Real-world evidence: What does the medical writer need to know?

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doi: 10.56012/wqvt4437

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Abstract

Evidence derived from real-world data is invaluable for expanding knowledge about medicines. As medical writers, we need to understand how to think about, handle, and communicate these data to ensure that they are credible and have a meaningful impact. This article shares what we have learned and what we wish we had known when we began working with real-world data.

Interest is growing in what real-world evidence (RWE) adds to medical research. This is not surprising if we consider why medicines are developed and why, as medical writers, we create content to support those medicines. The answer is, of course, to improve the lives of patients receiving care in routine clinical practice whose needs are not currently being met. Although the focus during clinical trials is quite rightly on maximising our understanding of what a medicine is doing by removing as many sources of variance as possible, medicines are ultimately destined for use in highly variable, often unpredictable real-world settings. This places the real world at the heart of the medicine development process. In fact, it is widely recognised today that real-world data (RWD), and the evidence that these data help to generate, complement clinical trials by providing important insights to multiple stakeholders involved across all stages of the medicine lifecycle.[1–3] New guidance is already shaping how RWE studies for use by regulators and payers are conducted to ensure harmonisation of standards, data transparency and reproducibility, as well as to support robustness of study design and the evaluation of bias.[4–7] Integration of RWE within the drug development and approval processes will only increase in the future. Thus, as medical writers, it is increasingly important that, as well as being aware of evolving guidance, we understand how to work with RWD and the unique insights that it can provide. This article outlines how and why RWD differ from data collected within randomised clinical trials and explores the factors that medical writers need to think about when writing about real-world studies.

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Why do real-world and clinical trial settings differ?

Medicines undergo rigorous testing in tightly controlled clinical trial conditions to ensure their safety and efficacy before they can be used in routine clinical practice. This research is planned in meticulous detail; from the careful selection of individual patients with similar characteristics who fulfil strict inclusion criteria to the use of specific clinical assessments conducted at regular timepoints, everything about the setting is pre-specified. Treatment decisions can also be precisely controlled with randomisation of patients to different treatment groups. While real-world studies can also be planned in detail, they are observational in nature, and neither their environment nor the characteristics of the patients who seek care can be strictly controlled (Table 1).

Treatments and clinical evaluations in the real world are at the discretion of the healthcare professionals who care for the patient. Their decisions are based on clinical experience, local considerations, such as treatment availability and reimbursement, and patient-specific aspects, such as individual goals, lifestyle, and preferences. These factors also influence how often patients see their doctor, undergo tests, and receive prescriptions, not to mention how often they fill their prescriptions and take their medicines. Therefore, while clinical trials typically offer gold standard treatments and regular, detailed assessments for every participating patient, it is unrealistic to expect comparable care in the real world. Furthermore, the documentation of patient care varies between settings, with many real-world sources being unstructured and more variable than the standardised and structured outputs of clinical trials. It is important that medical writers understand these differences between real-world studies and clinical trials and appreciate the strengths and limitations of RWD and the questions it can answer.

What types of research questions can real-world studies address?

Real-world studies, like other forms of medical research, are intended to add value by addressing relevant, unanswered questions. As a medical writer communicating RWE, it is useful to start by considering the research question and the knowledge gap that the study aims to fill, because these will dictate how we introduce it and the context that needs to be provided.

Improving understanding of diseases and patient populations

Real-world studies are often used to improve the understanding of a disease, patient population, and standard of care. For example, the aim of a study may be to quantify how many people are affected by a condition and how this is expected to change over time; to help understand the different stages of a disease and the patient journey; or to characterise the unmet medical needs of patients receiving current treatments. These types of studies can be used to explore the characteristics of any condition and are particularly valuable for expanding our comprehension of rare diseases.[8] Data addressing questions of this kind can also be extracted for use in other studies; a good example is the use of natural history data as an external control group within a single-arm clinical trial.[2]

Table 1. How do real-world studies differ from randomised clinical trials?

