GetReal - Project No. 115546

WP1: Deliverable D1.2 Review of current policies/perspectives

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Executive Summary

This report aims to provide a review of different stakeholders’ policies and perspectives on using Real World Data (RWD) for early drug development and clinical effectiveness assessment, and in doing so assesses the policies on RWD use, the context within which RWD is/ could be used, the perspectives of stakeholders on the advantages, disadvantages, and obstacles encountered when collecting and using RWD.

A literature review of documents published by relevant stakeholders in both academic and grey literature, as well as stakeholder interviews were conducted to achieve this aim. Policies on access to RWD available through pragmatic clinical trials (PCT’s), electronic health records (EHR’s), administrative claims databases, and so forth vary from region to region, country to country, state to state, and even institute to institute. Steps required to approve plans for real world studies by the relevant boards of governance vary according to the contexts within which such studies are conducted.

The majority of authors and interviewees refer to the need for harmonization of the type of RWD to be collected and evidence requirements between different stakeholders, as well as the methods/ tools for RWD collection and analysis. Some authors and stakeholders were of the opinion that a vast collection of RWD is already available, whether through health surveys, observational studies, administrative claims databases, etc. However, since these different types of data are collected for different purposes, they have their different strengths and limitations which complement one another. Therefore, one way to ensure that we unlock the full potential of RWD is by data linkage.

To allow for the systematic integration of RWD into decision frameworks for drug development and drug assessment, increased collaboration must exist between stakeholders to:

1. Develop a common understanding and definition of the terms ‘real-world data’, ‘real-world evidence’ and ‘real-world studies’;
2. Reach consensus regarding the relevance of RWD for answering different scientific questions in different drug development and assessment phases;
3. Harmonise RWD evidence requirements during different drug development and assessment phases;
4. Determine the best mechanisms for the governance of RWD collection efforts and develop policies accordingly;
5. Standardise and provide guidance on tools, methodologies and strategies for RWD collection and analysis.
Deliverable content

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1 Introduction

During pre-authorisation drug development phases, pharmaceutical manufacturers invest considerable time and funds in conducting phase 3 clinical studies to provide robust data on the safety and efficacy of their products. Such studies are designed as randomized clinical trials (RCT’s) which typically have strict inclusion and exclusion criteria for trial subjects and within which experimental products are often conventionally compared to a placebo arm, rather than an active treatment. Consequently, experimental products being presented for marketing authorisation are accompanied by data that provides safety and efficacy data with very high internal validity but whose results are perhaps not easily generalised to the broader, more heterogeneous clinical population (1).

Regulatory agencies are thus faced with the issue of making decisions based upon data with inherent uncertainties on the aspects of real-world effectiveness. Similarly, HTA agencies and healthcare payers often refer to RCT-generated evidence available at the time of initial authorisation to pass judgement on the relative effectiveness of the new products. Therefore, despite the high internal validity of RCT-generated evidence and its ability to robustly indicate the safety and efficacy of new products, it falls short of allowing for extrapolation from efficacy to clinical effectiveness (2).

Consequently, in the light of making decisions with high uncertainties on post-marketing performance of new drugs, regulatory and HTA agencies alike increasingly require applicants to fulfil post-marketing data collection commitments (e.g. post-marketing safety/efficacy studies, risk-sharing agreements) (3;4). Such data is better suited to answering questions on clinical safety & effectiveness, owing to the fact that they are collected from patients representing routine practice.

Attention for the post-authorisation evaluation of treatments in real world clinical practice has been increasing in the past years; especially on alternative clinical study designs, analytical methodologies for assessing relative effectiveness and the use of registries and electronic healthcare data to do so. It may thus be possible to improve the value of information available at initial market authorisation by incorporating these techniques into pre-authorisation drug development. If such data and methodologies could be harnessed in those early stages, drug manufacturers would be able to direct drug development to areas where value is likely to be highest for patients and health systems. In addition, regulatory and HTA agencies would be able to make better-informed decisions on relative effectiveness of new health interventions.

However, the incorporation of this real-world data (RWD) in a pre-authorisation environment is fraught with ideological, political and methodological problems. Not only is there very limited guidance on best practices to do so, discussions on, for instance, the type of RWD to be incorporated, the implications to different stakeholders when such new pathways to drug development are adopted, and the different sources of RWD available remain in their early stages.

The IMI-GetReal project is a three-year project initiated by the Innovative Medicines Initiative (IMI) in January 2014 which aims to address the questions surrounding the incorporation of RWD in drug development and relative effectiveness assessment. The project is divided into 5 work packages (WP), each one addressing specific questions for RWD collection and use. For instance,
WP1 aims to establish a political framework for the assessment of drug development strategies that provide evidence of relative effectiveness (for general information on IMI-GetReal, for a full list of WP-specific objectives, please refer to http://www.imi-getreal.eu/).

As part of WP1 efforts, this report aims to provide a review of different stakeholders’ policies and perspectives on using RWD for early drug development and clinical effectiveness assessment in order to shed light on the possibilities for the incorporation of RWD in both aspects. In more specific terms, this review aims to thoroughly assess the available policies of RWD use, the perspectives of stakeholders on the advantages, disadvantages, and obstacles encountered when collecting and using RWD, and the political and procedural considerations stakeholders should bear in mind when incorporating RWD in drug development and relative effectiveness frameworks.

Before proceeding, it is important to clearly express the authors’ understanding and definitions of real-world data (RWD) real-world evidence (RWE), and real-world study (RWS):

- RWD is defined as an umbrella term for data regarding the effects of health interventions (e.g. benefit, risk, resource use, etc.) that are not collected in the context of conventional randomised controlled trials. Instead, (RWD) is 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 (PRO) and health-related quality of life (HRQoL). RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies. (5).

- RWE is defined as the evidence derived from the analysis and/or synthesis of real-world data (RWD) (5).

- RWS is defined as all clinical studies investigating health interventions whose design does not follow the design of a randomised controlled clinical trial and aims to reflect health intervention effectiveness in routine clinical practice. Real world studies do not typically include randomisation of trial subjects, but there are exceptions (e.g. pragmatic clinical trials). For the purposes of GetReal, real-world studies include, but are not limited to, the following: pragmatic clinical trials, non-interventional/observational studies, drug utilisation studies, post-authorisation efficacy/safety studies. RWS, by definition, generate RWD, which can subsequently be analysed and/or synthesised to produce RWE. (5).

The definitions of RWD, RWE, and RWS used for this report have been developed with the cooperation of all work packages of the IMI-GetReal consortium as part of efforts for the cross-consortium glossary.

2 Methods (Literature Review)

This research aimed to gain insights into the policies and perspectives of relevant stakeholder groups regarding the use of RWD within the processes of drug development and relative effectiveness assessment. A literature review of documents published by relevant stakeholders in both academic and grey literature was used to achieve this aim.
2.1 Stakeholder Groups Identification

For the purposes of the IMI-GetReal consortium, eight relevant stakeholder groups were identified as being important for the achievement of its aims, namely: Health Technology Assessment (HTA) agencies, pharmaceutical industry, regulatory agencies (RA), academia, healthcare providers, healthcare insurers/payers, patient organisations and other initiatives using, or commissioning research on, RWD.

2.2 Literature Review

A systematic approach was used to search for relevant articles in both scientific literature and grey literature. PubMed was the academic database selected for this literature review. In addition, a hand-search was carried out in several academic journals including: Nature Reviews Drug Discovery, Drug Discovery Today, the British Journal of Clinical Pharmacology, Clinical Pharmacology & Therapeutics, and the WHO Bulletin. The search strategy used for the scientific literature search in PubMed was:


To locate grey literature, websites of 7 stakeholder groups were consulted, namely: HTA organisations, pharmaceutical industry, regulatory agencies, healthcare providers, healthcare insurers/payers, and initiatives. Google Scholar was also used for the search. When an option for using a simple search engine on websites were available, this was exploited, using terms such as: “real world data”, “real world evidence”, “clinical effectiveness data”, “real world outcome”, “comparative effectiveness” or “relative effectiveness” (see table 1 in appendix 8.1.1 for a list of stakeholders whose websites were searched for grey literature).

Initially, the PubMed search yielded 353 hits while the grey literature search yielded 66 hits. Search results from both scientific and grey literature were screened according to pre-defined inclusion and exclusion criteria (see table 2 in appendix 8.1.1). Of the original 376 hits, 27 were excluded due to their date of publication being before the 1st of January 2003, 5 were excluded due to their being primarily focused on methodologies for evidence synthesis, and 306 were excluded because they did not meet all inclusion criteria (see figure 1 in appendix 8.1.1 for a diagrammatic representation of the number of search results).

A standardised data abstraction form was created in Microsoft Excel and used to locate information in the 81 documents selected after screening. The main data elements included in the data abstraction form were in the following domains:
1. General information: e.g. author(s), publication year, document type, RWD sources mentioned.
2. Policy-level information: e.g. definition of RWD, existing policies on RWD collection/use, political considerations for RWD inclusion, procedural considerations for RWD inclusion.
3. Perspectives regarding RWD: advantages, disadvantages, context for implementation of RWD.
4. Experience with RWD: practical obstacles for collection/use of RWD.
(See table 3 in appendix 8.1.1 for data abstraction form domains and elements of information)

The text extracts from articles used to populate this data abstraction form were then used for the coding step described below.

2.3 Coding Analysis

In accordance with the grounded theory approach in qualitative research (6), a coding scheme was developed based on the iterative assessment of data extracted to populate the data abstraction form in the literature reviews.

The main codes developed were:

- Definition of RWD
- Policies on RWD collection/use
- Context for RWD collection/use:
  - Actual RWD collection/use
  - Perceived RWD collection/use
- Advantages of RWD collection/use
- Disadvantages of RWD collection/use
- Practical obstacles faced in RWD collection/use
- Political considerations for incorporating RWD collection/use
- Procedural implications for incorporating RWD collection/use

For a list of all codes and sub-codes generated, please see figure 2 of appendix 8.1.1.

Coding was performed by 2 authors (AM, AW). Discrepancies in coded segments were discussed and adjusted based upon results of the discussions.

Finally, the codes were analysed to determine: the most recurrent sub-codes (i.e. the frequency with which they were mentioned) and the number of documents within which the sub-codes were mentioned. This was done in order to avoid the possibility of results being skewed by a sub-code that is repeatedly mentioned in a limited number of literature documents.

3 Results (Literature Review)

3.1 Included Documents

Of the 81 documents that initially met all inclusion criteria, 31 documents were found to contain information on less than two of the domains described above, prompting the authors to remove them from the final list of included documents. Therefore, 50 documents were ultimately included in this literature review (see table 4 of appendix 8.1.1 for a list of included documents).
For an overview of the total frequency of mention per code, please see table 5 and figure 3 of appendix 8.1.1.

For a summary of the main recurrent themes mentioned for the codes context, advantages, disadvantages, practical obstacles, political considerations and procedural implications, please refer to table 6 in appendix 8.1.1.

3.2 Definition of Real-World Data: What is (RWD)?

In 6 of the documents selected, RWD was defined as healthcare data collected outside the context of randomised controlled clinical trials (RCT’s) (7-12). The second most-mentioned definition of RWD was health-care data collected in a non-controlled, non-randomised (i.e. non-interventional) setting (12-14). In one document, RWD was defined as healthcare data exclusively collected in a non-experimental setting (15).

Examples for the types of RWD mentioned in selected documents include: non-interventional / observational studies, pragmatic clinical trials, (electronic) patient registries, (electronic) health records, administrative data, claims databases, health surveys and patient-reported outcomes (PRO’s).

3.3 Policies on RWD collection/use

**Government (UK)**

Local Service Evaluations and Clinical Audits are two legal contexts where RWD may be obtained (13). Local service evaluations are aimed at generating data on performance of local health care centres, whereas clinical audits are part of a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria.

Although there are no regulatory frameworks explicitly developed for the conduct of RWS, a collection of guidance and rules exist for the conduct of clinical trials in general to protect the dignity and well-being of patients. To begin with, all trials conducted as part of real-world projects must undergo ethical approval by the National Research Ethics Committee. In addition, RWS conducted in a primary care setting must comply with requirements of the NHS Trust Research and Development departments which are responsible for research governance within hospitals and primary care units.

In the United Kingdom, the Data Protection Act of 1998 stipulates that patient consent is mandatory to gain access to identifiable medical records. However, the National Health Service (NHS) Act of 2006 grants researcher access to identifiable patient data only in exceptional circumstances and after the approval of the National Information Governance Board for Health and Adult Social Care (NIGB).

**Government (EU)**

In the European Union, a draft version of the European Parliament’s Data Protection Regulation (DPR) has been published which will set the scene for policies on access to identifiable patient data in Europe (16). A report that was published containing proposals by the European Parliament’s rapporteur on the then current draft of the DPR, included the following statement
“processing of sensitive data for historical, statistical and scientific research purposes is not as urgent or compelling as public health or social protection”. The report also stipulates that pseudo-anonymised data could only be used without consent in cases of “exceptionally high public interest”, such as bioterrorism.

Government (USA)

The Medicare Modernisation Act 2003 saw the birth of the Agency for Healthcare Research and Quality (AHRQ), an institute devoted to conduct research on outcomes and comparative clinical effectiveness (14). Furthermore, the American Recovery and Reimbursement Act (ARRA) of 2009 witnessed the donation of 1.1 billion U.S. Dollars to comparative effectiveness research (CER) (10). It is under this collection of mandates that RWD is often collected; whether by government initiatives such as the Centre for Medicare and Medicaid Services (CMS) or the Blue Button Initiative of the Department of Veteran Affairs (VA) (17), or by providing funds to healthcare providers for RWD collection through the Health Information Technology and Clinical Health Act (11). Furthermore, some states are creating all-payer claims databases (APCD) which require healthcare insurers, Medicaid, self-funded large employer coverage plans and other health care payers to make their claims data available to state government. This has been implemented in 19 states, and 21 are considering laws to do the same (17).

It is important to note that the AHRQ cannot base its conclusions solely on CER evidence, but must consider a comprehensive evidence base (18). Moreover, non-RCT data such as observational studies data is perceived as being of lower quality in comparison to other data sources in the hierarchy of evidence adopted by the AHRQ (19).

Access to RWD such as electronic health records or administrative claims data varies on a federal level between institutions and from state to state as well. Longstanding federal laws of the Department of Health (DoH) prohibit access to Medicare data available to CMS by entities with “commercial interests” (7;17;20). In addition, the VA generally releases data only to investigators with VA affiliation, rather than to entities outside of the VA, due to potential issues with re-identification of patients from anonymised data (17). On the other hand, Massachusetts, a state with a high degree of transparency and data access for researchers, makes de-identified patient data available to researchers under a data use agreement (11).

Health Technology Assessment (HTA) Agencies

HTA agencies generally refer to a comprehensive evidence base that combines data from several sources when assessing the clinical effectiveness of health interventions. Therefore, non-RCT evidence is also considered when performing health technology assessments (21-23). Please see citation 1 below for an example of this. Moreover, in instances when there are uncertainties regarding the safety and effectiveness of new medications, additional RWD may be requested at the time of initial reimbursement which would need to be collected within an agreed-upon time period. The collected RWD would then be used for reassessment of clinical effectiveness at the end of this period (23;24). These arrangements are often classified as Market Access Agreements (MAA’s), Coverage with Evidence Development (CED) schemes, or Payment for Performance (P4P) schemes (25;26). Please see citation 2 for an example of such guidance.
Citation 1: “Consideration of a comprehensive evidence base is fundamental to the appraisal process. Evidence of various types and from multiple sources may inform the appraisal. To ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and analysis, and their interpretation, are of the highest standard and are transparent. The evaluation of effectiveness requires quantification of the effect of the technology under appraisal and of the relevant comparator technologies on survival, disease progression and health-related quality of life so that this can be used to estimate QALYs.” – NICE, 2013 (22)

Citation 2: “Health care in the insured package must comply with the ‘established medical science and medical practice’ criterion. This criterion demands a black-and-white answer; however, sometimes having the room to say ‘yes, providing’ would be desirable. This would make it possible to reimburse health care that does not fulfil the statutory criterion, on condition that data are collected about the effectiveness of that care. Conditional reimbursement can promote the collection of data and provide patients with access to potentially valuable care. As of 1 January 2012 the Minister of VWS made conditional reimbursement possible and opted for conditional entry to the basic package instead of conditional reimbursement outside the package.” – ZIN, 2012 (27)

Several HTA agencies adhere to a hierarchy of evidence that places non-RCT data, such as observational studies data, at a lower level than RCT data (23;24;28). As a result, RWD is regarded as inherently being of lower quality thus conclusions made based on RWE are regarded as more circumspect. Clinical effectiveness is thus rarely solely determined on the basis of RWE (21-23;28). Causality is also not determined on the basis of RWE. Please see citations 3-5 below for examples.

