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What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews

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ABSTRACT

Background: Despite increasing recognition of the value of real-world data (RWD), consensus on the definition of RWD is lacking. **Objectives:** To review definitions publicly available for RWD to shed light on similarities and differences between them. **Methods:** A literature review and stakeholder interviews were used to compile data from eight groups of stakeholders. Data from documents and interviews were subjected to coding analysis. Definitions identified were classified into four categories: 1) data collected in a non-randomized controlled trial setting, 2) data collected in a non-interventional/non-controlled setting, 3) data collected in a non-experimental setting, and 4) others (i.e., data that do not fit into the other three categories). The frequency of definitions identified per category was recorded. **Results:** Fifty-three documents and 20 interviews were assessed. Thirty-eight definitions were identified: 20 out of 38 definitions (53%) were category 1 definitions, 9 (24%) were category 2 definitions, 5 (13%) were category 3 definitions, and 4 (11%) were category 4 definitions. Differences were identified between, and within, definition categories. For example, opinions differed on the aspects of intervention with which non-interventional/non-controlled settings should abide. No definitions were provided in two interviews or identified in 33 documents. **Conclusions:** Most of the definitions defined RWD as data collected in a non-randomized controlled trial setting. A considerable number of definitions, however, diverged from this concept. Moreover, a significant number of authors and stakeholders did not have an official, institutional definition for RWD. Persisting variability in stakeholder definitions of RWD may lead to disparities among different stakeholders when discussing RWD use in decision making.

Keywords: definitions, real-world data, real-world evidence, real-world studies, review, stakeholder definitions.

Introduction

Randomized controlled trials (RCTs) provide the ideal study design for demonstrating causality between the use of a specific medicine and intended and unintended effects under ideal conditions. In conventional RCTs conducted during phase III drug development, patients are based on stringent inclusion and exclusion criteria and subsequently randomized to different treatment arms to counteract the influence for known and unknown confounders [1,2]. In addition, monitoring and follow-up procedures for trial subjects are often highly controlled [1,2].

The highly selective populations examined within the setting of RCTs are often not comparable with the more heterogeneous populations in clinical practice in which medicines are administered to patients with varying genetic make-ups, who present with different comorbidities or already receive different medications for other morbidities. Consequently, experimental medicines being presented for marketing authorization are accompanied by data that provide efficacy as well as safety data with very high internal validity but whose results may not be easily generalizable to a broader, more heterogeneous population [2]. This disparity of findings on the therapeutic efficacy of medicines from tightly controlled RCT settings and the effectiveness of medicines in the real world has been previously defined by Eichler et al. [3] as the "efficacy-effectiveness gap."

Regulatory agencies are thus faced with the issue of making decisions on the basis of data with inherent uncertainties on the aspects of real-world effectiveness. Similarly, health technology assessment (HTA) agencies and health care payers conventionally exploit RCT-generated evidence available at the time of initial reimbursement decisions to assess the relative effectiveness of new products. As a result, many stakeholders such as the pharmaceutical industry, regulatory agencies, HTA agencies, and payers have begun exploring options for the use of real-world data (RWD) as a complementary source to RCT data for establishing a more robust evidence base on the effectiveness of medicines, as well as the relative effectiveness compared with existing products in clinical practice [4,5].

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Table 1 – ISPOR, ABPI, RAND Corporation, and IMI-GetReal definitions for RWD.

Term and source	Definition
RWD (ISPOR [7])	Data used for decision making that are not collected in conventional RCTs.
RWD (ABPI [8])	For the purposes of this guidance, "RWD" will refer to data obtained by any non-interventional methodology that describe what is happening in normal clinical practice.
RWD (RAND [9])	"RWD" is an umbrella term for different types of health care data that are not collected in conventional RCTs. RWD in the health care sector come from various sources and include patient data, data from clinicians, hospital data, data from payers, and social data.
RWD (IMI-GetReal [10])	An umbrella term for data regarding the effects of health interventions (e.g., benefit, risk, and resource use) that are not collected in the context of conventional RCTs. Instead, RWD are collected both prospectively and retrospectively from observations of routine clinical practice. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes, and health-related quality of life. RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies.