	Randomised clinical trial (RCT)	Real-world study
Classification	Interventional	Non-interventional (observational)
Patients	Homogeneous group; often healthier than the average patient in the real world	Heterogeneous group; may have multiple comorbidities and variable disease presentations
Population size	Small relative to the affected population; prespecified based on statistical power for primary outcome	Can be much larger than in RCTs; often unspecified and based on data availability
Doctor/care team	Experienced in the condition being studied; supported by detailed protocols and study team	No guaranteed disease-related experience
Treatments	Pre-specified in protocol; often testing an investigational product; restricted use of concomitant therapies	Local standard of care; dependent on availability and accessibility; wide range of concomitant therapies
Comparisons	Placebo or other medication; designed to detect differences between treatment groups	Often designed to find associations rather than conclude causality
Treatment assignment	Randomised	At the discretion of the treating physician
Treatment blinding	Double/single-blinded or open label	No blinding to treatment
Data collection	Prospective; structured, at consistent time intervals	Retrospective or prospective; often unstructured, at various time intervals
Assessments	Pre-specified in protocol to collect appropriate data for answering study question	Part of routine medical care at variable time points; often not performed with research in mind
Key outcomes	Efficacy and safety	Effectiveness (rather than efficacy) and safety; natural history; disease burden/unmet needs; treatment patterns; costs
Duration	Short; up to several years depending on the research question; limited by feasibility and cost	Can be much longer than RCTs; may cover decades in a retrospective analysis or prospective registry
Study documentation	Protocol, statistical analysis plan, final study report	Level and detail of documentation varies

Exploring treatment use, safety, and effectiveness

Real-world studies can answer questions about the uptake and impact of treatments in larger and more diverse patient populations and over longer time periods than is possible within clinical trials. For instance, a study on treatment patterns may seek to understand who is receiving long-term treatment with a particular medication and whether they are taking that medication as regularly as expected, as well as what other treatments are being prescribed alongside it. Following authorisation of a medicine, real-world studies frequently address questions about safety.[2] These types of investigations allow researchers to detect rare adverse events, monitor risk-management measures, and identify safety signals that warrant further study. Real-world studies can also provide evidence in support of medicine effectiveness by confirming or extending findings of efficacy from clinical trials.

Quantifying disease burden and healthcare impact

The burden of ill health and associated use of healthcare resources are often central themes within real-world studies. Research may measure the impact of a condition and its management by collecting data on direct costs (e.g., for medicines, procedures, and hospital visits) and indirect costs

Box 1. Checklist of questions to ask when writing about a real-world study: aim and audience

Question	Considerations
What is the aim of the study?	Any communication needs a compelling story. • Think about why the study has been done and the real-world question it is trying to answer. • Consider what background information the reader needs to know for them to appreciate the relevance and importance of the study.
Who is the intended audience?	Different audiences will have different areas of expertise and different priorities. • Avoid jargon and explain concepts in simple, unambiguous terms. • Ensure you have the appropriate template when developing documents such as trial protocols and clinical study reports.

(e.g., the impact on ability to work and need for caregiver support), as well as determining any cost savings associated with treatments. Studies may also demonstrate the burden of disease in terms of its impact on the patient's health-related quality of life. Such RWE is important for activities that aim to demonstrate the value of medicines by showing their clinical- and cost-effectiveness or affordability (cost-modelling).[3] For example, RWD may be used in a health economic analysis to help quantify the burden of disease in terms of the number of years of life lost or lived with disability, supporting value comparisons between an existing and future treatment.

Communicating real-world evidence effectively to different audiences

Given the broad range of questions that can be addressed by RWD, a variety of stakeholders are interested in the answers, and therefore it is helpful to consider the needs and expectations of your audience. Medical writers develop many different types of content, including study reports, integrated evidence plans, reimbursement submissions, regulatory documents internal training materials, publications, information for patients, and medical communication materials. The format and audience will influence how RWE is presented. We should also consider how content will be used in the future by different stakeholders. Different audiences will have different areas of expertise – for example, your audience may not be medically trained – therefore, communications need to be tailored appropriately, avoiding jargon and explaining concepts in simple, unambiguous terms. While the language chosen may differ depending on the expertise of the audience, our role as writers is to tell a compelling story that resonates with the reader, whether they are pharmaceutical industry professionals, regulators, payers, healthcare professionals, or patients. Overall, it is important that we think carefully about how to build a narrative that shows our audience(s) how the answer to a real-world question is relevant to them and why the evidence matters. (Box 1)