Citation 3: “A level of scientific evidence (HAS grading scheme) is allocated to each study. Level of scientific evidence (Levels I to IV)
I- High powered randomised controlled trials, meta-analyses, decision analyses.
II- Low powered randomised controlled trials, or non-randomised trials, cohort studies.
III- Case-control studies.
IV- Retrospective studies, case series, descriptive epidemiological studies, and controlled trials with bias.” – HAS, 2007 (24)

Citation 4: “The highest evidence level is allocated to RCTs and systematic reviews of RCTs, at least within the framework of therapeutic studies. In some classifications, individual RCTs are further graded into those of higher or lower quality. In this context, the conflation of the quality of concept and the quality of results has been criticized by some authors. The next levels include non-randomized intervention studies, prospective observational studies, retrospective observational studies, non-experimental studies (case reports and case series) and, at the lowest evidence level, expert opinions not based on scientific rationale. The Institute will adapt this rough grading system to the particular situation and research question and, if necessary, present it in more detail.” – IQWiG, 2013 (28)

Citation 5: “The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and end point occur more commonly in non-randomised studies and non-controlled trials than in RCTs... Inferences will necessarily be more circumspect about relative treatment effects drawn from studies without randomisation or control than those from RCTs. The potential biases of observational studies should be identified, and ideally quantified and adjusted
for. When possible, more than 1 independent source of such evidence should be examined to gain some insight into the validity of any conclusions.” – NICE, 2013 (22)

It is important to note that all guidance provided by HTA agencies does not dictate what sort of RWD data should be collected, the RWS design, the data collection tools to be used, or the statistical analysis methods to be used. However, HTA agencies will consult with applicants on the scientific questions that need to be addressed by RWS and the best strategies/study designs to collect such data.

Pharmaceutical Industry

Several companies realise the value of RWD throughout the product development lifecycle and have made statements in that regard (14;29-31). In addition to this, companies publish the results of completed and ongoing clinical trials in the public domain as a matter of policy (29;30).

No further documents were found published that explicitly outline company policies relating to the use of RWD. However, it is worth mentioning that several articles have been published by employees of industry stakeholders relating to best practices in methodology for using RWD (32-36).

Regulatory Agencies (RA)

In Europe, the UK and the USA, regulatory agencies are legally entitled to request post-marketing commitments from marketing authorisation holders if doubts exist regarding the safety and efficacy of their products (37-40). Such commitments can comprise a set of several different activities; for example, the market authorisation holder may be requested to set up a patient registry to monitor long-term safety of their product, conduct a post-authorisation safety study or post-authorisation efficacy study. Please see citations 6 and 7 below for examples.

Citation 6 – “Article 22: The Agency, acting in close cooperation with the national pharmacovigilance systems established in accordance with Article 102 of Directive 2001/83/EC, shall receive all relevant information concerning suspected adverse reactions to medicinal products for human use which have been authorised by the Community in accordance with this Regulation. Where appropriate, the Committee for Medicinal Products for Human Use shall, in accordance with Article 5 of this Regulation, draw up opinions on the measures necessary. These opinions shall be made publicly accessible. The measures referred to in the first paragraph may include amendments to the marketing authorisation granted in accordance with Article 10. They shall be adopted in accordance with the procedure referred to in Article 87(3). The holder of the marketing authorisation and the competent authorities of Member States shall ensure that all relevant information concerning suspected adverse reactions to the medicinal products authorised under this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation. Patients shall be encouraged to communicate any adverse reaction to health-care professionals.” Regulation EC 726/2004 (41)

Citation 7 – “Under section 505(o)(3) of the Act, FDA will require applicants to conduct a postmarketing study or studies or clinical trial(s) when the following conditions are met:
1. When the decision to require a postmarketing study or clinical trial is based on scientific data deemed appropriate by FDA, including information regarding chemically-related or pharmacologically-related drugs; and
2. When FDA has found —
   a. before requiring a postmarketing study, that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) will not be sufficient to meet the purposes described in condition 3 below; and
   b. before requiring a postmarketing clinical trial, that a postmarketing study will not be sufficient to meet the purposes in condition 3 below; and
3. When the purposes of the study or clinical trial, as described in section 505(o)(3)(B), are one or more of the following:
   • To assess a known serious risk related to the use of the drug
   • To assess signals of serious risk related to the use of the drug
   • To identify an unexpected serious risk when available data indicates the potential for a serious risk” – FDA, 2011 (39)

Regulatory agencies provide guidance for the conduct of studies to address phase IV commitments, which provide recommendations for the design and implementation of post-marketing studies (39;42;43). This guidance also refers to other guidelines for good practices generated by recognised pharmacoepidemiology societies, such as the International Society for Pharmaceutical Engineering (ISPE) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (42;44). Please see citation 3 below for an example.

It is important to note that such guidance does not dictate which specific study designs, data collection tools, or statistical analysis methods should be used. Instead, they provide general principles for the implementation of these steps. Please see citation 8 below for an example.

Citation 8 – “FDA does not endorse a specific type of study design for pharmacoepidemiologic safety studies that use electronic healthcare data because the choice should be made uniquely in the context of the drug, the safety issue, and the specific hypotheses of interest. Investigators should first establish the study questions of interest and then determine which data source(s) and design are most appropriate to address these questions. Investigators should discuss their rationale for selecting a particular study design in the study protocol and final report.” – FDA, 2013

3.4 Context for RWD collection/use

3.4.1 Actual context for RWD collection/ use (Literature Review)

RWD collection and use for reimbursement activities, such as relative effectiveness assessment, risk-sharing agreements and pharmacoeconomic analysis was the most noted actual context. A highly recurring theme was collection of RWD in the context of comparative effectiveness research and relative effective assessment (8-10;12;15;17;19;29;31;36;45-49). As payer’s demand for knowledge on drug utilisation studies, real-life safety and clinical effectiveness to inform payment decision increases, so does the need for RWD. This evidence, in turn, helps payers to “better understand the outcomes of various treatments and only pay for those which are most beneficial to society” (49). Such a role for RWE is quite prominent with conditional
reimbursement, according to several authors (12;47-50). Alternatively, RWD can also play a role in pharmacoeconomic modelling of health interventions by providing valuable input on costs, resource use and utility values. (8;12;14;15;19;22;31;45;47;51).

The second most recurring actual context for RWD collection and use was for regulatory activities. The theme most frequently mentioned within this context relates to the role of RWD in fulfilling post-marketing commitments. For example, RWS can be designed to collect information on long-term safety and effectiveness as part of phase IV, post-marketing safety and pharmacovigilance commitments (8;8;10;11;13;15;17;21;29;47;52). RWS can also demonstrate compliance of prescribing patterns in populations approved in marketing authorisations or adherence to national guidance. In some cases, they can also inform a need for treatment pathways, or license extension to a new indication or treatment population (8;13;47).

Collection and use of RWD during drug development was the third most-mentioned actual context (7;8;10;12;13;17;31;45). RWD is used, amongst other things, to help drug developers study the natural history of disease, define patient populations for clinical trials, standardise outcome measurements, define sub-populations for treatment, understand treatment patterns both pre- and at product launch, and, as previously-stated, long-term safety and effectiveness outcomes.

Another context that received equal mention was the use of RWD in drug utilisation studies to investigate, for example, drug dosing in clinical practice, patient compliance, standard of care and treatment flows in different clinical contexts (8;12;14;15;17;29;31).

3.4.2 Perceived context for RWD collection/ use (Literature Review)

The most noted perceived role of RWD was for informing appropriate use of health interventions, allowing for the delivery of the “right medication, to the right patient, at the right time” (7;9;11;36;46;53-55). This can occur by tailoring of treatment pathways to specific sub-populations or disease states on the basis of RWE (11;36;55), or by providing patients with possibilities to manage their own treatment based upon RWE (9;54).

The second most noted perceived context for RWD collection and use was drug development; whether by aiding drug developers in understanding natural history of disease (12;13;19), identifying patient sub-populations with higher benefit-risk profiles (7), or identifying novel disease relationships and therapeutic targets (11;45).

The third most mentioned perceived context relates to use of RWE in either medical adaptive pathways to patients (also known as adaptive licensing (52)) or exceptional marketing authorisation approaches, such as accelerated approval in the United States of America or conditional marketing authorisation in the European Union (2;9;45;52).

3.5 Advantages of RWD collection/use

The external validity (i.e. generalisability) of RWD was the most recurring advantage (8;9;12-15;18-20;31;36;43;45;46;56-61). Owing to the fact that RWS are conventionally conducted in a non-RCT setting, they have more relaxed inclusion and exclusion criteria for trial subjects, often no randomisation or treatment allocation procedures and are thus more representative of
Routine clinical practice. In addition, RWS conventionally include a larger, broader study population than RCT’s, implying that they are sufficiently empowered to significantly capture heterogeneity of treatment effects in clinical practice (8;13;15;19). RWS are also often conducted over a longer time horizon than RCT’s and as such their results can be more accurately extrapolated to future effects when compared to RCT results (8;57).

The ability of RWD to address knowledge gaps presented by RCT-generated evidence was the second most recurring advantage (7;12;13;18-20;43;45;47;62). For example, pragmatic clinical trials by design can be used to identify drug-drug interactions, overdosing or other forms of inappropriate use of medications (47). RWE is also a valuable source of safety and effectiveness data in exceptional circumstances where RCT’s are not ethical (e.g. narcotic abuse) or feasible (e.g. for the urgent reimbursement of a novel medication to treat a life-threatening disease) (19). In more general terms, the generalisability of results of RWE contributes to filling what has become to be known as the “efficacy-effectiveness gap”, defined by Eichler et al as “the observed discrepancy between effects of a health intervention in routine clinical practice as compared with the effects demonstrated in randomised controlled clinical trials.” (2;12;18).

The third most mentioned advantage is the ability of RWD to allow for assessment of long-term effects and rare serious adverse effects, owing to the larger number of patients for whom data is conventionally available and the wider range of health outcomes measured when compared to RCT’s (8;12;14;15;19;39;45;52;59-62). For instance, van Staa et Klungel refer to a recent safety study on cancer risks of patients initiating different classes of anti-diabetic medication using data from the Clinical Practice Research Datalink (CPRD) (63). They also refer to the use of electronic health record data for the prospective prediction of long-term risk; more specifically, the development of the QRISK score to predict the 10-year risk for cardiovascular disease (64).

It has been noted in several documents that collection and use of RWD allows for timely generation of valuable evidence (7;9;11;13;14;15;31;49). In fact, the use of automated outpatient pharmacy data, electronic health records by physicians, and applications on smartphones by patients, can provide real-time health data (7;9;14;49). This significantly reduces the time needed to gather sufficient RWD for relative effectiveness studies (11;49). Moreover, several authors mentioned that the use of electronic health records, pragmatic clinical trials, claims databases and existing patient registries for RWD generation is more cost-effective in comparison to setting up RCT’s (11;13-15;31;45). For example, the European Alliance for Personalised Medicine (EAPM) refer to the company Handle my Health which has the ability to aggregate patient data from multiple health smartphone applications (“apps”) into one data packet before sending it to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom for real-time verification of data, potentially in the context of early access to medicines schemes (9). Another example concerns the recently-published findings of a RWS by PatientsLikeMe, demonstrating that lithium did not affect amyotrophic lateral sclerosis. RWD for this study was self-generated by patients of the PatientsLikeMe community and preliminary results were published in peer-reviewed journal after only 9 months from study initiation (65).

3.6 Disadvantages of RWD collection/use

The liability of RWD to different form of biases (i.e. selection bias, information bias and confounding bias) was the most recurring disadvantage mentioned (1;12;14;15;18;19;22;28;31;36;43-45;47;48;55;58-62). Selection bias, defined by Delgado-
Rodriguez et Llorca as “the error introduced when the study population does not match the target population” (66), occurring due to the conventional absence of randomisation of patients in RWS was the kind of bias that was most frequently associated with RWD (12;14;18;19;31;36;43;44;59-61). One relevant example of how selection bias can lead to incorrect conclusions is the survivor treatment selection bias in observational studies on anti-HIV therapy (67;67-69). Typically in anti-HIV studies, correlation of longer patient survival with the treatment in question is mistakenly interpreted as evidence that treatment prolongs survival. However, it is the fact that patients who survive longer have more time and opportunities to decide on beginning treatment or gain access to treatment that leads to such a correlation.

Several authors went on to indicate that, as a result of biases, the determination of causality based on RWD should be done with caution (1;12;14;19;36;58;60;61). Others indicated that it might be impossible to determine causality from RWD, despite the presence of statistical methodologies to adjust for known and unknown confounders such as matching, propensity scoring, sensitivity analysis and prior event rate ratios (47;62).

The poor quality of RWD available was the second most frequently mentioned disadvantage (7;10;12;14;15;19;31;36;43;45;48;49;51;54;56). Incomplete or missing data was the specific disadvantage highlighted in relation to poor quality of RWD (10;12;14;15;19;31;36;43-45;48;49;51;54;56). This pertained to, among other things, databases with incomplete information (“gaps”) on certain collected elements, the absence of outcomes representing “mild” outcomes, or missing lab data (14;43). The phenomenon of incomplete data can be related to the type of healthcare database; for instance, claims databases inherently lack information on clinical disease severity and lifestyle habits (15). On the other hand, electronic healthcare records may also have data gaps on clinical outcomes or have incorrectly-coded medical diagnostic information (45).

On a similar note, several authors have noted that despite the presence of many different sources of RWD, such as electronic healthcare records and administrative claims databases, the majority of these databases have not been established to collect information for research purposes. For example, EHRs capture data on symptomatic outcomes of interest, but have little information on mild symptoms. Researchers therefore need to remain aware of different types of data sources and their corresponding limitations when initiating RWS’s (7;12;15;31;43).

Another important disadvantage that received little mention is the availability of RWD and RWE at the time of important decision-points in the product lifecycle (12;14;47). For instance, at the stage of reimbursement, payers often require data on the real-world relative effectiveness of new interventions that is usually not yet available for pharmaceutical industry.

### 3.7 Practical obstacles faced in RWD collection/use

Limitations related to policies on RWD collection or use was the most recurring practical obstacle (7;9-11;13;15;17;19;31;36;43;48;51;55;56;59;70;71). The obstacles specifically related to restrictive policies on RWD data access, and the lack of standard policy regarding patient data privacy/confidentiality. A couple of important examples of policies restricting access to RWD are those of the Centre for Medicare and Medicaid Services (CMS) and the recent European Union (EU) proposal for General Data Protection Regulation (DPR). The CMS, by policy, denies any entities with “commercial interests” access to patient data, which ultimately forbids...
pharmaceutical industry from being able to access Medicare and Medicaid data for real-world research (17). On the other hand, a report that was published containing proposals by the European Parliament’s rapporteur on the then current draft of the DPR, included the following statement “processing of sensitive data for historical, statistical and scientific research purposes is not as urgent or compelling as public health or social protection”. The report also stipulates that pseudo-anonymised data could only be used without consent in cases of “exceptionally high public interest”, such as bioterrorism. Once again, this has negative implications on access to RWD for researchers from several stakeholder groups (16). This will be further discussed in the following section (political considerations for incorporating RWD collection/use).

The lack of standardization of RWD collection methods and definitions of terms, as well as the lack of harmonization (regionally and internationally) of required RWD data was the second most frequently mentioned practical obstacle (7;9;10;12;31;45;47;51;52;55-57;62;71;72).

Costs, both monetary and non-monetary, were the third most-mentioned practical obstacle to implementing the collection and use of RWD. The costs required for setting up the required infrastructure for prospective RWS is substantial (11;12;14). Moreover, purchasing the licenses to gain access to available RWD can also be prohibitive (7). In addition to this, many organizations internally lack the capacity to conduct RWS; a lot of time must be invested in training of staff regarding data collection methods, set up sophisticated IT systems for data capture and analysis, and external partnerships are often required to complete such projects (10-12;14;44;44;45).