ABPI, Association of the British Pharmaceutical Industry; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; RCT, randomized controlled trial; RWD, real-world data.

In addition, RWD are currently used during drug development to examine aspects such as the natural history of a disease, delineating treatment pathways in clinical practice, determining the costs and resource use associated with treatment interventions, and determining outcomes related to comparator interventions [4,6]. Such knowledge may inform aspects of early drug development such as clinical trial design or the comparative effectiveness of comparator treatments within a given indication.

Despite the increasing popularity of RWD collection and use for drug development, drug regulation, and HTA, a certain degree of disparity remains among different stakeholders when it comes to thoroughly defining RWD [6]. Therefore, this study aimed to conduct a review of definitions for RWD available in literature and stakeholders' definitions of the term within the context of drug development, drug regulation, and HTA of pharmaceutical products to straighten out the similarities and differences between them. In addition, the article will review which data sources stakeholders believe as being RWD and which study designs they consider to generate RWD. Subsequently, the article will shed light on existing definitions for the term RWD developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [7], the Association of the British Pharmaceutical Industry (ABPI) [8], RAND Corporation [9], and the IMI-GetReal consortium [10] (see Table 1).

Methods

Two qualitative methods were used to compile data from relevant stakeholders: a literature review and stakeholder interviews. Data compilation from eight stakeholder groups was performed, namely, HTA agencies, the pharmaceutical industry, regulatory agencies, academia, health care providers, health care insurers/payers, patient organizations, and initiatives using, or commissioning research on, RWD (e.g., ISPOR and the Patient-Centered Outcomes Research Institute).

For the literature review, PubMed was used to search scientific literature from January 1, 2005, to December 31, 2016 (date of search). The search strategy used is presented in Appendix Figure i in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008. To locate gray literature, Web sites belonging to the eight stakeholder groups were consulted (see Appendix Table i in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008 for a list of Web sites consulted). Search functions on stakeholder Web sites were used when available, using terms such as "real-world data," "real-world evidence," "clinical effectiveness data," "real-world outcome," "comparative effectiveness," or "relative effectiveness." Search results from both scientific and gray literature were independently screened by two of the authors according to predefined inclusion and exclusion criteria (see Appendix Table ii in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008). Any discrepancies for inclusion and exclusion of articles were resolved by consensus between the two authors.

A standardized data abstraction form was created in Microsoft Excel and used to locate information in the documents selected after screening. Data elements included in the data abstraction form were author name(s), publication year, the type of document, definition(s) of RWD provided, and data sources considered as RWD and study designs considered to generate RWD (e.g., claims databases and observational studies, respectively). Two of the authors extracted data independently from the selected documents. Any discrepancies in the extracted data were resolved by consensus between the two authors.

With regard to stakeholder interviews, stakeholders from the eight previously mentioned groups were selectively sampled on the basis of seniority and function, with a preference for senior representatives involved in work on RWD use within their respective organizations. Information for identifying representatives was retrieved from stakeholder Web sites and/or the authors' professional network. All representatives were approached by email using a standardized invitation to participate in semistructured interviews. To increase the validity of stakeholder views, participants were provided the freedom to invite colleagues they deemed relevant to take part in the interviews. Tailored questionnaires were developed for each stakeholder group and sent to stakeholders who agreed to participate 2 weeks before the interview to guide discussions (see Appendix Figures ii to iv in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008 for examples of questionnaires sent to three stakeholder groups). Interviews were conducted, recorded, and subsequently transcribed for further analysis.

The sampling of stakeholders and interview protocols were compared with recommendations in the consolidated criteria for reporting qualitative studies (COREQ) [11] to ensure good quality. The COREQ checklist provides guidance for explicit and comprehensive reporting of qualitative studies using interviews and focus groups.

It is important to note that the interviews were conducted as part of a larger study on policies and perspectives on RWD [6], and thus the scope of questions posed during the interviews extended beyond the definition of RWD. All questionnaires, however, included the following three questions:

1. What is your understanding of the term RWD?
2. Could you provide your own specific definition for RWD?
3. Is RWD routinely collected/used in the context of stakeholder-specific activities and if so, what type of RWD?