Understanding data sources and collection methods

To write about a study accurately and highlight its strengths and limitations, we need to understand how it was conducted and why certain methods were chosen over others. Transparent explanations of data source selection and study design are essential when reporting the results of a real-world study.[7,9] Before starting to write a report or publication, it is important to ensure that the source materials that have been provided contain all the necessary study details. If any essential study information is missing or unclear, this should be communicated to the data owner as early as possible, so that the pertinent details can be clarified. Reporting guidelines for non-interventional studies, such as STROBE,[10] which has separate checklists for cross-sectional, case-control, and cohort studies, are useful tools for checking which information needs to be included in a manuscript, and many journals now require the relevant checklist to be completed alongside submissions. Other key guidelines and templates include HARPER which supports the transparent reporting and reproducibility of RWE study protocols.[4] Make sure to read any guidance that applies to your content before starting work.

RWD can be obtained from many different sources, some of the most common being electronic health records, pharmacy and healthcare claims, and product or disease registries (Figure 1), and different types of data come with different strengths and challenges.[11] Databases of medical and pharmacy claims, for example, offer structured data associated with requests for reimbursement for medications or procedures related to a specific diagnosis. In contrast, electronic health records are unstructured but provide much more detail about the health of each patient and the medical care that they received. Patient-reported data, such as responses to surveys or interviews, are highly variable yet give a detailed picture of the true impact of a disease or treatment from the patients' perspective. In order to include comprehensive information in a study, data on individual patients are often combined from different sources, which may be formatted differently and require harmonisation before use. With the increasing availability of large databases of patient information, techniques for converting RWD to RWE are becoming more advanced and incorporating the use of big data, artificial intelligence, and machine learning methods. It is important to bear in mind that the sources used in real-world studies often contain patient data that were not collected with research in mind and may not be fully anonymised, so care must be taken to ensure that these data are reported ethically. Manuscripts should include confirmation of informed consent if appropriate, and either details of ethics committee approval or an explanation of why this was not required.

Data collection outside of the well-defined environment of a randomised controlled trial is inherently variable; therefore, the endpoints used in real-world studies may be more complex than