3.8 Political considerations for incorporating RWD collection/use

Aspects relating to governance and accountability of RWD collection and use were the most recurrent political consideration. Firstly, several authors raised the issue of the lack of clear policy on which stakeholder(s) is/are responsible for RWD collection and RWE generation; to what extent should both public and private sectors be involved with funding, implementing RWD collection, and analysing it? (14;18;19). Secondly, bearing in mind the comparative nature of many RWS’s, who subsequently has the right to communicate and disseminate findings of RWE? Should such a communication and dissemination strategy be pre-defined as part of the RWS research contract? (42;44;47;70). The most repeated theme was that of policies on access to RWD. Authors highlighted that public and private sectors alike should develop, or adapt existing policies to, among other things: clarify rights to intellectual property, clearly define and address current policies on terms for access to RWD already available through data programmes/initiatives, and determine how access to data is to be practically implemented (7;9;11;13;17-20;42;45;49;55;70). Finally, patient data privacy and confidentiality also received notable mention by several authors. Policies should address: who has access to patient-level data, circumstances that necessitate the anonymisation of patient-level data, and the risk for re-identification of patients despite anonymisation of patient-identifiers (e.g. in a specific, limited population such as veterans or orphan diseases patients) (7;11;17;19;20;44;45;48;73).

The second most recurrent political consideration refers to the need for increased collaboration among stakeholders on a number of issues (7;9-11;13;17;19;31;36;47;49;52;61;71). Firstly, authors have stated that agreement must exist between HTA agencies and regulatory agencies as to evidence requirements RWD should fulfil; phase IV, post-marketing studies conducted for regulatory purposes can provide very useful insights for questions on relative effectiveness relevant for reimbursement decisions. Therefore, more dialogue needs to take place on harmonizing data needs from these two stakeholder groups. Secondly, authors also state that key
stakeholders (patients/patient organizations, regulatory agencies, HTA agencies, pharmaceutical industry, payers/insurers and academia) should come together as co-designers of projects when identifying RWE requirements and designing RWS’s.

Ambiguity regarding the applicability of RWE to decision-making was the third most mentioned political issue. Due to several factors such as the lack of consensus among stakeholders on the value of RWE and lack of guidance on using RWE in decision-making, ambiguity remains on how RWE should be used decision-making processes (9;10;12-15;60).

Receiving notable mention was the presence of a cultural barrier against the use of RWD. This mainly refers to the adherence of certain stakeholders to the hierarchy of evidence, which stipulates that RCT’s are the most reliable sources of data. As a result of adherence to such a hierarchy of evidence, RWE is automatically regarded as being of lower quality, thus of lower value in decision-making. Although this perception is beginning to change, it remains an important political barrier to RWE adoption (12-15;60).

3.9 Procedural implications for incorporating RWD collection/use

Harmonisation and standardization of tools and methodologies for RWD collection and analysis was the most-mentioned procedural consideration. This included standardizing terminology and definitions of common terms, coding of outcomes and diseases, tools for data capture, as well as statistical methodologies for data analysis. Additionally, the need for guidance development for RWD collection and analysis was significantly mentioned. (7;9;11-14;19;36;43;45;47-49;54;57;72;74).

The second most mentioned procedural consideration relates to the educational and infrastructural needs for collecting and using RWD. (7;9;10;14;15;19;20;36;45). For example, considerable effort first needs to be invested to set up an informatics platform for data acquisition in healthcare institutions, data warehouses need to be established for data storage, and tools for efficient and detailed analysis of such data need to be developed. Moreover, RWD collectors, both researchers in the context of RWS or physicians in the context of clinical practice, should be adequately trained to do so.

Data linkage was the third most-mentioned procedural consideration. Several authors mentioned the need to link data of the same type (e.g. from EHR’s, administrative claims databases, or mobile health applications) but from different sources (e.g. different databases, different countries) together, thus allowing for greater patient study populations, comprehensiveness and continuity of coverage when analysing patient-level data (7;9;31;43;45;49). Other authors have emphasized the need for linkage of data from different RWD sources, such as EHR’s and claims databases, to allow for the use of multiple data sources to investigate research questions (11;15). This way, weaknesses of one type of RWD can be complemented by the strengths of another.

4 Methods (Stakeholder Interviews)

This research aimed to gain insights into the policies and perspectives of relevant stakeholder groups regarding the use of RWD in the processes of drug development and clinical effectiveness assessment. To do so, semi-structured interviews with selectively-sampled stakeholders were conducted.
4.1 Stakeholder Groups Identification

For the purposes of the IMI-GetReal consortium, 8 relevant stakeholder groups were identified as being important for the achievement of its aims, namely: Health Technology Assessment (HTA) agencies, pharmaceutical industry, regulatory agencies, academia, healthcare providers, healthcare insurers/payers, patient organisations and initiatives using, or commissioning research on, RWD.

4.2 Semi-structured Interviews

Stakeholders from the 8 previously-highlighted stakeholder groups (both IMI-GetReal partners and external stakeholders) were selected and invited via e-mail to participate in semi-structured interviews to provide their perspectives on RWD. Tailored questionnaires were developed per stakeholder group and sent to participants who agreed to take part prior to the interview (see appendix 8.2.2 for stakeholder-specific questionnaires).

The interviews were held over the telephone and lasted 60-90 minutes. With consent of participants, the interviews were recorded and transcribed. Transcripts generated were used for the coding step described below.

A summary of the interview was generated and sent to interviewees in order to verify whether the author’s interpretations of the interviewees’ answers were correct.

The sampling of stakeholders and interview protocol were compared to the consolidated criteria for reporting qualitative studies (COREQ) (75) to ensure good quality.

4.3 Coding Analysis

In accordance with the grounded theory approach in qualitative research (6), a coding scheme was developed based on the iterative assessment of transcripts of interviews. The main codes formulated were:

- Definition of RWD
- Policies on RWD collection/use
- Context for RWD collection/use:
  - Actual RWD collection/use
  - Perceived RWD collection/use
- Advantages of RWD collection/use
- Disadvantages of RWD collection/use
- Practical obstacles faced in RWD collection/use
- Political considerations for incorporating RWD collection/use
- Procedural implications for incorporating RWD collection/use

Sub-codes were similarly generated based on the grounded theory approach (please see figure 4 in appendix 8.2.1 for the detailed coding schemes).

Coding was performed by 2 authors (AM, AW). Discrepancies in coded segments were discussed and adjusted based upon results of the discussions.
Finally, the codes were analysed to determine: the most recurrent sub-codes (i.e. the frequency with which they were mentioned) and the number of stakeholders by whom the sub-codes were mentioned. This was done in order to avoid the possibility of results being skewed by a sub-code that is repeatedly mentioned by a limited number of stakeholders.

5 Results (Stakeholder Interviews)

5.1 Overview of Interviews

Interviews with 19 different stakeholders were conducted spanning 7 of the 8 stakeholder groups: HTA agencies, pharmaceutical industry, academia, regulatory agencies, healthcare payers/insurers, patient organisations, and initiatives (see table 7 in appendix 8.2.1 for the number of stakeholders per group and the number of interviewees per stakeholder). Healthcare providers were approached for interviews, yet did not indicate their interest to participate within a time-span feasible for the completion of this deliverable.

It is worth noting that of the 19 interviews mentioned, the first 5 were conducted as pilot interviews, meaning that interviewees were asked to provide their feedback and comments regarding the interview protocol.

For an overview of the frequency with which main codes were mentioned, please see table 8 and figure 5 in appendix 8.2.1.

For a summary of the main recurrent themes mentioned for the codes context, advantages, disadvantages, practical obstacles, political considerations and procedural implications, please refer to table 9 in appendix 8.2.1.

5.2 Definition of Real-World Data: What is (RWD)?

Approximately half of interviewed stakeholders defined RWD as healthcare data collected outside the context of randomised controlled clinical trials (RCT’s) conducted for, for example, phase 3 regulatory studies.

The second most-mentioned feature of RWD is observational health-care data collected in a non-interventional, non-randomised setting, i.e. from routine clinical practice.

Examples for the types of RWD mentioned in semi-structured interviews include: non-interventional / observational studies, pragmatic clinical trials, adaptive clinical trials, bridging studies, (electronic) patient registries, (electronic) health/ medical records, patient diaries, administrative data, claims databases and health surveys. Several stakeholders explicitly stated that patient-reported outcomes (PRO’s) and supplements to RCT trials cannot be considered as RWD sources.

It is important to note that definitions and types of RWD provided by stakeholders sometimes varied greatly. While some were still exploring the dimensions of what does or does not encompass RWD, others had formulated specific operationalised definitions. This can be demonstrated by some examples of the range of ideas expressed by the following stakeholders when asked to provide their definition of RWD:
“It is not a term that I am very familiar with at all, to me RWD probably means data coming from an experiment, some description whether it’s a survey or a RCT or systematic review.” – Initiative A

“Well I think any information that is collected wherever that might be. And I would think that that would be everything from, notes on a patient record or data which is collected by a health practitioner in a record system and then there is data that is gathered in like a hospital system, summaries, coding for payments and reimbursement” – Patient Organisation B

“To me the term RWD is about the scientific process. So I think of it as a step that isn’t done in a RCT. So it is a definition by exclusion. It 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 B

“We base our definition on the ISPOR criteria. In simple terms we are looking at data that are collected outside of the conventional randomized clinical trial, including survey, administrative, electronic medical record, pragmatic clinical trials, observational studies, and registries. We do not focus so much on patient report outcomes or piggybacking instruments onto RCTs as part of our definition, nor scope, for RWD.” – Pharmaceutical Industry B

5.3 Policies on RWD collection/use

HTA Agencies: Three of the five HTA agencies interviewed asserted that they can consult with applicants on the following RWD-related aspects: the scientific questions to be answered by RWD, the design of studies generating RWD and the data collection strategy. What HTA agencies would not do, however, is explicitly stipulate the type of RWD that should be collected (e.g. patient registry data, or electronic health record data).

Policies for request of data varied considerably:

- One stakeholder draws up binding legal contracts for RWD data collection
- One stakeholder always demands national RWD for economic assessment of intramural drugs. On the other hand, RWD for assessment of therapeutic effectiveness is not obligatory, and need not be national.
- One stakeholder always demands information on study design and methods for data collection when appraising data from observational studies.
- One stakeholder maintains a stance of tolerance to RWD but does not directly ask for its submission. The organisation asks for all data on a given technology (e.g. in single technology assessments) which would inevitably include RWD, especially in calculating costs related to use of the technology.

One stakeholder referred interviewers to two guidelines published by the organisation that relate to RWD. The guidelines outline steps for design of studies and how data resulting from such studies would be analysed during re-assessment of the relative effectiveness of the technology. Another stakeholder referred to one guideline that includes three paragraphs on non-randomised evidence (thus potentially RWD) and how it would be appraised by the HTA committee.

Results from the interview indicate that the acceptability of RWD for decision-making remains
controversial: available guidelines often clearly state that non-RCT evidence will be regarded circumspect, implying that RWD would have a lower impact on decision-making.

All decisions on health interventions made by HTA agencies, whether influenced by RWD or not, are published in the public domain as a matter of policy.

**Pharmaceutical Industry:** All four stakeholders interviewed asserted that RWD was routinely collected for the majority of products belonging to their organisations. Typically, RWD use and engagement in its collection occurs during drug development and as part of post-marketing commitments or risk-sharing agreements. One stakeholder added that use of existing RWD sources (e.g. electronic medical records and claims data) is first made before de novo data collection is begun. This de novo collection then aims to address gaps in current RWE available.

It is standard policy according to all industry stakeholders interviewed to attempt to publish the findings from RWS in the public domain. One stakeholder added that though observational studies on their own products are always published, there are stricter organisational policies regarding publication of RWE of comparative nature. On the other hand, it is organisational policy to attempt to publish RWE on disease pathways, burden of disease or standard of care in the public domain, since this would offer a peer-reviewed evidence base for future modelling. Another stakeholder also attempts to register RWS that involve their products on clinicaltrials.gov.

**Regulatory Agencies:** As is the case with HTA agencies, regulatory agencies can consult with applicants on the scientific questions that need to be answered by RWD, the study designs of the corresponding trials and the data collection strategy. Regulatory agencies will not stipulate the type of RWD to be collected.

Guidelines published by regulatory agencies that relate to RWD generation are mainly those that provide guidance on post-marketing commitments. One stakeholder referred to guidelines for post-marketing RWD studies and drug utilisation studies published by their organisation. This stakeholder also added that new policies and guidance specifically addressing RWD should begin to emerge as discussions regarding adaptive pathways to medicine authorisation (also known as “adaptive licensing” or “medicine adaptive pathways to patients (MAPP’s)” (S2)) and reimbursement continue to evolve.

**Academia:** All three stakeholders interviewed expressed that it was standard policy to attempt to publish the finding from studies involving the collection and analysis of RWD in academic literature. However, the stakeholders also explicitly mentioned that they otherwise do not have any direct policies addressing the collection and use of RWD.

**Healthcare insurers/payers:** According to the stakeholder interviewed in this group, RWD is systematically collected by the organisation across all members of the public health insurance scheme. As is the case with HTA agencies, this stakeholder can consult with the applicant regarding the design of the study and the scientific questions that need to be addressed to prove relative effectiveness. Eventually, however, the choice of the study design and methodologies for data analysis are left at the discretion of the applicant. The stakeholder can, if needed, provide the applicant with access to RWD data collected by their organisation to conduct the studies.
Patient organisations: The two stakeholders interviewed were not directly involved in the collection or use of RWD, and as such did not have explicit policies in that regard. However, both stakeholders participated in discussions on the design and set-up of studies collecting RWD with the aim of representing and protecting patient interests.

Initiatives: One of the two stakeholders interviewed indicated that findings from studies collecting RWD are ultimately published either in the public domain or academic literature. However this publication can be delayed due to the time needed for a political entity to reach a decision based upon the study findings submitted. Moreover, it is standard policy that this stakeholder will review all protocols for the commissioned RWS before its initiation. The second stakeholder was not directly involved in commissioning or conducting real-world studies, and as such did not have explicit policies in that regard.

Healthcare providers: There is little information in this report on policies for RWD use/collection for this stakeholder group, owing to the fact that no stakeholders agreed to participate in the timeframe of the project as well as the absence of documents on stakeholders’ policies on RWD.

5.4 Context for RWD collection/use

5.4.1 Actual context for RWD collection/use

RWD collection and use for the purposes of reimbursement activities was the most recurring context. More specifically, the majority of HTA and industry stakeholders repeatedly indicated that RWD played a notable role in the following three areas:

1. As input on effectiveness in relative effectiveness assessments (REA’s). RWD is used as part of REA modelling or to support models. For example, a combination of RWD and RCT is used to conduct indirect treatment comparisons (ITC’s). Alternatively, RWD is used to model natural history of a disease, which is subsequently applied to relative effectiveness estimated from RCT’s.

2. As input for pharmacoeconomic (PE) modelling. According to one stakeholder, this is particularly relevant for medicines with high budget impact. RWD plays a role in both cost (resource use) and effectiveness data (establishing effectiveness in the control arm of the model, or assigning utility values to health states based upon findings from observational data).

3. Conditional reimbursement, especially at the stage of re-assessment of relative effectiveness.

RWD collection and use during early drug development was the second most recurring context. According to industry stakeholders, RWD is useful to study the natural history of disease, namely to define patient populations, different health states, and disease progression. In addition, RWD provides information on local treatment pathways, both in early drug development and before product launch. This helps to provide valuable insight into potential channelling bias and confounding by indication for comparators, as well as potential channelling biases occurring after product launch. Moreover, RWD is used to assess effectiveness of licensed alternative health interventions in order to provide information on patient populations or unaddressed health needs.

RWD collection and use for regulatory activities was the third most recurring context, being cited
by the majority of industry and regulatory agencies stakeholders. The theme that was most notable under this code was RWD collection in the context of fulfilling post-marketing commitments to address uncertainty over safety and efficacy triggered by, for example, safety signals in RCT’s. This data collection almost always falls in the scope of mandatory requirements by national regulatory agencies for post-marketing safety and pharmacovigilance data. One stakeholder also mentioned that additional data could alternatively be collected to serve other purposes; for example, to provide basic epidemiologic data on disease prevalence, or validate assumptions made in pharmacoeconomic models.

### 5.4.2 Perceived context for RWD collection/use

The perceived role for RWD in drug development was the most noted context. There was a specific focus on two themes, namely the use of RWD to study natural history of disease and the importance of findings from RWD analysis to inform the design of phase 3 trials. For example, RWD can help to better define disease states and stratify trial populations accordingly, inform choice of comparators, define health outcomes to be measured and map out the network for relative effectiveness of available comparators.