This allowed for the standardized collection of data on stakeholders' definitions of RWD, data sources they consider to be RWD, and study designs they consider to generate RWD.

Data extracted from documents selected from the literature review and transcripts of stakeholder interviews were subjected to a coding analysis using MaxQDA software 11.0 (VERBI Software GmbH Location: Bismarck straße 10-1210625 Berlin Germany). Following the grounded theory approach in qualitative research [12], data were iteratively assessed by two of the authors independently to identify repeating themes and tag them using codes. Any discrepancies in codes created were resolved by consensus between the two authors. Subsequently, the codes of repeating themes were iteratively refined and grouped into categories. The generated categories formed the categories for RWD definitions and RWD sources for subsequent analyses. The final coding scheme developed was discussed among all authors to ensure consensus. The scheme generated was as follows:

1. Categories of RWD definitions
   - Category 1: Data collected in a non-RCT setting (i.e., all health data except those collected in the setting of a conventional phase III RCT setting);
   - Category 2: Data collected in a non-interventional/non-controlled setting (i.e., data collected without interference with treatment assignment, and/or patient monitoring/follow-up, and/or selection of study population);
   - Category 3: Data collected in a non-experimental setting (i.e., in a setting in which the investigator has no control over any of the conditions and no de novo data collection occurs on the basis of a pre-established study protocol);
   - Category 4: Others (i.e., none of the aforementioned).
2. Categories of RWD sources
   - Category A: Data sources (e.g., claims databases and registries);
   - Category B: Study designs that generate RWD (e.g., observational studies and pragmatic clinical trials [PCTs]).

For category 1 (data collected in a non-RCT setting), the term "RCT" referred to the design of a conventional phase III RCT that involves implementation of inclusion/exclusion criteria for trial subjects, randomization of subjects to different treatment arms, and consistent monitoring and follow-up procedures for trial subjects and implicit de novo data collection. This interpretation of the term corresponds to several sources in scientific literature [1,2,10].

For category 2 (data collected in a non-interventional/non-controlled setting), the term "non-interventional/non-controlled" referred to a setting in which the investigator may not be able to interfere with one or more of the following aspects: treatment assignment, monitoring and follow-up procedures, and inclusion/exclusion criteria. De novo data collection may or may not occur in this setting. Although the authors are aware that several non-identical definitions already exist to define intervention in clinical trials [13,14], the interpretation of the term "non-interventional" for the category developed here depended on definitions available from the compiled data.

For category 3 (data collected in a non-experimental setting), the term "non-experimental" referred to a setting in which the investigator cannot alter any of the factors or conditions observed in the study and as such no de novo data collection occurs other than data collected in routine clinical practice. This interpretation of the term "non-experimental" corresponds to several sources in scientific literature [10,14].

It is important to note that categories 1 to 3 are not mutually exclusive. For example, data collected in a non-interventional/non-controlled setting are theoretically equivalent to data collected in a non-RCT setting. Nevertheless, not all data collected in a non-RCT setting are collected in a non-interventional/non-controlled manner. Similarly, all data collected in a non-experimental setting are theoretically equivalent to that from a non-interventional/non-controlled setting but not vice versa. Therefore, there are subtle qualitative differences between the categories that have implications on defining RWD. This is elaborated upon later in the Discussion section.

Analysis

Each RWD definition identified was classified into one of the four definition categories (1 to 4) created. The number of definitions per definition category was recorded. In addition, definitions in each category were qualitatively analyzed to highlight differences within, and between, the categories.

Each RWD source identified was classified into one of the two source categories (A and B) created. The number and type of sources per category were recorded.

A subanalysis was performed for definitions provided by three stakeholder groups that are directly involved with RWD collection or appraisal to determine drug effectiveness: the pharmaceutical industry, regulatory agencies, and HTA agencies. Definitions identified were compared both within and between the three stakeholder groups.

