional.

Writing Style for RWE/NIS: Study Protocol

Study Protocol – Database Studies:

- Clearly describe database(s) used.
- In introduction give brief rationale why databases were selected.
- Describe methodology of selection of “study participants” from the database (e.g. timeframe, all vs. subset, “inclusion and exclusion criteria”).
- Will the database be used retrospectively, prospectively or mixed
- Report who will be responsible for the different steps of analyses
  - selection
  - extraction
  - analysis
  - reporting

Writing style for RWE/NIS: Study Report/ Manuscripts

Writing in the Study Report:

Interpret all p-values and statistical measures not as differences between drugs but between patient cohorts.

Do not speak of Drug X being effective and safe.

State effectiveness and tolerability in patients treated with X in routine clinical care.

Be careful with conclusions regarding the Drug.

You can be specific with conclusions regarding patient outcomes!

Writing Style for RWE/NIS: Study Report/ Manuscripts

Do not try to mimic result interpretations from an RCT.

Use graphs and flow-charts to clarify treatment outcomes.

Use means and 95% CI or odds ratios to describe results and differences between cohorts/timepoints. These give clear descriptions on the size and relevance of changes without suggesting statistical significance (which usually cannot be attributed to a drug).

Be careful in using and interpreting p-values.

No need to include all types of appendices as required in ICH E3 in study reports.

Documents for RWE/NIS:

Study Report/ Manuscripts

Writing Manuscripts for NIS:

Prefer journals with a clinical focus over those with a scientific focus.

NIS results are often only of interest in the country/ region where the study was conducted.

Results on health outcomes/ costs or epidemiology may be submitted to the respective specialty journals/ congresses.

Writing Style for RWE/NIS:

Study Report/ Manuscripts

Be clear that you are reporting from an NIS but mention this only once in detail (e.g. in the methods section) and refer to the “study” elsewhere.

Discuss all possible types of biases of NIS in the discussion but mention also the advantages.

Do not try to mimic CTR results or try to directly compare results from CTR with your NIS.

Mention all methods (e.g. ERB, monitoring, queries, investigator training, database quality and validation) used to improve data quality in the study.

Writing Style for RWE/NIS:

Study Report/ Manuscripts

Explain why objectives were formulated and that an NIS/RWE study is the best (not the cheapest) methodology to answer that objective.

Discuss the different statistical imputation and modeling approaches to assess the influence of confounding factors.

Stress (if possible) the consistency and robustness of results achieved with different statistical methodologies.

Writing for RWE Databases:

Study Report/ Manuscripts

The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.

If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.

Writing for RWE Databases:

Study Report/ Manuscripts

The population selection (such as codes or algorithms used to identify subjects) should be listed in detail.

Any validation studies of the codes or algorithms used to select the population should be referenced.

If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.

Writing for Databases:

Study Report/ Manuscripts

A complete description of variables and algorithms used to classify outcomes and confounders, should be provided.

Provide information on the data cleaning methods used in the study.

Limitations: Discuss the implications of using data that were not created or collected to answer the specific research question(s).

Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.

Summary Writing for RWE Research

- Do not write like for Randomized Clinical Trials (RCT)
- Be proud that you report RWE data that is best suited for answering your research objectives
- Be transparent about limitations and advantages of your RWE approach
- Have in mind that your target audience might not be very knowledgeable about the type of research you present.
- You will have realized that writing for RWE is more complicated than for your average phase III comparative RCT.