The use of RWD to forecast the clinical effectiveness of new health interventions was the second most recurring context. For example, some stakeholders indicated that findings from meta-analysis of RCT results can be adjusted to a different population baseline (assuming that relative effectiveness estimates are robust to variance in population characteristics). As previously mentioned, RWD can contribute to modelling of cost-effectiveness, both by providing potential resource use costs or utility values for different disease states.

The third most recurring context relates to the perceived use of RWD in analysing real-world utilisation patterns of health interventions. For example, several stakeholders highlighted the ability of using RWD to thoroughly study adherence to health technologies, which would consequently allow for predictive modelling to forecast acceptance of a new health technology.

### 5.5 Advantages of RWD collection/use

The external validity (i.e. generalizability) of RWE was the most frequently mentioned advantage. Some stakeholders indicated that RCT’s have strict inclusion and exclusion criteria so results generated do not represent safety and effectiveness of the treatment on the broader population exposed to a specific treatment in clinical practice, which might include patients with co-medications or co-morbidities. They indicated that on the other hand, RWE is derived from clinical practice, allowing for more accurate determination of real-life effectiveness of health interventions in a given population and extrapolation beyond this population. Other stakeholders added that RWE might also allow for transferability of relative effectiveness estimates between different countries or regions.

“There is clearly a purpose and a benefit from using RWD, in terms of completing the label of a new drug or a new indication because you’re much more inclusive; you include patients with co-morbidities or co-medications, so you can use the data generated there to augment or improve labelling, for example. So the prescriber out there gets more accurate and more complete information about a new drug or new indication. So the added benefit is clearly completeness of a wider and more inclusive population” – Regulatory Agency B
The ability of RWD to address the knowledge gaps presented by RCT-generated evidence (i.e. address scientific questions that cannot be answered by RCT’s) was the second most-mentioned advantage of using RWD. Several stakeholders referred to RWE’s benefits in addressing the efficacy-effectiveness gap, defined by Eichler et al as the observed discrepancy between effects of a health intervention in routine clinical practice as compared with the effects demonstrated in randomised controlled clinical trials (2). Stakeholders also emphasized that RCT’s are conventionally too short to capture long-term adverse effects and long-term therapeutic effects of health interventions. In contrast to this, observational studies and large simple trials, both examples of real-world studies, can provide critical information on long-term and rare effects of interventions.

5.6 Disadvantages of RWD collection/use

Due to the fact that RWD is conventionally collected in a non-randomised setting, the majority of stakeholders mentioned that RWD is subject to the three main categories of bias (selection bias, information bias and confounding bias). As a result, large uncertainties in findings based upon RWD can prevent establishment of causality from RWE. In addition, several stakeholders mentioned that with some sources of RWD, such as registries, there is often no control group against which absolute effectiveness can be determined. The lack of blinding in pragmatic clinical trials can also lead to detection bias. Moreover, the absence of random assignment of patients to treatments in most RWS, in contrast to RCT’s, implies that RWD is liable to confounding bias; an important factor that must be kept in consideration when using RWE to estimate relative effectiveness of interventions. One stakeholder mentioned that although individual patient data can help account for confounding bias, it cannot help adjust for other forms such as detection bias or attrition bias. A similar opinion was reflected by another stakeholder:

“Particularly in the non-randomised setting, you know. We have tools and we have systematic techniques to try to balance groups when we do studies without randomisation. But there is always the possibility of residual confounding and unmeasured confounding that we cannot even understand.” – Pharmaceutical Industry D

“If I don’t have any idea of the possible bias of data, then it is not interesting for me knowing about the generalisability of these data” – HTA Agency E

Numerous aspects on the poor quality of RWD was the second most recurring disadvantage. To begin with, some stakeholders emphasised that there is no common understanding between different organisations of “good quality” for data collection methods and data analysis. For example, even though some databases undergo rigorous quality checks (e.g. the Clinical Practice Research Datalink (CPRD)), there rarely are any checks performed for electronic medical records. As a result, many stakeholders have noted that RWD encountered in practice is often “messy” or of “low quality”. Data elements collected often do not comprehensively demonstrate standard of care procedures and databases are frequently incomplete. The following quote from one academic stakeholder demonstrates several of the previously-mentioned points:

“As we go to routinely-collected RWE, the issue there is very obviously not the expense, but rather the data quality. We have looked at data routinely collected from primary care and in theory, you get absolutely everything on a patient and that might not be accurate. There is quite a lot of data
cleaning required and people often say: ‘Wouldn’t it be great if we have a lot of routinely-collected data?’ Well, yes it would but it would also require a lot of data cleaning.” – Academia B

The lack of RWD availability was the third most recurring issue. The majority of stakeholders referred to the absence of RWD availability at the time of initial reimbursement decisions, since these mostly occur directly after marketing authorisation approval. A number of stakeholders also expressed concern on the low quantity of RWD available at the time of re-assessment of relative effectiveness of health interventions in the context of conditional reimbursement. One exception to this trend that was mentioned relates to applications of “old” products for new indications, in which case RWD on adverse events can be abundant.

Stakeholders also indicated that key data elements on standard of care, such as hospital treatment and drug dosing, are usually not available for specific disease areas thus necessitating prospective data collection. The purposeful removal of several patient variables such as ZIP codes or location when combining EHR and claims databases, often due to protection of patient privacy, also limit patient follow-up across different databases. Both patient organisations interviewed further emphasised that the unavailability of RWD is particularly evident for rare diseases, where there are critical gaps of information on basic parameters such as prevalence. Moreover, data on diagnostics and treatment impact is usually not available for orphan diseases.

5.7 Practical obstacles faced in RWD collection/use

The lack of harmonisation and standardisation of several aspects of RWD collection and use was the most frequently-mentioned practical obstacle. According to stakeholders, there is generally no coordination at an international level for RWD collection. In addition, there is an absence of harmonisation on evidence requirements between different stakeholders. For example, marketing authorisation holders may face the situation of simultaneously conducting different RWS’s to fulfil post-marketing commitments of RA and relative effectiveness requirements of HTA or health payers/insurers. This results in tensions between the regulatory and reimbursement dossiers of pharmaceutical manufacturers.

“On the regulatory side there are many researchers that would like to be able to use RWD and to achieve getting it into the labelling so that we can promote on those results. We think that there is a huge hurdle at the Food and Drug Administration (FDA) at least in doing that. If the results of RWD agree with clinical trials then there is no reason to put it in the labelling. If they don’t agree, than we also consequently believe the gold standard is not the RWD. It is a real hurdle from that perspective. It may be easier in the EU a little bit, as they seem to embrace the RWD a little bit more. Form the HTA perspective, they really want the RWD.” – Pharmaceutical Industry D

The absence of standardisation of RWD data sources, data collection methods/tools, data analysis methods, and standard of care are examples of elements where concerns were voiced by the majority of stakeholders. Moreover, a dearth in guidance on such topics was also mentioned.

“The other thing is that we can bring data in-house together but there are different sorts of data from different countries, different... So you know it is very time consuming to run clear results from more than one specific piece of the data set that you can pull together. So to accommodate models is a quite time consuming, quite expensive programme the way it (currently) works” – Pharmaceutical Industry A
“Standardization also of the data collection is relevant, because sometimes especially for physicians it is not so immediately clear how to interpret the data. We normally are open and normally collect RWD from all the physicians that are able to prescribe it in practice, not just a selection of physicians. So, it is still an obstacle to standardize this way of data collection in a way that it gives out some robust answer to our question.” – HTA Agency C

Several limitations related to policies on RWD collection or use were the second most-mentioned practical obstacle. These limitations revolved around the policies restricting access to RWD, the lack of standard policy regarding data privacy/confidentiality, regulatory policies explicitly stipulating that RWD can only be used for supplementary evidence thus discouraging researchers from using RWD, and the cumbersome policies for gaining approval for real-world studies.

“In terms of the obstacles, I think it’s about access to good quality electronic health care records, across different countries. The (country X) is quite well organized and the (country Y) is quite organized in terms of having research access to electronic health care records. In other parts of the world you’d have to find a partner and then you’d have to negotiate kind of a collaboration between maybe multiple parties in terms of that have access to some of the data. So it is a very practical issue; each study needs the phase of collaboration and partnership building which is often quite difficult to do and quite time and resource intensive.” – Pharmaceutical Industry A

“A rationalisation of clinical trial regulations is needed to stop the madness and circus of people filling out forms.” – Academia C

5.8 Political considerations for incorporating RWD collection/use

The presence of a cultural barrier preventing the full incorporation of RWD in decision-making for drug development and drug assessment was the most recurrent theme. The cultural barrier mentioned refers to stakeholders’ regard of RWD evidence as being of lower quality when compared to RCT-generated evidence, as well as stakeholders’ adherence to the traditional hierarchy of evidence which stipulates that RCT-generated data is of higher quality thus of higher reliability in decision-making.

For example, some industry stakeholders very clearly indicated that the acceptance of RWD by regulators such as the FDA is perceived as very low. Some representatives of other stakeholders like HTA agencies or healthcare insurers/payers hinted at similar issues, indicating that the hierarchy of evidence is still in the mind of a lot of decision makers that affects the acceptance of RWD substantially.

“For the decision-making in commission, there is obviously the hurdle of the mind set. Some are still convinced that only RCT’s provide the appropriate answers which is probably a difficulty to ask them to look at observational data.” – Healthcare Insurer/ Payer A

Issues related to governance and accountability of RWD collection and subsequent use were the second most recurrent theme. More specifically, the points raised under this theme included: who is responsible for RWD generation?; who should bear the cost of RWD collection?; who controls access to RWD?; and who should have access to RWD?. For patient representatives the question on who should have access to RWD is particularly important.
“You know everyone will immediately say: “Who is going to have access to this information? Who is going to control the access to it?” – Patient Organisation B

One of the issues that was addressed by some stakeholders was the ambiguity regarding the funding of the data collection. Although in many cases the applicant/company is responsible for the data collection, in some countries also public programs exist that contribute to the collection of data. However, the selection criteria for receiving public funding do not seem to be very clear.

“The only way that you can attempt that you get to that point, is that you pay for it. So, right now, we don’t pay healthcare providers for submitting that data. We basically use those data to pay them. How do you tribute to the national burden of these healthcare providers to submit data that is not necessarily needed for payment, that is very challenging.” – Initiative B

Some stakeholders indicate that trust between the different stakeholders is essential to increase the acceptance of RWD and therefore increased dialogue between HTA, regulators and companies is essential to bring the use of RWD forward. An example for the need of an increased dialogue is, according to some representatives from industry and regulatory stakeholders, that requirements for RWD (for instance study design) for regulators and HTA are substantially different and that this makes it very difficult to develop a RWD program that provides a good return on investment.

“So I would say that my suggestions for improvement is that we need a further dialogue in this respect. Because there has to be a balancing of what value this RWD would bring to a certain development and eh what needs they would fulfil on the point of few from the regulators, from the HTA’s and from the companies.” – Regulatory Agency A

5.9 Procedural implications for incorporating RWD collection/ use

The need to harmonise RWE requirements and standardize methodologies and tools for RWD collection and use was the most recurrent procedural consideration. Representatives from pharmaceutical industry, HTA and regulatory agencies specified different issues relating to a very clear wish for harmonization of RWD-generated evidence. Some focused on common protocols for data collection, for instance between HTA agencies in Europe, while others indicated that it is very important to have this harmonization/standardization between all stakeholders and over all countries. Some of the representatives of the pharmaceutical industry even indicated that a harmonization across Europe was not sufficient; this should also include collaboration with the stakeholders in the rest of the world (for instance, with the FDA).

“I think the biggest opportunity, especially thinking about the direction that we’re heading inside and outside the US; better standardization of data collection in and integration across the electronic medical record systems would be a great first step, standardization across countries and all the methodological considerations that are contemplated through numerous efforts are certainly critical but I do think that it is a great starting point.” – Pharmaceutical Industry B

Additionally, the needs for development of guidance and best practices for RWD collection and analysis was notably mentioned, as demonstrated by the quote below:
“Eh, again.. if RWD are accompanied by good practices in that field, I should say something equivalent to Good Clinical Practice (GCP) set for clinical studies, if we would make that available for RWD, and from ISPOR there is something available guidance on this issue also.. if such good practices would exist in working procedures, if we put more awareness on this and distribute it, and that with academics we receive the messages on how to use it and when not to use this data, , then I think we can go much further.” – Pharmaceutical Insurer/ Payer A

Another procedural consideration that was considerably recurrent was adequate linkage of RWD from different sources. This mainly refers to the coupling of data currently available such as electronic health records, claims databases and patient registries by using patient identifier data. Stakeholders seemed to be quite interested to build on existing data, referring to all kinds of sources such as claims data, electrical medical, health, patient records (EMR, HER, EPR) and biobank data. However, some of these representatives also indicated that they fear that this linkage is difficult to achieve. Some are even quite sceptic because they feel that completeness of data is very important and very difficult to achieve, in order to control for confounding biases.

6 Discussion

As demonstrated by the results of both the literature review and stakeholder interviews, the collection of RWD and subsequent analysis/synthesis to produce RWE is becoming increasingly evident in the field of drug development and relative effectiveness assessment. Authors and interviewees alike have indicated, with great degree of overlap, both the actual and perceived contexts for RWD and RWE use in drug development (e.g. to determine natural history, define subpopulations with better benefit-risk profiles, inform the design of pivotal trials), drug regulation (e.g. fulfilment of post-marketing commitments, conditional marketing authorisations and adaptive pathways, examining drug utilization and adherence to approved indications) and drug reimbursement (e.g. as inputs for resource use and effectiveness data for pharmacoeconomic modelling, relative effectiveness assessment, and marketing access agreements).

However, despite this apparent consensus on the value of RWD and RWE, there remains a fundamental disagreement and lack of consensus regarding the definition of RWD. Different authors and stakeholders have quite variable, and sometimes contradicting, ideas over what RWD comprises. A recurrent example of contradiction is the association of RWD by some with data being collected in a non-randomised, non-interventional setting, and by others as data being collected exclusively in a non-experimental setting. The second condition implies, therefore, that only observational data from retrospective registry cohorts or EHR’s can be classified as RWD, whereas data from other study designs such as pragmatic clinical trials (PCT’s) or observational studies with prospective data collection and experimental protocols are not.

Another example of a critical ideological conflict exists between the two most common definitions for RWD encountered; the first being “data collected outside the context of a RCT” and the second being “data collected in a non-randomised, non-interventional setting”. Once again, these differing concepts raise controversy around certain types of RWS, most prominently the PCT. Patients in PCT’s are initially randomized to different treatment arms until preliminary results allow for shifting of responders/non-responders to other arms. Yet depending on which of the two definitions one chooses to adopt, PCT would either classify or not classify as a RWS,
thus a source for RWD. Controversy also exists on whether studies supplemental to RCT’s classify as RWS’s, as a third example. Some authors and stakeholders explicitly exclude supplemental studies, while others do not or are even unaware of their consideration as RWS. Until consensus is reached amongst all stakeholders on the definition of RWD, the types of studies that qualify as RWS and data sources will also remain debatable.

A cultural barrier clearly presents itself against RWD and RWE, thereby affecting the acceptability of RWD among stakeholders and the applicability of RWE to decision-making in drug development and relative effectiveness assessment. Many stakeholders still adhere to the concept of a hierarchy of evidence which places data from RCT on a level above non-RCT data. Due to significant limitations of RWD, such as their liability to bias (both known and unknown confounders) and the poor quality of RWD often collected, HTA agencies and RA explicitly state in their guidelines that inferences made relating to effectiveness of health interventions that are based on RWE will be regarded as being more circumspect (22-24;28). This has been published repeatedly in review documents and mentioned frequently during interviews. Therefore, even though the value of RWD and RWE is becoming increasingly apparent in light of the limitations of RCT-generated evidence on clinical effectiveness, the cultural barrier described lowers their impact on decision-making thus further discouraging other stakeholders from investing in RWD collection.

Some may argue that adherence to such a hierarchy of evidence should not be used to automatically down-grade RWE in decision-making, especially in circumstances where disease characteristics yield RCT’s an unfeasible study design. This can be demonstrated in the case of orphan diseases, where issues relating to low prevalence and ethics (e.g. absence of alternative treatment) restrict possibilities for conducting RCT’s. In some of these conditions, manufacturers and HTA agencies alike have resorted to RWE for decision-making throughout the product lifecycle. In brief, a single, static model for a hierarchy of evidence may be too simplistic an approach for decision-making. Stakeholders therefore should discuss the relevance of RWE in answering scientific questions in varying settings. Accordingly several alternative hierarchies will need to be developed that adapt to the context within which evidence is generated.