Results

Initially, the PubMed search yielded 496 hits, whereas the gray literature search yielded 66 hits. Of the 562 total hits, 509 were excluded because of the following reasons: document did not focus on RWD use in pharmaceutical drug development, regulation, or HTA (n = 490); it was not published in English (n = 7); it was not in one of the document formats outlined in the inclusion criteria (n = 6); it focused solely on data analysis or evidence synthesis (n = 5); or it comprised only a summary/abstract (n = 1) (see Appendix Figures v and vi in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008 for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams of document inclusion and exclusion from PubMed and gray literature searches, respectively). Eventually, 53 documents were selected (see Appendix Table iii in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008 for a list of included documents).

Twenty stakeholders from the eight stakeholder groups agreed to participate (see Appendix Table iv in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.008 for a list of interviews conducted). Eight of the 20 interviews included at least two representatives per stakeholder, and 2 included three representatives per stakeholder.

In total, 20 definitions were identified in literature documents and 18 definitions were provided in interviews. No definitions were identified in 33 documents nor provided in two interviews; one interviewee stated not to be familiar with the term at all and the second indicated they cannot provide a definition for RWD. Twenty of the 38 definitions identified (53%) were category 1 definitions. Nine of 38 (24%) were category 2 definitions. Five of the 38 (13%) definitions were category 3 definitions. Four of the 38 (11%) were category 4 definitions; these either provided definitions too general to fit in one of categories 1 to 3 or had defined the concept of "real-world trials" rather than RWD. For an

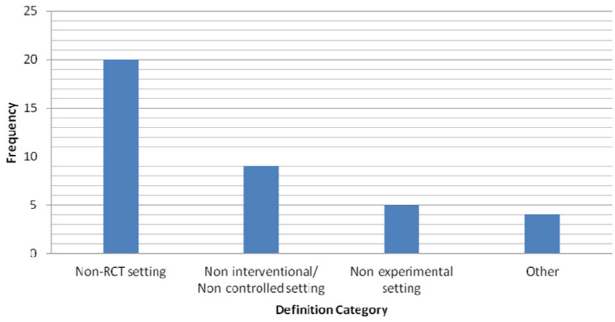

Fig. 1 – Overview of the total number of definitions classified under each of the four definition categories created. RCT, randomized controlled trial.

overview of the total number of definitions identified per category, see Figure 1. For examples of definitions identified per category from literature documents and interviews, see Table 2.

For category 2 definitions, it was not always clearly stated what authors and stakeholders perceived as non-interventional or non-controlled settings. According to some, non-interventional data collection related specifically to the researcher not interfering with treatment assignment and patient management and follow-up (see citations for Pleil [26] and Initiative B in Table 2). Others focused on another aspect of intervention, namely, the selection of study population. One stakeholder believed that RWD should be collected from the population in clinical practice without the implementation of any inclusion or exclusion criteria for selection of patients, whereas another implied that there might be a selection of study population albeit on the basis of less stringent criteria than those of an RCT (see citations for HTA Agency B and HTA Agency C in Table 2). Another stakeholder focused on patient randomization as a criterion for intervention, stating that RWD should thus be collected in a setting in which no randomization of patients occurs (see the citation for Initiative B in Table 2). Meanwhile, other stakeholders cited PCTs and large simple trials (LSTs) within their definitions of RWD, despite the fact that both study designs involve randomization of patients between treatment arms.

Table 2 – Examples of definitions from literature documents and stakeholder interviews that have been classified under the four definition categories created.