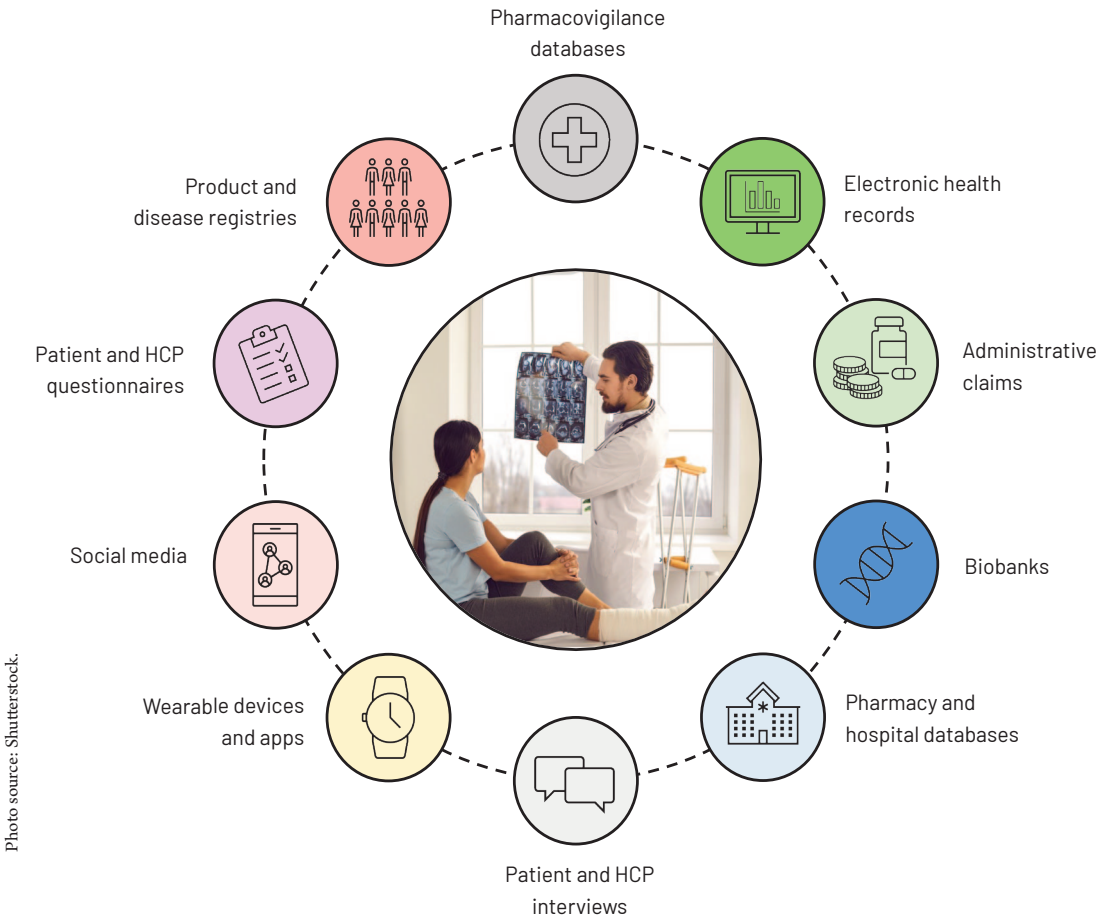

Figure 1. Data sources used in real-world studies

Abbreviations: HCP, healthcare professional

those in clinical trials, particularly if data were collected over long time periods during which diagnostic codes, assessment methods, guidelines, or policies have changed. If data on specific clinical variables are not available, surrogate or composite measures may be used to indirectly determine key outcomes. When reporting outcomes, clarity on the timeframe for follow-up and the patients included in each analysis is essential, as subgroup analyses and missing data are common. As medical writers, we need to think about the nature of the data being reported, how each variable relates to the question we are answering, and what the reader needs to know to understand the study results. (Box 2)

Addressing biases and limitations in real-world studies

Real-world studies have greater potential for bias than randomised controlled trials; therefore, clear reporting of statistical methodology is paramount for building trust that study conclusions are robust. Typical sources of bias in real-world studies include selection bias, information bias, and confounding.[12,13] Selection bias occurs when the selection of individuals or data for a study is not random, and the sample population may therefore not be representative of the wider patient population. This includes self-selection bias, which is relevant when participants choose to be in the sample population, for example, by volunteering to answer an online questionnaire. Information bias arises when key study variables are inaccurately measured or recorded. This includes recall bias, which is a common limitation of studies based on interviews or surveys. Confounding occurs when an uncontrolled variable influences both the independent variable (exposure) and the dependent variable (outcome), so that the results obtained do not accurately reflect the actual relationship between the independent and dependent variables.

Details of the strategies used for minimising bias and handling missing data should be described in the study methods. Common strategies for reducing bias in real-world studies include:[14]

- **Restriction** (strict inclusion and exclusion criteria to create a more homogeneous patient population)
- **Stratification** (dividing the study population into subgroups based on potential confounding variables)
- **Regression analysis** (statistical adjustments using multivariable regression models that take confounding factors into consideration)
- **Propensity score matching** (effectively mimicking randomisation by creating treatment and control groups that are balanced in terms of specific baseline variables)

Sensitivity analyses, which test the potential influence of unmeasured confounders, are also

Box 2. Checklist of questions to ask when writing about a real-world study: source information