Policies on access to RWD available through PCT’s, EHR’s, administrative claims databases, and so forth vary dramatically from region to region, country to country, state to state, and even institute to institute. As previously demonstrated by results of the literature review, recent policies on data access in the European Union (EU) will lead to a restrictive environment for researchers seeking access to pseudo-anonymised patient data (9;16); whereas in the United Kingdom (UK), the NHS can allow (in a few exceptions) researchers access to patient-level data without patient consent after approval by the NIGB (13). The CMS in the USA forbids entities with “commercial interests” from accessing CMS patient data, whereas the state of Massachusetts does not deny researchers access to de-identified patient data, so long as researchers sign a data use agreement (11;17;76). Researchers in the U.S. can also alternatively gain access to data for commercially insured patients or Medicare Advantage populations. The presence therefore of such a non-uniform, but generally restrictive, policy environment poses a great barrier to healthcare researchers from all stakeholder groups who wish to conduct RWS.

Steps required to approve plans for RWS by the relevant boards of governance also vary according to the contexts within which such studies are conducted. For example, RWS’s for Local Service Evaluations and Clinical Audits in the UK require no approval by national ethics boards, as
opposed to other RWS’s (13). Similarly, in the USA, whether an established RWD network/database is classified as a public health surveillance activity or research activity has a great influence on whether it is complies by the privacy provisions of the Health Insurance Portability and Accountability Act (HIPAA) or the Common Rule for protection of human subjects (76). It is therefore no surprise that stakeholders would be discouraged to face the cumbersome task of gaining approval for RWS in the midst of a myriad of governance structures.

In addition to this, many important issues relating to the governance of RWD collection and use remain glaringly unaddressed by any policy documents found during the literature review. These include issues on which party(s) should bear the cost of RWD collection and RWE generation? Should this vary from context to context (e.g. RWE in a pre-authorisation phase where a pharmaceutical company is still in product development vs. RWE for the determination of quality of healthcare delivery by health care providers to inform reimbursement decisions by healthcare payers/insurers). Consequently, who should own the RWD generated by such efforts, assuming that costs (both monetary and non-monetary) are to be shared by several parties? Apart from some rare, general guidance on data ownership processes in documents (43;44), answers to such critical questions, and many others, remain to be formed. The ambiguity created in the absence of such answers will only discourage stakeholders from investing in RWE generation.

The majority of authors and interviews have referred to the need for harmonization of the type of RWD to be collected and RWE requirements between different stakeholders, as well as the methods/tools for RWD collection and analysis. Currently, RWE requirements vary between stakeholders such as HTA agencies and regulatory agencies. Much of the evidence generated to fulfil post-marketing commitments of regulatory agencies, such as post-authorisation safety/efficacy studies (PASS/PAES) can also provide very important insights into questions posed by HTA agencies in reimbursement discussions. However, little dialogue exists between these stakeholders to harmonise their RWE requirements, leading to a tension between regulatory and reimbursement dossiers, as well as a duplication of efforts by pharmaceutical industry. Guidelines issued by both stakeholder groups also remain quite general and do not directly address RWD-related issues. It should be noted that different stakeholders have different mandates and goals to fulfil (for example, patient organisations versus HTA agencies, or healthcare providers versus HTA agencies). Therefore, though harmonisation of RWE requirements across all 8 stakeholder groups mentioned in this report would be ideal, in reality it would be quite difficult to achieve. Alternatively, it would be worthwhile to start harmonising RWE requirements among a sub-set of stakeholders in the first instance, for example, regulatory agencies, HTA agencies and pharmaceutical industry.

On the other hand, several pieces of guidance are available that address the design and conduct of RWS’s such as pharmacoepidemiological studies (37;40;42-44). Multi-stakeholder consortia such as Strengthening the Reporting of Observational studies in Epidemiology (STROBE) and the International Society for Pharmaceutical Engineering (ISPE) have also published valuable guidance for the conduct of observational studies. Other consortia such as OMERACT and the COMET Initiative which focus on the development and propagation of core health outcome sets for such studies can provide valuable guidance for RWD collection (77;78). Furthermore, guidance and expertise can be found regarding RWD collection methods/tools; the EU project Patient Registries Network (PARENT), lists available registries in Europe and is currently in the process of developing guidelines for the establishment of disease-specific registries. Meanwhile, initiatives such as the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
(IMI-PROTECT), European Union Adverse Drug Reactions (EU-ADR), Observational Medical Outcomes Partnership (OMOP), and the Canadian Network for Observation Drug Effect Studies (CNODES) explore the possibilities for the combination of heterogenous EHR databases to allow for standardized querying of multiple RWD sources. Finally, the IMI-GetReal project also aims to provide clear guidance on best practices for evidence synthesis and network meta-analysis of RWD. Perhaps outputs from initiatives and consortia such as these can provide a foundation upon which to achieve standardization of RWD collection tools and analysis methods. To echo the opinions of the majority of stakeholders interviewed, we also hope that harmonization and standardization can be achieved on a regional level (e.g. across the EU) and subsequently proceed to become global.

Some authors and stakeholders were of the opinion that a vast collection of RWD is already available, whether through health surveys, observational studies, administrative claims databases, etc. However, since these different types of data are collected for different purposes, they have their different strengths and limitations which complement one another. Therefore, one way to ensure that we unlock the full potential of RWD is by data linkage. This linkage could be between RWD of the same type, but of different sources, as is the case with efforts trying to combine heterogenous EHR’s (IMI-PROTECT, EU-ADR, OMOP, and CNODES). Alternatively, and more importantly, the linkage could be made between RWD of different types. Prime examples of RWD databases that achieve this are the FDA’s Mini-Sentinel, the National Patient-Centred Clinical Research Network (PCORnet) and the NIH Health Care Systems Research Collaboratory’s Distributed Research Network (NIH Collaboratory DRN). Data linkage from different sources automatically increases the size of the potential patient population for RWS’s, expanding the possibilities for statistically robust findings on a range of health outcomes and rare/long-term adverse/therapeutic effects. It is, however, important to keep in mind that there are several challenges that make achieving data linkage practically difficult including: insufficient patient identifying information, non-standard coding of medical terminology, interoperability of different electronic formats of database structures, and different privacy regulations associated with different databases (11;45;76).

Cultural barriers, ambiguities on policies, unanswered questions on governance of real-world research, lack of harmonization of RWD definition and RWE requirements, and lack of standardization of real-world research methods create significant scepticism regarding the conduct of RWS, use of RWD and incorporation of RWE in drug development and relative effectiveness assessment. In order to overcome this, increased collaboration between stakeholders from all groups to address these issues is necessary. Trust among stakeholders is a crucial facilitator for this increased and transparent dialogue among one another to achieve this. One context within which we believe this stakeholder collaboration can take place is in that of adaptive pathways (also known as medical adaptive pathways to patients (MAPP’s) or adaptive licensing)(52). In this model of drug development, pharmaceutical industry, HTA agencies, regulatory agencies, patients/patient organisations, and healthcare payers/insurers jointly design plans for cyclic generation of evidence during the early stages of drug development. This co-designing of evidence development plans (both RWE and RCT evidence) fosters a climate of transparent dialogue in which accountability is shared among stakeholders and evidence requirements are harmonised.

6.1 Strengths
This project aimed to conduct a review on the policies and perspectives of stakeholders on RWD collection and use by combining findings from stakeholder interviews and a literature review. This approach provided the authors with a chance to compare and contrast the results of two well-acknowledged qualitative research methods. Consequently, conclusions reached are substantiated by a stronger evidence basis.

Moreover, the prior identification of important stakeholder groups and subsequent consultation with other GetReal work package 1 (WP1) members on the choices made regarding the groups helped ensure that we have a comprehensive, multi-stakeholder view of policies and perspectives on RWD.

Incorporation of grey literature along with academic literature in our search strategy helped ensure that critical documents such as policy statements, guidelines, and news articles related to RWD and RWE, which typically would not feature in academic databases, were not missed.

6.2 Limitations

Only one academic database (PubMed) has been searched for academic literature on RWD. Moreover, a comprehensive systematic review of all websites of the 8 stakeholder groups for grey literature was not feasible in the timeline of this project. Nevertheless we have hand-searched recognised academic journals in the pharmaceutical innovation and policy arena (e.g. Nature Reviews Drug Discovery, Drug Discovery Today, the British Journal of Clinical Pharmacology, Clinical Pharmacology & Therapeutics, and the WHO Bulletin) and have purposively sampled websites of 7 different stakeholder groups to avoid overlooking critical literature.

The ability to capture the full perspective of a stakeholder is theoretically not possible unless a significantly representative sample within an organisation is interviewed. Therefore, it can correctly be argued that the stakeholder interviews conducted were inadequate to thoroughly assess stakeholder perspectives. In an attempt to account for this, approached stakeholders for this project were specifically asked if they would like to recommend & invite other colleagues to participate. Eventually, 8 of the 19 interviews did include a minimum of 2 people per stakeholder, and 2 of the 9 included three interviewees per stakeholder.

Results from one critical stakeholder group that are missing from this report are those of healthcare providers. Bearing in mind how important providers are in collecting RWD at the different points of primary and secondary healthcare, we regret that interviews with stakeholders could not be planned within the time span of this project and that there was a dearth on literature of provider’s policies on RWD. The authors also realise that the absence of this stakeholder group is an important limitation.

7 Conclusion

The recognition of the importance of RWD and RWE in decision-making throughout drug development and drug assessment continues to grow. RWD can offer many advantages, such as increased external validity (generalisability) of study results, and better assessment of long-term health outcomes and rare adverse effects of health interventions. However, it is also liable to many forms of biases (e.g. selection bias and information bias) and much of the data currently
available is incomplete or of poor quality. Additionally, many unresolved political and procedural issues exist that strengthen the cultural barrier against RWD collection and use in decision-making. This subsequently leads to reluctance on behalf of stakeholders to invest in RWD.

Therefore, in order to allow for the systematic integration of RWD and RWE into decision frameworks for drug development and drug assessment, increased collaboration must exist between stakeholders to:

6. Develop a common understanding and definition of the terms ‘real-world data’, ‘real-world evidence’ and ‘real-world studies’;
7. Reach consensus regarding the relevance of RWD for answering different scientific questions in different drug development and assessment phases;
8. Harmonise RWE requirements during different drug development and assessment phases;
9. Determine the best mechanisms for the governance of RWD collection efforts and develop policies accordingly;
10. Standardise and provide guidance on tools, methodologies and strategies for RWD collection and analysis.

In doing so, one would be able to overcome the current scepticism around RWD incorporation in decision-making, improve the quality of RWD collected and thereby increase confidence of all stakeholders in the considerable potential RWD bears.
Reference List


Ref Type: Generic


Ref Type: Generic

Ref Type: Generic


(21) Hermanowski T. Real world data and transferability of economic evaluations in Poland. 2008.
Ref Type: Generic

Ref Type:Generic

Ref Type: Generic

Ref Type: Generic

Ref Type: Generic


Ref Type: Generic
(28) IQWiG. General Methods. 28-11-2013. Ref Type: Generic

(29) Sanofi. Main Sanofi positions on CSR topics. 2013. Sanofi. Ref Type: Generic

(30) Novartis. Leaders in Clinical Trial Data Transparency. 2014. Ref Type: Generic

(31) Olson M. Introduction to the use of Observational Data. 2013. Novartis. Ref Type: Generic


(37) EMA. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. 2014. European Medicines Agency. Ref Type: Generic


(40) FDA. Guidance for Industry and FDA Staff: Procedures for Handling Post-Approval Studies Imposed by PMA Order. 2009. Food and Drug Administration. Ref Type: Generic


Ref Type: Generic


Ref Type: Generic


Ref Type: Generic


(45) van Staa TP, Klungel OH. Background Paper 8.4 Real-life data and learning from practice to advance innovation. 2013.


(49) EFP. Real World Data Report, 2013-2014: How Real World data are being used to change the pharmaceutical business model. 2014. Eye for Pharma.

Ref Type: Generic


Ref Type: Generic


Ref Type: Generic


(59) Kaló Z. Real World Data for Pharmacoeconomic Evaluation in Hungary. 2008. Ref Type: Generic


(72) HOPE. Towards patient-focused financing for healthcare provision. 2013. Ref Type: Generic

(73) Merck. Merck and Israel’s Maccabi Healthcare to Leverage Unique Real-World Database to Inform Novel Health Approaches. 2013. Merck Newsroom Home, Merck. Ref Type: Generic

(74) Tesar T. Using real-world data for pricing and reimbursement decision within the Slovak republic. 2008. Ref Type: Generic


1. Deviations from Description of Work

Not applicable.
2. Appendix

8 Appendices

8.1 Appendix 1 – Methods & Results Supplement for Literature Review

8.1.1 Tables and Figures

Table 1 - Websites of stakeholder groups searched for grey literature

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Stakeholder</th>
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<tr>
<td>HTA Agencies</td>
<td>National Institute for Health and Care Excellence (NICE)</td>
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<tr>
<td></td>
<td>Zorginstituut Nederland</td>
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<td></td>
<td>Haute Autorite de Sante</td>
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<td></td>
<td>Institute for Quality and Efficiency in Health (IQWiG)</td>
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<td></td>
<td>Centre for Practice and Technology Assessment (USA)</td>
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<td>Genzyme</td>
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<td>Regulatory Agencies</td>
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<td>Food and Drug Administration (FDA)</td>
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<td>The Federal Join Committee (G-BA)</td>
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<td></td>
<td>European Hospital &amp; Healthcare Federation (HOPE)</td>
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<td></td>
<td>The Standing Committee of European Doctors (CPME)</td>
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<td>Healthcare Payers/ Insurers</td>
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<td>Zorgverzekeraars Nederland</td>
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<td>Patient Organisations</td>
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<td>Association of Standing Health Insurance Funds (GKV Spitzyband)</td>
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<td>The Galen Institute</td>
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**Table 2 - Inclusion and exclusion criteria for document selection**

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<th>Inclusion criteria</th>
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<tr>
<td>Document is published between January 1st 2003 and July 10th 2014</td>
<td>Document does not meet all inclusion criteria</td>
</tr>
<tr>
<td>Document is published in English</td>
<td>Document only focuses on methodology of RWD analysis, best practices of evidence synthesis, or evidence synthesis</td>
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</tbody>
</table>
Inclusion criteria | Exclusion criteria
--- | ---
Document focuses on Real World Data in the context of healthcare, including a specific focus on use of RWD in the context of drug development and drug assessment |  
Document is either a scientific article, opinion article, editorial, report or guideline. |
In the case of a scientific article, opinion article, editorial, report or guideline, the document must be published in a peer-reviewed publication. |  
In the case of a guideline or report, the document must be published on the official website of a recognised institute/organisation. |

**Figure 1 - Flowchart of search strategy results**

**Table 3 - Domains and information elements included in the data abstraction**
### Table 4 - List of documents included in literature review

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<tr>
<th>Primary Author</th>
<th>Date of Publication</th>
<th>Document Title</th>
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<td>Barker, R.</td>
<td>2010</td>
<td>A flexible blueprint for the future of drug development.</td>
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<td>Carpenter, W.</td>
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<td>Doležal, T</td>
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<td>Real-world data in Czech Republic 2008</td>
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<td>Eichler, H. G.</td>
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<td>Adaptive Licensing: taking the next step in the evolution of drug approval</td>
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<td>Bridging the efficacy-effectiveness gap: a regulator’s perspective on addressing variability of drug response</td>
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<td>Epstein, M.</td>
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<td>Guidelines for good pharmacoepidemiology practices (GPP)</td>
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<td>European Union</td>
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<td>eHealth Task Force Report: Redesigning health in Europe for 2020</td>
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<td>Eye for Pharma</td>
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<td>Real World Data Report, 2013-2014: How Real World data are being used to change the pharmaceutical business model.</td>
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<td>Foltz, D.</td>
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<td>Real-world effectiveness of new medicines should be evaluated by appropriately designed clinical trials</td>
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<td>Heranowski, T.</td>
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<td>Can managed care organizations partner with manufacturers for comparative effectiveness research</td>
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<td>Merck and Israel's Maccabi Healthcare to Leverage Unique Real-World Database to Inform Novel Health Approaches</td>
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<td>Real World Data and its promise for medicine and research</td>
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<td>van Staa, T. P.</td>
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<td>Background Paper 8.4 Real-life data and learning from practice to advance innovation</td>
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**Figure 2 – Coding Scheme for Literature Review**
Figure 3 - Literature Review Coding Overview