Category of definition	Citations from literature documents	Citations from stakeholder interviews
Data collected in a non-RCT setting	"We settled on a definition that reflects data used for decision-making that are not collected in conventional RCTs" [7]	"RWD to us means any health record information that is not collected as part of a strict clinical trial (an RCT). So that the physicians and the patients are acting as they are in normal clinical practice. It is more observational in nature"—Pharmaceutical Industry A
Data collected in a non-interventional/ non-controlled setting	"In general, real-world data are observations of effects based on what happens after a prescriptive (treatment) decision is made where the researcher does not, or cannot, control who gets what treatment and does not, or cannot, control the medical management of the patient beyond observing outcomes" [26]	"[RWD is] observational data without blinding and no specific inclusion or exclusion criteria"—HTA Agency B "To us the term RWD is about the scientific process. So we think of it as a step that is not done in a RCT … [RWD] more closely matches the population who will be receiving the drug, or is actually derived from that population. So it is something that was not done in the controlled condition"—HTA Agency C "RWD is data that is generated from the delivery of healthcare in non-controlled settings. Non-controlled settings will generally imply the lack of random assignment"—Initiative B
Data collected in a non-experimental setting	"With RWD, we mean data that are not collected under experimental conditions, but data generated in routine care" [27]	"RWD is data collected from daily clinical practice. This means that it is not collected in a protocol-driven way. Any additional procedures that are conducted because of a research protocol endanger the 'real world' aspect of the data"—Regulatory Agency A
Other	"RWT's are heretofore ill-defined as a class and, when conducting literature searches, appear to include a large design spectrum ranging from uncontrolled studies or NROTs (stand-alone or follow-up of RCTs' to properly randomised trials that differ only in a few aspects from conventional phase 3 trials. Their stated objective includes the term 'effectiveness' as opposed to 'efficacy,' implying that assessment of benefit or risk is taking place in a setting closer to real world clinical practice …" [2]	"RWD are data about effectiveness of treatments collected in the real world. This can be in the setting of a pragmatic trial, collecting for example evidence over time, or a setting where data is collected by health professionals. It can be done retrospectively or prospectively"—Patient Organization A

HTA, health technology assessment; RCT, randomized controlled trial; RWD, real-world data; RWT, real-world trial.

Table 3 – List and frequency of occurrence of RWD sources and study types that generate RWD retrieved from literature documents and stakeholder interviews.

Data source/study type	Literature	Interviews	Total
Data sources			
Registries	17	8	25
Electronic health records	16	6	22
Claims databases	12	4	16
Administrative databases	6	4	10
Patient-reported outcomes	10	–	10
Health surveys	4	2	6
Hospital data	3	3	6
Electronic health data	2	3	5
Clinicians	1	2	3
Payers	1	2	3
Social media	3	–	3
Patient charts	2	–	2
Pharmacy data	2	–	1
Clinical databases	1	–	1
Study designs			
Observational studies	22	6	28
Pragmatic clinical trials	16	6	22
Postmarketing studies	5	2	7
Supplements to RCTs	3	–	3
Drug utilization studies	1	–	1
Large simple trials	1	–	1

RCT, randomized controlled trial; RWD, real-world data.

The five RWD data sources cited most in literature documents and interviews were registries (18 documents, seven interviews), electronic health records (EHRs) (16 documents, six interviews), claims databases (12 documents, four interviews), administrative data (6 documents, four interviews), and patient-reported outcomes (10 documents). Meanwhile, the three study designs mentioned on more than five occasions were observational studies (22 documents, six interviews), PCTs (16 documents, six interviews), and postmarketing studies (5 documents, two interviews). For a list of the different data sources and study designs retrieved from documents and interviews, as well as the frequency of their mention, see Table 3.

All four pharmaceutical industry stakeholders interviewed defined RWD as health data collected in a non-RCT setting (i.e., category 1). Of the three regulatory stakeholders interviewed, one defined RWD as data collected in a non-RCT setting (category 1), whereas the remaining two defined RWD as data collected in a non-experimental setting (category 3). Of the five HTA stakeholders interviewed, two defined RWD as data collected in a non-RCT setting (category 1), two as data collected in a non-interventional/non-controlled setting (category 2), and one was unable to provide a definition. Importantly, only 4 of the 12 stakeholders in the subanalysis had an official, institutional definition for RWD.

Discussion

Stakeholders' recognition of the value of RWD in enriching evidence on the effectiveness of medications has been steadily increasing. This can be observed in the guidelines of HTA agencies that now conventionally include sections on the use of data from non-RCTs [15–17], documents produced by regulatory agencies on postmarketing effectiveness and safety studies [18,19], as well as referral of industry stakeholders to their use of RWD in product development [8,20,21]. Nevertheless, consensus on the value of RWD is contrasted by a lower degree of consensus on what RWD precisely constitutes. As a result, disparity arises among stakeholders regarding the definition of RWD, the data sources considered as RWD, and study designs that generate RWD.