Question	Considerations
Do you have all the study details and data you need?	Be prepared/have all the details to hand. • Check guidelines such as STROBE and HARPER for the information that should be reported for real-world studies. The field is evolving rapidly so keep an eye out for new guidance and templates that support data transparency. • Ask the data owner for any missing information as soon as possible.
What data source(s) and study endpoints were used?	RWD sources are numerous and can be very different. • Make sure that you understand the data sources and how they are formatted in enough detail to explain them. • Be clear on how endpoints relate to the study question. • Include sufficient context in the methods and results to allow the reader to assess the data and understand its meaning.
Do any details need to be removed to maintain patient anonymity?	Remember that the data reflect real people. • Keep a look out for details that could compromise anonymity and make sure that they are masked or removed. • Real-world sources such as interviews and free text in questionnaires may contain information that needs to be reported sensitively.
Were patient consent and ethics approval obtained?	Ethics processes for real-world studies may be less straightforward than for clinical trials. • Include some form of statement about ethical review; check with the data owner if the requirements for the study are not clear. • These factors may not be applicable if fully anonymised data were used, in which case, this exemption should be explained clearly.

used to demonstrate the robustness of the results.

As a medical writer developing content based on RWD, it is important to consider the factors that will build confidence in the RWE being presented and to be transparent about potential study limitations. Non-interventional studies are often designed to find associations rather than to conclude causality; therefore, caution with using causal language is needed, particularly when findings are based solely on descriptive statistics. When writing the discussion section of a manuscript, being clear about the generalisability of the results (e.g., that the study only looked at patients of a certain age or from a specific ethnic background) does not diminish the validity of the study but provides essential context for the reader to understand what the results mean. Discussion of limitations is always important, and the inherent limitations of real-world studies should be acknowledged. Any specific limitations identified in study design, data integrity, or interpretation of results should be discussed with the authors to agree on how they should be addressed and whether future studies are warranted. RWD are, by nature, variable and complex; however, real-world studies provide insights that cannot be obtained in clinical trials, and any limitations should be considered in the context of the study's strengths. (Box 3)

Conclusions

The role of medical writers is to develop clear, accurate, and transparent communications, with the ultimate goal of helping to bring evidence-based medicines to patients. When we talk about RWE, it is often caveated with a list of issues that must be addressed, such as data quality, bias, and a general lack of methodological rigor, all of which make it sound challenging. However, RWE is worth the effort – it helps us to fill gaps in clinical trial evidence, offers improved patient-centred insights, lets us look at cost-effectiveness in different geographies, and is receiving growing interest in regulatory and policy circles where it may ultimately help to speed up decision making. By reporting real-world studies effectively and transparently, medical writers can support the pharmaceutical industry in building trust in the diverse and valuable insights gained from RWD.

Acknowledgements

The authors would like to thank Claire Price for reading the article and providing valuable feedback.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

Disclosures and conflicts of interest

Harriet S. Crofts is an employee and shareholder of Oxford PharmaGenesis Ltd. The authors declare no conflicts of interest.

Box 3. Checklist of questions to ask when writing about a real-world study: data interpretation

Question	Considerations
What steps were taken to minimise bias?	Real-world studies have more potential for bias than randomised controlled trials. ● Check the protocol and statistical analysis plan (if available) and ask the data owner if unsure. ● Include sensitivity analyses if these were conducted, and results of any other analyses that support data robustness.
Have the outcomes been described appropriately?	Choice of language is important. ● Remember that real-world studies tell us about effectiveness, not efficacy. ● Avoid language around causality/associations if findings are based solely on descriptive statistics.
What are the study strengths?	Non-interventional studies examine what happens in real life in a way that clinical trials cannot. ● Make sure to highlight the strengths of the study, not just the limitations. ● Ask the authors if you are not sure what these are.
What are the study limitations?	Study limitations should be discussed transparently. ● Consider potential sources of bias and the inherent limitations of RWD. ● Discuss potential limitations with the authors to agree on how they should be addressed.
How generalisable are the findings?	The reader needs to understand what the findings mean in a broader context. ● A statement on the generalisability of the study is always important to include. ● Think about the demographics and clinical characteristics of the patients in the study – how representative are they of the global patient population?

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