Table 5 - Overview of coding for literature review

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<td>Context RWD (Perceived)</td>
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<td>Advantages of RWD</td>
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<td>Disadvantages of RWD</td>
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<td>Practical Obstacles</td>
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<td>Political Implications</td>
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<td>Recurring Themes</td>
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<tr>
<td>Context for RWD collection/use (Actual)</td>
<td>1- Reimbursement activities: relative effectiveness assessment, risk-sharing agreements and pharmaco economic analyses</td>
</tr>
<tr>
<td></td>
<td>2- Regulatory activities: fulfilling post-marketing commitments</td>
</tr>
<tr>
<td></td>
<td>3- Drug development: e.g. study natural history, standardise treatment outcomes, define patient sub-populations</td>
</tr>
<tr>
<td></td>
<td>4- Drug utilisation studies: e.g. test drug dosing, patient compliance, standard of care</td>
</tr>
<tr>
<td>Context for RWD collection/use (Perceived)</td>
<td>1- Informing appropriate use of interventions</td>
</tr>
<tr>
<td></td>
<td>2- Drug development e.g. study natural history, define patient sub-populations, identifying novel disease relationships/ therapeutic targets</td>
</tr>
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<td></td>
<td>3- Medicine adaptive pathways to patients (MAPP’s) and exceptional marketing authorisation approaches</td>
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<td>Advantages of RWD collection/use</td>
<td>1- External validity (i.e. generalisability)</td>
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<td></td>
<td>2- Address knowledge gaps presented by RCT-generated evidence</td>
</tr>
<tr>
<td></td>
<td>3- Assessment of long-term health outcomes and rare serious adverse effects</td>
</tr>
<tr>
<td></td>
<td>4- Timely generation of evidence</td>
</tr>
<tr>
<td>Disadvantages of RWD collection/use</td>
<td>1- Liability to biases: selection bias, information bias, confounding bias</td>
</tr>
<tr>
<td></td>
<td>2- Poor quality: incomplete or missing data</td>
</tr>
<tr>
<td></td>
<td>3- Databases originally not established for research purposes leading to inherent limitations in information available</td>
</tr>
<tr>
<td></td>
<td>4- Availability of RWE at important decision-point times in product lifecycle</td>
</tr>
<tr>
<td>Practical obstacles</td>
<td>1- Policies on RWD collection/use: restrictive policies on RWD access, non-standardised policies on patient data privacy/ confidentiality</td>
</tr>
<tr>
<td></td>
<td>2- Lack of standardisation on data collection methods and lack of harmonisation or required RWD</td>
</tr>
<tr>
<td></td>
<td>3- Costs (monetary &amp; non-monetary): setting up ICT infrastructure for data collection, purchasing license for RWD access, lack of capacity within individual organisations to conduct RWS</td>
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<tr>
<td>Political Considerations</td>
<td>1- Governance and accountability: responsibility of conducting research, communication of findings, access to data, patient data privacy/ confidentiality</td>
</tr>
<tr>
<td></td>
<td>2- Increased collaboration amongst stakeholders: collectively harmonising evidence requirements, co-designers of real-world studies</td>
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<tr>
<td></td>
<td>3- Ambiguity on applicability of RWE to decision-making</td>
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<td></td>
<td>4- Cultural barrier against RWD use: adherence to hierarchy of evidence during evidence appraisal</td>
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<td>1- Harmonisation and standardisation of tools and methodologies for RWD collection and analysis: definitions, outcomes, statistical methodologies</td>
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<td></td>
<td>2- Educational and infrastructural needs for collecting and using RWD</td>
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<td>3- Data linkage: combination of RWD of the same type but from different sources and the combination of different RWD types from multiple sources</td>
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8.2 Appendix 2 – Methods & Results Supplement for Stakeholder Interviews

8.2.1 Tables and Figures

Table 7 - Overview of interviewed stakeholders and number of participants per interview

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<th>Stakeholder Group</th>
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Figure 4 – Coding Scheme for Semi-structured Interviews
Figure 4 – Coding Scheme for Semi-structured Interviews (Cont’d.)
Figure 5 - Semi-structured Interviews Coding Overview

Table 8 - Overview of coding for semi-structured interviews

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<td>Total</td>
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Table 9 - Summary of Recurrent Themes

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<th>Recurring Themes</th>
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<tr>
<td>Context for RWD collection/use (Actual)</td>
<td>1- Reimbursement activities: relative effectiveness assessment, pharmacoeconomic analyses, conditional reimbursement</td>
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<td>2- Drug development: e.g. study natural history, define patient sub-populations, local treatment pathways</td>
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<tr>
<td></td>
<td>3- Regulatory activities: fulfilling post-marketing commitments</td>
</tr>
<tr>
<td>Context for RWD collection/use (Perceived)</td>
<td>1- Drug development e.g. study natural history, inform phase III trial design, define patient sub-populations, define health outcomes, inform choice of comparators</td>
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<td></td>
<td>2- Forecasting clinical effectiveness</td>
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<td>3- Drug utilisation studies: adherence to treatment</td>
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<td>Advantages of RWD collection/use</td>
<td>1- External validity (i.e. generalisability)</td>
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<td>2- Address knowledge gaps presented by RCT-generated evidence: efficacy-effectiveness gap, long-term health outcomes</td>
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<tr>
<td>Disadvantages of RWD collection/use</td>
<td>1- Liability to biases: selection bias, information bias, confounding bias</td>
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<td></td>
<td>2- Poor quality: low quality of data, incomplete or missing data</td>
</tr>
<tr>
<td></td>
<td>3- Availability of RWE at important decision-point times in product lifecycle</td>
</tr>
<tr>
<td>Practical obstacles</td>
<td>1- Lack of standardisation on data collection methods and lack of harmonisation on required RWD: absence of clear guidance on these topics</td>
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<td>2- Policies on RWD collection/use: restrictive policies on RWD access, non-standardised policies on patient data privacy/ confidentiality</td>
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<tr>
<td>Political Considerations</td>
<td>1- Cultural barrier against RWD use: adherence to hierarchy of evidence during evidence appraisal</td>
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<tr>
<td></td>
<td>2- Governance and accountability: responsibility of conducting research, funding of data collection, regulation of access to data</td>
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<td></td>
<td>3- Increased collaboration amongst stakeholders: collectively harmonising evidence requirements</td>
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<td>Procedural Implications</td>
<td>1- Harmonisation and standardisation of tools and methodologies for RWD collection and analysis: RWD evidence requirements, development of guidance and best practices on RWD collection/ analysis</td>
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<td>2- Data linkage: combination of RWD of the same type but from different sources and the combination of different RWD types from multiple sources</td>
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8.2.2 Tailored Stakeholder Interview Questionnaires

HTA Questionnaire

**Current reimbursement/drug assessment policy**
1. Could you briefly verify whether the information provided by us, regarding your current reimbursement methods, is up to date?
   a. According to your experience, what are the most relevant advantages and disadvantages of this general approach on reimbursement?
2. Do you consider decisions on a case-by-case basis, or is there a need for learning from past decisions or even integrating datasets between decisions?

**RWD**
1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?
2. Do you request the use of RWD in HTA submissions for the purposes of decision-making for reimbursement?
   a. What sort of RWD is ideally preferred and requested for HTA assessments?
   b. What sort of RWD is currently available, in comparison to ideal requirements?
   c. Is this related to Coverage with Evidence Development (CED) or conditional reimbursement after market authorization?
   d. Specific types of products/disease areas?
      - Is this particularly relevant for orphan diseases?
   e. Relevant examples?
3. What are the policies governing the use of RWD data in HTA submissions at your organization?
   a. Did you publish any guidelines regarding the use of RWD for reimbursement decision-making?
4. Are you satisfied with text-based reports of the submitted evidence, or would you prefer these reports to be supported by the underlying structured data sets and/or statistical models (in electronic format)?

**Perceived usefulness**

*Extent to which a person believes RWD can positively contribute to drug development licensing and market access*
1. What are, according to your perceptions, the added benefits of using RWD for HTA submissions, in comparison to, for example, RCT data?
2. What are, according to your perceptions, the limitations of submitting RWD for HTA submissions. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are submitted to you?
   b. Do you have any suggestions to improve the quality of RWD?
3. To what extent do you use RWD data in relative effectiveness modelling performed by your institution?
4. Can RWD be used as evidence in pre-licensing studies, market applications and/or to forecast clinical effectiveness?
   a. Is this expected in reimbursement files from manufacturers?
   b. If yes, how is this assessed by your organization?
5. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?

6. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?

7. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?)

8. Would you be willing to consider/perform an assessment of relative effectiveness that is predicted from the available RWD data sources? If so, what types of structural uncertainty regarding, for example, assumptions made or parameter definitions, should primarily be addressed?

9. What is your opinion regarding uncertainty arising from synthesising evidence for relative effectiveness assessment that are due to, for example, assumptions made or parameter definitions?
   a. Are sufficient sensitivity analyses performed relative to key assumptions being made?
   b. Which data sources may enhance the credibility of predictions regarding relative effectiveness?

10. What software do you currently use (if any) for evidence synthesis and/or predictive modelling?
    a. What is your opinion of such software? Are there any important gaps in functionality or usability of such software?

11. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

**Perceived ease of use**

*Degree to which effort is needed to collect and use RWD.*

1. What are the current obstacles faced in the collection of RWD as well as the implementation of policies for the use of RWD in the decision-making process of your institution?
   a. Do you have any suggestions for improvements?

2. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?

3. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
Industry Questionnaire

RWD

1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?
2. Do you collect RWD for all your licensed products? Why or why not?
   a. Does it vary depending on the type of product?
   b. If you do not collect RWD for all your products, could you specify for which types of products you collect RWD?
   c. What is the type of RWD collected in such cases?
   d. Is real-life data also collected for comparators of your products or more generally, e.g. for a disease area?
3. What is timing of collection of RWD in relation to the lifecycle of your products?
   a. Does your company only collect RWD after marketing authorization or also premarketing authorization? Could you specify the timing?
4. Is the collection of RWD mostly connected to mandatory obligations from EMA (e.g. risk management) or part of national reimbursement requirements (coverage with evidence or conditional reimbursement)?
   a. Are there other reasons for your company to collect RWD, for example, for relative effectiveness assessments?
5. Are results from studies with RWD made public, for instance by publication in peer-reviewed journals?
   b. If not, under what conditions, and in what form, would it be likely for RWD data to be made public?

Perceived usefulness

Extent to which a person believes RWD can positively contribute to drug development licensing and market access

1. What are, according to your perceptions, the added benefits of using RWD in drug development, in comparison to, for example, RCT data?
2. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?
3. To what extent do you use RWD data in relative effectiveness modelling performed by your institution?
4. Can RWD be used as evidence in pre-licensing studies, market applications and/or to forecast clinical effectiveness?
   a. Is RWD presently included in submission files to regulators and reimbursement agencies?
5. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?
6. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?
7. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?)

8. Would you be willing to consider/perform an assessment of relative effectiveness that is predicted from the available RWD data sources? If so, what types of structural uncertainty regarding, for example, assumptions made or parameter definitions, should primarily be addressed?

9. What is your opinion regarding uncertainty arising from synthesising evidence for relative effectiveness assessment that are due to, for example, assumptions made or parameter definitions?
   a. Are sufficient sensitivity analyses performed relative to key assumptions being made?
   b. Which data sources may enhance the credibility of predictions regarding relative effectiveness?

10. Are you satisfied with text-based reports of RWD evidence used as an input for evidence synthesis/predictive modelling, or would you prefer these reports to be supported by the underlying structured data sets and/or statistical models (in electronic format)?

11. What software do you currently use (if any) for evidence synthesis and/or predictive modelling?
   a. What is your opinion of such software? Are there any important gaps in functionality or usability of such software?

12. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use

Degree to which effort is needed to collect and use RWD

4. What are the current obstacles faced in the collection of RWD as well as the implementation of policies for the use of RWD in the decision-making process of drug development?
   a. Do you have any suggestions for improvements?

5. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?

6. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
Regulatory Agencies Questionnaire

RWD

1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?
2. To which extent is the collection of RWD officially linked to official regulatory requirements of your institution?
   a. Could you please specify?
3. Do you request the use of RWD as supportive evidence in marketing authorisation applications?
   a. What sort of RWD is ideally preferred and requested for clinical efficacy assessments?
   b. What sort of RWD is currently available, in comparison to ideal requirements?
   c. Specific types of products/ disease areas?
      i. Is this particularly relevant for orphan diseases?
   d. Relevant examples?
4. What are the policies of your organisation governing the collection of RWD data from post-marketing studies?
   a. Did you publish any guidelines on this subject?

Perceived usefulness

Extent to which a person believes RWD can positively contribute to drug development licensing and market access

1. What are, according to your perceptions, the added benefits of using RWD for marketing authorization submissions in comparison to, for example, RCT data?
2. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?
3. To what extent do you use RWD data in relative effectiveness modelling performed by your institution?
4. Can RWD currently generated in a post-marketing setting (e.g. PASS, PAES or other observational approaches) be used to predict real-world efficiency of drugs?
5. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?
6. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?
7. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?
8. What software do you currently use (if any) for evidence synthesis and/or predictive modelling?
   a. What is your opinion of such software? Are there any important gaps in functionality or usability of such software?
9. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use

Degree to which effort is needed to collect and use RWD.

1. What are the current obstacles faced in the collection of RWD as well as the implementation of policies for the use of RWD in the decision-making process of drug assessment at your institution?
   a. Do you have any suggestions for improvements?
2. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?
3. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
Academia Questionnaire

RWD

1. What is your understanding of the term real-world data (RWD)?
   a. What would be a correct definition, in your opinion, of RWD?
2. Is RWD as part of drug development and/or relative effectiveness assessment activities routinely collected for research activities within your institution?
   a. Could you provide us with some relevant examples?
   b. What is the type of RWD collected in such cases?
   c. In what context would such RWD be used?
3. Are results from studies with RWD made public, for instance by publication in peer-reviewed journals?
   a. If not, under what conditions, and in what form, would it be likely for RWD data to be made public?

Perceived usefulness

Extent to which a person believes RWD can positively contribute to drug development licensing and market access

1. What are, according to your perceptions, the added benefits of using RWD in drug development and drug assessment, in comparison to, for example, RCT data?
2. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?
3. To what extent do you use RWD data in relative effectiveness modelling performed by your institution?
4. Can RWD be used as evidence in pre-licensing studies, market applications and/or to forecast clinical effectiveness?
   a. Is RWD presently included in submission files to regulators and reimbursement agencies?
5. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?
6. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?
7. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?
8. Would you be willing to consider/perform an assessment of relative effectiveness that is predicted from the available RWD data sources? If so, what types of structural uncertainty regarding, for example, assumptions made or parameter definitions, should primarily be addressed?
9. What is your opinion regarding uncertainty arising from synthesising evidence for relative effectiveness assessment that are due to, for example, assumptions made or parameter definitions?
a. Are sufficient sensitivity analyses performed relative to key assumptions being made?
b. Which data sources may enhance the credibility of predictions regarding relative effectiveness?

10. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use

**Degree to which effort is needed to collect and use RWD.**

1. What are the current obstacles faced in the collection of RWD as well as the implementation of policies for the use of RWD in the decision-making process of drug development?
   a. Do you have any suggestions for improvements?
2. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?
3. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
Healthcare Providers Questionnaire

RWD

1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?
2. Does your organization regularly collect RWD (e.g. in the form patient healthcare data, patient registries or electronic health records)?
   a. What type of data is collected in these circumstances?
   b. Could you provide us with some relevant examples?
   c. Is this only done for pharmaceutical products?
3. To what extent does your organization currently make use of RWD in the context of its performed tasks?
   a. Could you provide us with some relevant examples?
4. Are results from studies with RWD made public, for instance by publication in peer-reviewed journals?
   a. If not, under what conditions, and in what form, would it be likely for RWD data to be made public?

Perceived usefulness

Extent to which a person believes RWD can positively contribute to drug development licensing and market access

1. Do you think that RWD should play an important role in decision making for prescriptions and/or formulary decisions?
2. What are, according to your perceptions, the added benefits of using RWD for decision-making with regards to prescriptions/formularies, in comparison to, for example, RCT data?
3. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?
4. Can RWD currently generated in a post-marketing setting (e.g. PASS, PAES or other observational approaches) be used to predict real-world efficiency of drugs?
5. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?
6. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?
7. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?)
8. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use

Degree to which effort is needed to collect and use RWD.
7. What are the current obstacles faced in the collection of RWD as well as the implementation of policies for the use of RWD in the decision-making process of drug development and drug assessment?
   a. Do you have any suggestions for improvements?
8. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?
9. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
Healthcare Payers/Insurers Questionnaire

RWD

1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?