Although results demonstrate that RWD are perceived as health data that are not collected in the setting of an RCT in most of the cases (20 of 38 cases), this perception is not unanimous. In addition to the qualitative differences between the three categories of RWD definitions, critical disparities emerge between definitions of the same category, namely, in the category of RWD as data from a non-interventional/non-controlled setting (category 2). Stakeholders differed, and sometimes disagreed, on whether the intervention pertains to treatment assignment, patient monitoring and follow-up, or selection of the study population. This demonstrates, moreover, that some stakeholders may have an incorrect understanding of which aspects of a clinical trial study design classify as an intervention. According to the European Commission, for example, *intervention* is defined as the researcher's control of treatment assignment or the implementation of additional diagnostic or monitoring procedures [13]. This implies that the implementation of selection criteria for the study population would not qualify as an intervention, according to the European Commission's definition.

The aforementioned results indicate that observational studies, registries, EHRs, PCTs, and claims databases were the RWD sources most mentioned, respectively. The discussion points mentioned in the previous paragraphs notwithstanding, this would imply that some degree of consensus exists regarding these RWD sources. Nevertheless, observational studies, the most recurrent example, featured in only 22 of 52 literature documents and 6 of 19 interviews. Looking beyond the five most common types, stark controversy exists on whether supplements to RCTs classify as RWD; although the seminal article by Garrison et al. [7] and other literature documents included supplements to RCTs in their list of RWD types, other stakeholders explicitly stated in interviews that they do not consider them as RWD. Therefore, it may be argued that consensus on what sources constitute RWD is also weak.

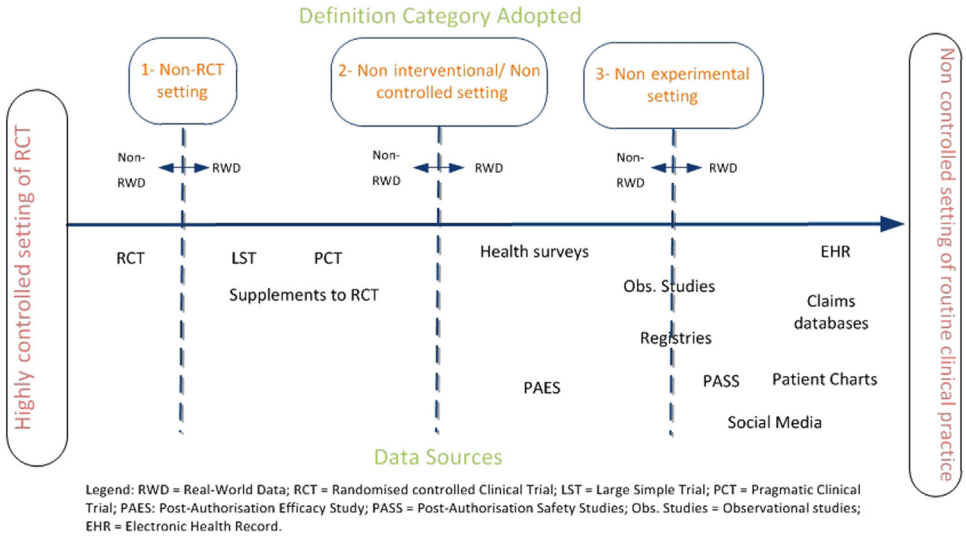

Fig. 2 – Data spectrum in relation to RWD definition categories. EHR, electronic health record; LST, large simple trial; Obs., observational; PAES, postauthorization efficacy study; PASS, postauthorization safety study; PCT, pragmatic clinical trial; RCT, randomized controlled trial; RWD, real-world data.

Moreover, different stakeholders cited data sources and study designs interchangeably as RWD. Although this is not theoretically incorrect, it can lead to disparities between various stakeholders when discussing which sources of data qualify as RWD. For example, depending on their design, observational studies may be regarded as interventional or non-interventional by different stakeholders, thus more, or less, representative of RWD. Similarly, whether a registry qualifies as a source for RWD mainly depends on the protocol used for data collection: Is data collection purely observational of routine care or is there intervention in the form of additional quality-of-life surveys for included patients?