2. Does your organization regularly collect RWD (e.g. in the form patient healthcare data, patient registries or electronic health records)?
   a. What type of data is collected in these circumstances?
   b. Could you provide us with some relevant examples?
   c. Is this only done for pharmaceutical products?

3. To what extent does your organisation currently make use of RWD in the context of relative effectiveness assessment and its other performed tasks?
   a. Could you provide us with some relevant examples?

4. Are results from studies with RWD made public, for instance by publication in peer-reviewed journals?
   a. If not, under what conditions, and in what form, would it be likely for RWD data to be made public?

Perceived usefulness

Extent to which a person believes RWD can positively contribute to drug development licensing and market access

1. Do you think that RWD should play an important role in decision making for prescriptions and/or formulary decisions?

2. What are, according to your perceptions, the added benefits of using RWD for decision-making with regards to prescriptions/ formularies, in comparison to, for example, RCT data?

3. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?

4. Can RWD currently generated in a post-marketing setting (e.g. PASS, PAES or other observational approaches) be used to predict real-world efficiency of drugs?

5. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?

6. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?

7. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?

8. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use
**Degree to which effort is needed to collect and use RWD.**

1. What are the current obstacles faced in the collection of RWD as well as the implementation of policies for the use of RWD in the decision-making process of drug reimbursement?
   a. Do you have any suggestions for improvements?
2. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?
3. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
Patient Organisations Questionnaire

RWD
1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?
2. Does your organisation collect RWD or participate in RWD collection efforts made by industry, academia or government?
   a. For what purposes is RWD collected in such a context?
   b. What is the type of RWD usually collected in such a context?
   c. Could you provide us with some relevant examples?

Perceived usefulness
Extent to which a person believes RWD can positively contribute to drug development licensing and market access
1. For what purposes could RWD be used in the context of your organization?
   a. Could you please provide specific examples?
2. What are, according to your perceptions, the added benefits of using RWD for the prediction of relative effectiveness, in comparison to, for example, RCT data?
3. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?
4. Do you believe that sufficient RWD is being collected in your disease area of expertise?
5. Can RWD be used as evidence in pre-licensing studies, market applications and/or to forecast clinical effectiveness?
6. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?
7. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?
8. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?)
9. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use
Degree to which effort is needed to collect and use RWD.
7. To which extent should patients be encouraged to participate in the collection of RWD?
8. Do you think that patient participation in the design of real life data collection should be mandatory, for instance, in case of coverage with evidence development for new expensive drugs?
9. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently
Initiatives Questionnaire

RWD

1. What is your understanding of the term real-world data (RWD)?
   a. Could you provide a specific definition, in your opinion, of RWD?
2. Could you explain in detail how your organisation is involved in the collection, use and assessment of RWD?
   a. Could you provide specific examples?
3. What are the policies governing the collection, analysis and use of RWD data in research commissioned by your organisation?
   a. Did you publish any guidelines regarding the use of RWD for decision-making regarding the effectiveness of medicinal products?

Perceived usefulness

Extent to which a person believes RWD can positively contribute to drug development licensing and market access

1. What are, according to your perceptions, the added benefits of using RWD in drug development, in comparison to, for example, RCT data?
2. What are, according to your perceptions, the limitations of collecting and using RWD for drug development. And what are the possible solutions to such limitations?
   a. How do you value the quality of RWD that are collected during studies?
   b. Do you have any suggestions to improve the quality of RWD?
3. Can RWD be used as evidence in pre-licensing studies, market applications and/or to forecast clinical effectiveness?
4. Are you familiar with evidence synthesis strategies, such as meta-analysis, mixed treatment comparisons or network meta-analysis, and how do you value the quality of information resulting from such analyses?
5. What is your opinion regarding the quality of the methodology and/or software used to synthesise the evidence for relative effectiveness assessments? Do you have any suggestions for improvements?
6. To what extent is the methodology available for evidence synthesis of relative effectiveness applicable in a real-world setting?
   a. Can the available methodology directly be implemented?
   b. If not, which types of required data are typically not at hand? (i.e. can the available methodology directly be implemented, or is some of the required data typically not at hand?
7. What is your opinion regarding uncertainty arising from synthesising evidence for relative effectiveness assessment that are due to, for example, assumptions made or parameter definitions?
   a. Are sufficient sensitivity analyses performed relative to key assumptions being made?
   b. Which data sources may enhance the credibility of predictions regarding relative effectiveness?
8. What (if any) should be the role of structured decision aids such as multiple criteria decision analysis (MCDA) in decisions on relative effectiveness?

Perceived ease of use

Degree to which effort is needed to collect and use RWD.

1. What are the current obstacles faced in the collection of RWD as well as the
implementation of policies for the use of RWD in the decision-making process of drug development?
   a. Do you have any suggestions for improvements?
2. How challenging is the implementation (or assessment) of statistical/mathematical models for data synthesis in relative effectiveness assessment?
   a. Is this a routine in-house task or do you frequently need external expertise?
3. What is the role of software in enabling efficient use of RWD (for example, efficient analysis of data, efficient communication of results)?
   a. Is there key software that you use or that you feel is needed but currently missing?
8.3 Appendix 3 – List of RWD Initiatives Relevant to the IMI-GetReal Project

1. International Society for Pharmacoeconomic and Outcomes Research (ISPOR)
2. Patient-Centred Outcomes Research Institute (PCORI)
3. Centre for Comparative Effectiveness Research
4. Patient Registries Initiative (PARENT)
5. International Society for Pharmaceutical Engineering (ISPE)
6. New Drug Development Paradigms Initiative (NEWDIGS)
7. European Patients’ Academy on Therapeutic Innovation (IMI-EUPATI)
8. FDA Sentinel Initiative
9. Observational Health Data Sciences (Previously OMOP)
10. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European consortium (IMI-PROTECT Project)
11. EU-ADR Project
12. Canadian Network for Observational Drug Effect Studies (CNODES Project, Canada)
13. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP initiative)
14. NHS - Patient-Reported Outcomes Measures (NHS PROMS Programme)
15. The Health Improvement Network (THIN)
16. European Alliance for Personalised Medicine (EAPM)
17. European Network for HTA (EUnetHTA)
18. Centres for Medicare and Medicaid Service (CMS)
19. CMS Virtual Research Data Centre (CMS – VRDC)
20. Health Leadership Council (HLC)
21. Indiana Network of Patient Care
22. IMI-European Medical Information Framework (IMI-EMIF) project
23. Agency for Healthcare Research and Quality (www.ahrq.gov)
24. SOS project (safety of NSAIDs project) sos-naids-project.org
25. Aritmo project (www.dsrud.org/aritmo)
26. Farr institute (www.farrinstitute.org)
27. Mondriaan project (www.projectmondriaan.nl) extracts/provides/links EHR data in Netherlands
28. ESCHER Project (TI Pharma)
29. Canadian Agency for Drugs and Technologies in Health (CADTH)
30. Centre for Practice and Technology Assessment (USA)
31. National Pharmaceutical Council (USA)
32. RAND Corporation
33. Centre for Medical Technology Policy (CMTP)
34. IMI-Electronic Health Record Systems for Clinical Research (EHR4CR)
35. The BioIndustry Association (BIA)
36. TAPESTRY Programme (Canada)

Examples of Prominent RWD Databases:
37. Integrated Primary Care Information System (IPCI)
38. Clinical Practice Research Database (CPRD)
39. The Blue Button Initiative
40. NIHR Clinical Research Networks (NIHR-CRN)
41. FDA Mini-Sentinel
We would like to thank all reviewers who have provided valuable feedback on the report presented. Below is a detailed table outlining the authors’ responses.

Please note that some comments were received by interviewed stakeholders asking for minor editing of quotes belonging to them which were cited in this report. In order to maintain the anonymity of interviewed stakeholders, these comments were removed from the table below.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Organisation</th>
<th>Section</th>
<th>Comments Received</th>
<th>Authors’ Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB</td>
<td>VU</td>
<td>Section 1</td>
<td>What does RWE mean?</td>
<td>RWE had not been explained by line 110, thus has been changed to RWD (which had been previously explained and abbreviated).</td>
</tr>
<tr>
<td>MB</td>
<td>VU</td>
<td>Section 1</td>
<td>This document is about use of real world data but does not address the gap between registration RCTs and RWD that should be filled with pragmatic trials. I note that in the ‘Get Real’ initiative pragmatic trials are part of Work package 3. Perhaps good to mention that pragmatic trials are addressed elsewhere, or the misunderstanding persists that RCTs should be equated by industry-funded registration RCTs. Another principal question is whether ALL prelaunch trials should be directed at efficacy in a highly selected population, or that pragmatic trials should be part of registration requirements. In my view, for the immediate future post launch long-term pragmatic RCTs (probably funded and run by society (or 50%-50% with industry)) should be part of the solution, not just observational data.</td>
<td>The arguments presented by the reviewer here are valuable. However, they are beyond the scope of the report at hand, which only provides a review of policies and perspectives on RWD, since they offer PCT’s as a solution to addressing the efficacy-effectiveness gap. Therefore, the points made did not lead to a change in the text.</td>
</tr>
<tr>
<td>MB</td>
<td>VU</td>
<td>Section 3.7</td>
<td>practical obstacles. The development and maintenance of core outcome sets should be propagated, so people get guidance on key data to collect. See omeract.org and comet-initiative.org</td>
<td>This point has been incorporated in the discussion section (section 6) lines 1354 - 1356.</td>
</tr>
</tbody>
</table>
Thank you for the opportunity to comment on this important project and for the comprehensive status review based on feedback from a variety of stakeholders. It is clear that there is a wide appreciation of the efficacy–effectiveness gap and the dichotomy between pre approval randomised studies and the post approval RMP requirements for RWD. It thus appears that there is a regulatory focus on purity of design and control because it can be controlled and facilitates assessment regardless of whether it is fit for purpose or not. While it can provide determination (not proof) of efficacy and safety, only real world clinical use can (in an ongoing) manner provide a reflection of that proof.

Sponsors use Phase II studies as proof of concept or principle before confirmatory Phase III RCTs. It might be more useful to consider that the present Phase III RCTs are no more than Proof of Concept for real life use, but are very expensive, inefficient and dubiously effective. As such I believe that Get Real should further build on the summary that has been put together here and make proposals for inclusion of RWD to change the current Phase III process. This will require determination of methods to address bias, data quality, prospective design and stratification to ensure that any RWD approach is not simply an increment to Phase III RCTs.

I believe there are some specific techniques that can be investigated to increase the reliability of RWD from the relatively simple observational studies that lack sufficient robustness for efficacy determination, and with further thought can address some of the concerns of bias. This includes addressing the lack of a control / placebo group which can be overcome. Thinking about RWD as a tool in a different type of study rather than in its current

The reflections provided through this comment are valuable. Although they move beyond the scope of this report, which aims to provide a review of policies and perspectives on RWD, the GetReal consortium will take such reflections up in future discussions. Therefore, no subsequent changes to the text were made.
incarnation may be a more radical approach, but may assist in building additional utility. The stakeholder engagement approach discussed in the document is an encouraging first step to openly review opportunities for inclusion.

It seems unfathomable that the hurdle to approve a medicine relies on studying a very strictly controlled population, to allow broader use. While post approval assessments of benefit risk are taken based upon a mix of spontaneous safety reports and PASS studies which are predominantly observational with limited reference to benefit. Defining and adopting a blended approach to studies that can better reflect broader utility and safety and efficacy (stratified wherever possible) pre approval would increase the utility, relevance and predictability of development programmes while aiming to streamline the time and cost of studies.

I would hope to see Get Real propose substantial challenges to the accepted methodology to improve the relevance of development to the clinical population and investigate pilot projects for this approach that can test and investigate the ability to streamline development and increase the relevance of pre-approval studies thus reducing the schism between these are post approval activities.

I would be happy to discuss any aspects of this further and look forward to supporting this important initiative.

The paper seems to suggest that the main problem with a wider acceptance of RWE is ‘cultural’. We would disagree with this and propose that the main concern is the increased risk of bias and the lack of methodology to analyse RWE to overcome such bias. Until evidence of efficacy (or effectiveness) from RWE can be analysed to reduce the risk of bias, we would suggest that the reflections provided through this comment are valuable. Although they move beyond the scope of this report, which aims to provide a review of policies and perspectives on RWD, the GetReal consortium will take such reflections up in future discussions. Therefore, no subsequent changes to the text were made.
The main problem is a lack of scientific validity. The paper also concentrates on the use of RWE for efficacy/effectiveness. From the perspective of HTA, RWE can be used, and is often used, for many purposes other than the establishment of relative efficacy. In fact, other than relative efficacy, the TA methods guide does not specify that other model parameters are preferably sourced from RCTs. I think the document is missing the perspective of this wider usefulness of RWE in HTA.

If this wider perspective for the use of RWE in HTA is accepted, then the following are the main issues that we come across in SA:

1. Methodology to analyse RWE that can deal with bias, particularly ‘unmeasured confounders’ that randomisation addresses (I think further papers on this are planned)
2. Routinely collected data is often not in a format that allows its use for HTA – measures to collect data in a useful format should be addressed and will not add significantly to cost as this data is already being collected
3. Linking of data from different sources is often impossible – particularly when patients may receive some care in hospital and some in primary care
4. Access to data is often restricted and is time consuming and costly to access (identified in the document)
5. Many companies are concerned about the costs of data collection as well as ownership if this is mandated as part of coverage with evidence development.

<table>
<thead>
<tr>
<th>ZG</th>
<th>NICE</th>
<th>Page 8</th>
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<tbody>
<tr>
<td>NICE use the best available evidence in our decision making which in some instances could be only RWE. Therefore including the citation to the NICE methods guide in the sentence “Clinical effectiveness is thus never solely determined on the basis of RWE (21-23;28)” is This statement has been corrected to say “Clinical effectiveness is thus rarely solely determined on the basis of RWE” line 377, section 3.3.4.</td>
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<td>Author</td>
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<td>NICE</td>
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<td>ZG</td>
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<td>General</td>
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<td>JC, JH</td>
<td>Pfizer</td>
<td>Page 2</td>
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<tr>
<td>MB, DW</td>
<td>criteria..&quot;</td>
<td>section 1.</td>
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<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Page 2</td>
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<tr>
<td>&quot;which experimental products are often conventionally compared.&quot;</td>
<td>The suggestion has been implemented in line 76 of section 1.</td>
<td></td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Page 2</td>
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<tr>
<td>&quot;(e.g. post-marketing safety/ effectiveness studies)&quot;</td>
<td>Although authors agree that post-marketing efficacy studies practically provide data on effectiveness, they are still specifically named efficacy studies in EMA reference documents and longstanding guidelines. Therefore, no subsequent changes to the text were made.</td>
<td></td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.2</td>
</tr>
<tr>
<td>Would quasi-experiments -- where the investigator assigned patients to an intervention non-randomly – be considered “real-world”? I think so.</td>
<td>The reviewer provides a valuable reflection in this instance, which is, however not implementable in the context provided. Therefore, no subsequent changes to the text were made. The authors would refer the reviewer to the GetReal glossary, where this issue is clarified through the definitions of real world studies, effectiveness studies, etc.</td>
<td></td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.2</td>
</tr>
<tr>
<td>In epidemiologic observational studies excluding randomized trials, on the other hand, the patients assigned themselves to the treatment (self-selected, for example, to smoke or not to smoke tobacco).</td>
<td>The reviewer provides a valuable reflection in this instance, which is, however not implementable in the context provided. Therefore, no subsequent changes to the text were made. The authors would refer the reviewer to the GetReal glossary, where this issue is clarified through the definitions of real world studies, effectiveness studies, etc.</td>
<td></td>
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<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.2</td>
</tr>
<tr>
<td>Patient-reported outcomes are also included in randomized controlled trials.</td>
<td>The reviewer provides a valuable reflection in this instance, which is, however not implementable in the context provided. Therefore, no subsequent changes to the text were made. It should be noted that PRO's are included in the scope of RWD types. The authors would...</td>
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</tbody>
</table>
refer the reviewer to the GetReal glossary, where this issue is clarified through the definitions of RWD.