Bearing the previous points in mind, it would seem that from the perspective of RWD definitions, data sources, and study designs identified in literature documents and stakeholder interviews, a spectrum of data exists, on one end of which the highly controlled, randomized setting of the RCT lies (least representative of RWD) and on the other end the non-experimental setting of EHRs, in which no intervention is implemented by the investigator and no extra data are collected other than those from routine clinical practice (most representative of RWD). Other data sources and study designs such as PCTs, observational studies, and registries fall between both ends of the spectrum (see Fig. 2). Whether such data sources and study designs qualify as RWD is subsequently determined by the categories that the stakeholders adopt for defining RWD. These categories, set in order of least representative of RWD to most representative of RWD, are all data collected in a non-RCT setting (category 1), data collected in a non-interventional/non-controlled setting (category 2), and data collected in a non-experimental setting (category 3).

If one were to adopt category 1, all data sources/study designs other than RCT would qualify as RWD—from PCTs to claims databases and EHRs. If one were to adopt category 2, only observational studies whose protocols do not interfere with treatment assignment, patient follow-up, or study population selection would qualify as RWD sources. This would effectively exclude PCTs, LSTs, and some observational study designs. Finally, if one were to adopt category 3, only data sources such as claims databases and EHRs would qualify as RWD (please see Fig. 2 for a diagrammatic representation). Therefore, the choice of categories for defining RWD has direct implications for the types of data and study designs that subsequently classify as RWD.

Several definitions for RWD have been developed over the past years by dedicated task forces, the seminal examples being provided by ISPOR [7], the ABPI [8], RAND Corporation [9], and IMI-GetReal [10]. The ISPOR definition, developed by a dedicated task force, formed the starting point for subsequent ones by the ABPI, RAND Corporation, and IMI-GetReal and succinctly stated that RWD referred to data collected outside the setting of a conventional RCT. To the authors' knowledge, definitions proposed by the ABPI and RAND Corporation were developed by similar task forces within the respective institutions through internal rounds of discussions. The recent definition developed by IMI-GetReal underwent internal rounds of review within the consortium, as well as external procedures of public consultation, whereby all stakeholders from the wider community were able to provide their opinions on the proposed definition. Eventually, a comprehensive definition was agreed upon by multiple stakeholders that included elements from the ISPOR, ABPI, and RAND Corporation versions on the concept of RWD, the domains of information RWD can inform, and the types of data that constitute RWD. Moreover, the consortium introduced the term "real-world studies" to shed light on the types of study designs that generate RWD, thereby distinguishing these from data sources [10].

Definitions developed by these institutions may provide a starting point for discussions among the wider community to achieve consensus on what RWD constitutes. This is particularly important when different stakeholders with differing mandates attempt to discuss the use of RWD in decision making within the context of drug development, drug regulation, and HTA of pharmaceutical products. Nevertheless, definitions of RWD developed by ISPOR, the ABPI, RAND Corporation, and IMI-GetReal were rarely cited in literature documents and stakeholder interviews. Moreover, several documents either proposed their own definition or lacked one entirely [20,22–25]. In addition to this, a significant number of stakeholders interviewed from the pharmaceutical industry, regulatory agencies, and HTA agencies did not have an official, institutional definition of RWD nor had adopted any of the aforementioned definitions.

Strengths

Several steps were taken to ensure good research practice during data compilation and analysis. Within the literature review

performed on academic and gray literature, the inclusion and exclusion of documents and subsequent data extraction from selected documents were conducted independently by two of the authors and all discrepancies were resolved by consensus. Within stakeholder interviews, the sampling of stakeholders and interview protocols were compared with recommendations in the COREQ [11] to ensure good quality. Moreover, coding analysis of data extracted from literature documents and interview transcripts was performed independently by two of the authors and all discrepancies were resolved by consensus. Finally, categories developed for definitions of RWD and sources of RWD on the basis of results of the coding analysis were discussed among all authors to ensure consensus.

Two methods were used to compile data needed to achieve the aims of this article, namely, a literature review and stakeholder interviews. This provided multiple sources from which the authors could triangulate data on definitions of RWD on the basis of two well-acknowledged qualitative research methods. Moreover, the selection of stakeholders from eight diverse groups for the gray literature search and interviews helped ensure that a comprehensive view of definitions currently used by relevant stakeholders was available.

Limitations

To capture the full perspective of a stakeholder's view on RWD, a representative sample within an organization should be interviewed. Therefore, it can be argued that stakeholder interviews conducted were insufficient to gather stakeholder perspectives comprehensively. We attempted to account for this by selectively sampling stakeholders, explicitly offering stakeholders approached the opportunity to invite colleagues they deemed relevant to participate in the interviews, and by interviewing more than one person per institute. Eventually, 8 of the 20 interviews included at least two representatives per stakeholder, and 2 of the 20 interviews included three representatives.

Definitions provided in documents and interviews varied in length and degree of detail, thus implying that the extent of familiarity and experience of different stakeholders with RWD varied. For example, although some were quite detailed in citing a definition of the concept and several data sources, other stakeholders indicated that they were unfamiliar with the term. The degree of variance in length and level of detail provided in different definitions was not analyzed in this article, because the aim was not to compare the quality of definitions provided. Instead, the focus of this article was on providing an overview of available definitions of RWD and qualitative differences between them.

Criteria used for defining RCTs to create category 1 of RWD definitions (data collected in a non-RCT setting) may present an inherent limitation when trying to conceptualize the placement of certain data sources within the categories created. For example, gene therapy trials, often conducted as open-label, single-arm trials, do not fall under the adopted definition of RCTs. Meanwhile, they are also not non-interventional trials. Another example relates to open-label extension of RCTs that conventionally precede long-term postauthorization studies. Such open-label extension studies are neither RCTs nor non-interventional studies. A final example relates to PCTs and LSTs; such trial designs feature randomization, yet implement broader inclusion/exclusion criteria and outcome measures more relevant for clinical practice. As such, they are neither RCTs nor non-interventional studies. In accordance with the grounded theory approach, the criteria for RCTs adopted to develop category 1 were directly elucidated from the data compiled from literature documents and stakeholder interviews. This alludes to a dichotomous attitude among stakeholders toward the difference between RCTs and non-RCTs. The authors of this article do not favor such a dichotomous representation and have subsequently developed the notion of a data spectrum demonstrated in Figure 2 to re-assert the idea that a wide spectrum of data is generated within both RCT settings and non-RCT settings.

Conclusions

Stakeholders' acknowledgment of the potential value of RWD throughout the product life cycle is increasing. Nevertheless, despite awareness of the promise RWD brings, disparities persist regarding what RWD precisely is, the types of data sources considered as RWD, and study designs generating RWD. Despite the fact that most documents and stakeholders defined RWD as data not collected in the context of an RCT, this perception was not unanimous. Other definitions identified differed and often contradicted one another. Moreover, a significant number of authors and stakeholders do not have an official, institutional definition for RWD, nor have adopted definitions developed by ISPOR, the ABPI, RAND Corporation, or IMI-GetReal.

From the perspective of RWD definitions, data sources, and study designs identified in literature documents and stakeholder interviews, a spectrum of data exists, on one end of which the highly controlled, randomized setting of the RCT lies (least representative of RWD) and on the other end the non-experimental setting of EHRs, in which no intervention is implemented by the investigator and no extra data are collected other than those from routine clinical practice (most representative of RWD). All stakeholders concede that data generated by RCTs are not RWD. Nevertheless, the question whether health data originating from other data sources or study designs within such a spectrum qualifies as RWD depends on varying categories adopted by stakeholders in their definitions.

To ensure that future work involving the collection or use of RWD for drug development, drug regulation, and HTA delivers the greatest value to the widest audience, we should move toward developing a common understanding among stakeholders of what RWD precisely means, the types of information domains it may inform, the types of data sources that qualify as RWD, and study designs that generate RWD. Definitions developed by previous initiatives such as ISPOR, the ABPI, RAND Corporation, and IMI-GetReal provide a good starting point for discussions among the wider community to do so.

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Supplemental Materials

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