<table>
<thead>
<tr>
<th>JC, JH, MB, DW</th>
<th>Pfizer</th>
<th>Section 3.3.3</th>
<th>Agree with Jim’s comment. Nice to see mention of restriction of Medicare data, but it would be of interest to note the availability of both commercially insured populations and Medicare Advantage populations from non-government insurers which does create some inconsistencies in what is available for research. The reviewer raises a good point, which has subsequently been added to lines 1306 - 1308 of section 6.</th>
</tr>
</thead>
<tbody>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.3.3</td>
<td>Not sure if you want here/HTA section below, but Do you want to note that the largest insurers beyond CMS often have research organizations that conduct observational research with their RWD Also, there was an article in the Pink Sheets a few years back on how WellPoint used RWD for decision making citing an example of CER for statins to inform their decision. Also, there seem to be more commercially available de-identified payer datasets in the US. The examples raised by the reviewer here are valuable ones of how RWD has influenced decision-making within the payers/insurers stakeholder groups. Although the authors recognise their relevance for sections 3.3 and 5.3, it is difficult to incorporate them since they have not been located during the literature review or previously mentioned during the stakeholder interviews. Additionally, their inclusion will not significantly alter the flow of ideas and discussions introduced in this report. To avoid affecting the validity of methodologies used and results reached, the authors have therefore decided to not incorporate these examples in sections 3.3 or 5.3.</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.3.5</td>
<td>Please consider these articles from industry colleagues on RWD use practices: <strong>M.L. BERGER</strong>, M. Mamdani, D. Atkins, M.L. Johnson. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources. The ISPOR good research practices for retrospective database analysis task force report – Part I. Value in Health, The point raised by the reviewer here is relevant: some employees of industry stakeholders have indeed cited best practices for using RWD. However, the context in the report relates to documents officially citing company policies on collecting &amp; using RWD, of which none could be found during the literature review. The statement in the report has accordingly</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.3.5</td>
<td>ISPOR good practice reports should be included here.</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 3.7</td>
<td>Interoperability of EHR is another component here which limits the ability to follow patients across settings and systems. See that this is mentioned under procedural, but I think it given lack of clear standards and the number of EHR vendors, it would be relevant here as well.</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 5.2</td>
<td>I concur with remark on PRO's and trial supplements not being considered as RWD</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 5.2</td>
<td>Pts consider removing these transcription expressions from the quotes?</td>
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<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 5.3</td>
<td>&quot;Typically, RWD use and engagement in its collection occurs during drug development and as part of post-marketing commitments <strong>and value proposition support</strong> or risk-sharing agreements.&quot;</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 5.6</td>
<td>Additionally consider removal of variables when combining datasets (e.g., removal of zip code/state/location when combining EHR/claims or limitations on linking death information to other info) and how those HIPAA considerations limit the value of linking datasets.</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 5.6</td>
<td>Data captured in routine practice often reflects qualitative information that will inform treatment decisions, but not quantitative measures over time (e.g. “pain” as a symptom, but not on a 0-10 pain score).</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 5.8</td>
<td>On FDA perception of RWD as being of low quality: Except in the case of safety studies...but there is often not a balance of safety/effectiveness from FDA in post-marketing (e.g. mini-Sentinel).</td>
</tr>
<tr>
<td>JC, JH, MB, DW</td>
<td>Pfizer</td>
<td>Section 7</td>
<td>It could be emphasized here and elsewhere that RWD and RWE can help with generating hypotheses that can be studied further in prospective studies, either from a randomized controlled trial or other study design (quasi-experimental, observational).</td>
</tr>
</tbody>
</table>
### I like the 5-bullet suggestions on how to better integrate RWD and RWE into decision frameworks for drug development and drug assessment, but it feels a bit brief. I’ve seen similar conclusions in other publications, so as it stands does it go beyond what’s been said previously? Could the authors provide recommendations that are a bit more in-depth? Given this is coming out of the GetReal work-stream, which is well-known and with prominent individuals, is there opportunity to be a bit stronger / detailed? Just a thought – but the paper is good as is.

The authors agree that the issues outlined in the conclusions need to be addressed in a more detailed manner by the GetReal consortium throughout the project. This report, however, only serves as a starting point for subsequent work by the consortium. Therefore, no subsequent changes to the text were made.

### For what it’s worth, I think the key question arising is listed in the end section as:

2. Reach consensus regarding the relevance of RWD for answering different scientific questions in different drug development and assessment phases

This is kind of hinted at through the paper, but I think the problems arise when the questions about RWD are asked very generally which is when you get the response about RWD’s lowly ranking in hierarchies of evidence. If you get more specific eg we have a question about aspect X of a drugs performance in disease Y: what are the best sources of evidence that we can find to answer this question? Then RWD may come to the fore. The hierarchies of evidence approach kind of implies that you can chose whether to deliver evidence via RWS or an RCT, so if you choose the RWS route you’ll get discounted. But this isn’t the case is it? If the question you want answering is not suitable for a randomisation study, or because some characteristics of

The authors agree to the majority of points made here regarding evidence hierarchies and the relevance of altering the perception of RWE as being inherently of lower quality (especially in areas such as orphan diseases). A paragraph has been added to section 6 (lines 1286 - 1295) addressing this point.
the disease (esp in rare diseases) mean that case studies or other sources of evidence are as good as you’re going to get. Incidentally, orphan drugs might be a good area to pursue in more depth – there are a lot of cases where non RCT data has been used for approval.

<table>
<thead>
<tr>
<th>SF, RH</th>
<th>MHRA</th>
<th>Definition of RWD, RWE, RWS</th>
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<tbody>
<tr>
<td>• The papers highlight that the various definitions are controversial and this is endorsed. I think that the definitions would benefit from some further reflection. In particular, the definitions mix the data source with the experimental design. The paper includes a pragmatic design as RWD, and more controversially (incorrectly) all adaptive clinical trials, many of which are very clearly RCTs. The border between an RCT (the definition of which doesn’t necessitate tight inclusion and exclusion criteria), a large simple trial and a pragmatic trial can be blurred. A large simple trial collecting data with an unlicensed treatment, with informed consent, collecting data through CRFs that may or may not be collected in routine clinical practice would appear to be a CT, as defined by the relevant legislation. A large simple trial using EHRs may be RWD. Without considering both the data collection and the trial design it is not clear that definitive definitions can be reached. Furthermore, it is not clear how single arm clinical trials are classified in the definitions.</td>
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<td>The points raised by the reviewer are quite valid; indeed, many stakeholders agree that a clear, pragmatic definition for RWD is essential. The definitions of RWD and RWS have been updated accordingly. The authors also refer the reviewer to the GetReal glossary for confirmation.</td>
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<tr>
<th>SF, RH</th>
<th>MHRA</th>
<th>Definition of RWD, RWE, RWS</th>
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<tr>
<td>• There is some internal inconsistency in the definition of pragmatic clinical trials between the two documents that were circulated, one indicating that a randomisation ratio changing over time being part of the definition of what constitutes PCT (Section 6, paragraph 3), and this aspect being absent / replaced in the definitions in the</td>
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<td>Even though the definitions in the documents referred to both indicate that randomisation is part of PCT’s definition, the wording in the glossary was not as clear as in the report. Therefore, the definition in the glossary was re-worded to</td>
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second document. highlight the fact that the design of PCT’s involves randomisation of the trial population.

| SF, RH | Definition of RWD, RWE, RWS | Overall, it seems preferable to promote a continuum of data collection and a toolbox of study designs than a dichotomy of RCT and RWD. Although this is a relevant point, it has been discussed in section 6 in the context of the role RWE can play in the context of adaptive licensing. Therefore, no subsequent changes to the text were made. |
| SF, RH | Representation of regulatory standards | • It is difficult to say in general terms that experimental are conventionally compared to placebo. It should be noted that the definition of efficacy in the ‘effectiveness vs efficacy’ debate is not obviously the same as the definition of therapeutic efficacy in the pharmaceutical legislation, in particular the therapeutic effect as compared to placebo under ideal conditions is not a regulatory standard, in particular if ‘ideal conditions’ includes adherence to treatment. The reviewer provides a valuable reflection in this instance, which is, however not implementable in the context provided. The authors would refer the reviewer to the GetReal glossary, where this issue is clarified through the definitions of efficacy, effectiveness, relative efficacy and relative effectiveness. Therefore, no subsequent changes to the text were made. |
| SF, RH | Representation of regulatory standards | • It is implied that post-authorisation work is only because of concerns over extrapolation from efficacy to effectiveness (i.e. because of lack of external validity of clinical trials). I think this is not generally true and that post-authorisation work is more commonly related to reducing uncertainties in the evidence base for licensing; only a subset of which will relate to this perceived problem. This comment relates to the readers' interpretation. The report states that post-marketing commitments address uncertainties in evidence of both safety and efficacy. Therefore, no subsequent changes to the text were made. |
| SF, RH | Representation of regulatory standards | • It is implied that there is an under-use (in part due to ‘culture’) of RWD in regulatory decisions. It is not reflected in the paper that most of the research supporting regulatory submissions of experimental compounds is conducted, including Phase III trials – as demanded by legislation – in the controlled environment of clinical trials. In section 5.7 it is asserted that relative effectiveness generated by real-world studies ‘can be ignored’ by regulatory authorities. This The authors agree with the point made by the reviewer here regarding the over-simplification of regulatory procedures. This has been incorporated by making changes to the old statement this comment refers to; please see lines 1100-1102. However, it is important to note that the tensions we refer to here relate to Phase IV studies and other REA studies, rather than phase III |
criticism is at best an oversimplification. Presumably it is therefore equally asserted that this type of data ‘can be recognised’ by regulatory authorities; and to some extent this will depend on whether the applicant proposes / or the regulators deem necessary a variation to the licence based on the data collected, within the confines of our mandate defined in the relevant legislation. It should be recognised that there is no legal mandate on Marketing Authorisation Holders to make the drug available as widely as possible by removing warnings, restrictions etc. from the label, unless relevant Specific Obligations are set at Marketing Authorisation. The ‘tensions’ described between regulatory and reimbursement dossiers are in part described by our different mandates; with regulators refusing an application for marketing authorisation where therapeutic efficacy has not been demonstrated or benefit-risk is not positive. An assessment of therapeutic efficacy differs from an appraisal of cost-effectiveness or relative-effectiveness and this is not recognised in the paper. Of course, this does not preclude conversations between stakeholders about evidence being generated in the most efficient way to meet the needs of all.

<table>
<thead>
<tr>
<th>SF, RH</th>
<th>MHRA</th>
<th>Section 3.4.2</th>
<th>The terminology in the third paragraph is potentially misleading; the wording may lead to confusion of MAPPs with Marketing Authorisation under Exceptional Circumstances.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF, RH</td>
<td>MHRA</td>
<td>Section 3.4.1</td>
<td>• Some RWD uses are described that are non-controversial and are already encouraged; in particular in relation to defining disease states, population stratification, designing CTs etc. I expect these were not really considered as RWD by some stakeholders.</td>
</tr>
</tbody>
</table>

The sentence to which the reviewer refers was reworded to make it clear that adaptive pathways and exceptional MA's were different contexts. Please see lines 535 - 538 of section 3.4.

The reviewer provides a valuable reflection in this instance, which is, however not implementable in the context provided. Therefore, no subsequent changes to the text were made. However, the
as they inform rather than aim to RCTs.

authors indicate that use of RWD for defining disease states, population stratification and designing clinical trials has been mentioned in stakeholder interviews.

<table>
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<th>SF, RH</th>
<th>MHRA</th>
<th>Appendix 8.1.1</th>
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<tr>
<td></td>
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<td>• In Table 1 it can be noted that a European guideline on Flexible (Adaptive) designs also exists and gives a definition that might be reflected here.</td>
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<td>This table provides a list of stakeholders whose websites were consulted for the grey literature review. Therefore, this comment does not directly fit in this context and no subsequent changes were made to the text. However, it is a valid comment for the GetReal glossary, and the source mentioned has indeed been used to adapt the definition for adaptive clinical studies therein.</td>
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<tr>
<th>SF, RH</th>
<th>MHRA</th>
<th>Section 3.5/5.5</th>
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<td></td>
<td></td>
<td>• The arguments against the external validity of RCTs are qualitative in nature. Better quantification would be helpful in selling the possibilities to all stakeholders. There is a conditioning that CTs do not adequately capture real-world effects and it is true that not all patient ‘types’ ultimately covered by the product licence will not be represented in Phase III CTs, but exactly what can and cannot be extrapolated from the totality of evidence in a drug development programme remains unclear. For example there is usually a rather good understanding of clinical pharmacology at the time of licensing that can complement evidence in Phase III RCTs, e.g. ADME is quantified, drug-drug interactions are understood and described in labelling (viz use with concomitant medications) and changes in exposure in special populations (weight, renal / hepatic impairment etc.) are quantified and described.</td>
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<td>Although the reviewer makes quite a good point in quantifying the nature of evidence gaps throughout the drug development cycle to define the evidence gap generated by RCT data, the authors recognise that GetReal and the wider community are far from quantifying such an issue; it is a challenge to first reach consensus on the sorts of evidence gaps present. Furthermore, for the purposes of GetReal, consensus should first be reached on the relevance of RWE for answering various scientific questions that rise due to such an evidence gap. Perhaps as experience builds in RWE use and the evidence gaps present, quantification may become possible. Therefore, the point raised by the reviewer can certainly be valuable for future GetReal work, but moves a step further in scope than the aims of this report and current state of experience in the</td>
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</table>
• Building on the quote from the HTA Agency E in Section 5.6, an important objective of work in this area is to improve quantification of the extent to which the full drug development process leaves open questions on the external validity of the totality of findings and, perhaps more importantly, under what circumstances are RWD reliable (free from important bias) for stakeholder decision making. It should not be the case that methodological issues are ignored by stakeholders simply because they cannot yet be resolved.

Please see the response to the comment provider by the reviewer above, which is also applicable to this comment.

• In trying to harmonise evidentiary standards for all stakeholders (regulatory agencies in different regions, HTAs in different EU member states etc) do we miss the opportunity to harmonise for a subset of stakeholders, at least in the first instance? It is not yet obvious, not least because of the different mandates and interests of different stakeholders, that all solutions will be the same for all stakeholders.

The authors agree with the comment made by the reviewer. In light of significantly different mandates of relevant stakeholders, harmonisation of RWE requirements should be harmonised among a sub-set of stakeholder in the first instance; more specifically between regulatory agencies, HTA agencies and pharmaceutical industry. This has been added to section 6, lines 1343 - 1349.

GPRD is now known as CPRD but is referenced here consistently as GPRD – Please use Clinical Practice Research Datalink (CPRD).

This has been corrected in lines 568 and 1065.

- I had problems with the beginning of the discussion which was not so clear to me.

The lay-out of section 6 has been edited to be more coherent. More specifically, the new structure of the discussion follows the order in which issues were raised in throughout.
<p>| SK  | ZIN | Section 6 | - I struggled a bit with the structure of the discussion, you discuss issues, opportunities, issues, summary, example of positive collaboration. I would prefer to have 1) all issues listed 2) opportunities listed and then summarise in the conclusion how to deal with these. Maybe subheading would be an options for structuring? I have suggested some subheadings. | The lay-out of section 6 has been edited to be more coherent. More specifically, the new structure of the discussion follows the order in which issues were raised in throughout the report which also introduces a logical progression of arguments. The authors believe that this should make section 6 more accessible to readers. |
| SK  | ZIN | Section 7 | I deleted the last statement of the conclusion and abbreviated this statement as it seemed a bit overly persuasive: &quot;In order to raise the quality of RWD collected and thereby increase the confidence of all stakeholder in RWD and its value for decision-making we recommend to:&quot; | In order to maintain consistency in conveying the messages delivered by this report, the authors agreed to keep the concluding statements unchanged. |
| SK  | ZIN | Section 7 | Replace RWE needs to RWE evidence requirements | The authors agree that the term evidence 'requirements' is more accurate for the purposes of this report than evidence 'needs'. This was implemented throughout the report. |
| PA  | ZIN | Section 1 | RWD definition: impact instead of effect | In order to maintain consistency with the definitions of terms such as effectiveness and relative effectiveness in the GetReal glossary, the authors decided not to adopt this change. |
| PA  | ZIN | Section 1 | RWS definition: revise term scientific studies; perhaps clinical studies | The authors agree that changing the term 'scientific studies' to 'clinical studies' provides a more accurate definition. Therefore, the proposed change has been implemented. |</p>
<table>
<thead>
<tr>
<th>PA</th>
<th>ZIN</th>
<th>General</th>
<th>How does this relate to the assessment vs. Appraisal debate?</th>
<th>Although the question raised by the reviewer here is intriguing, it lies beyond the scope of this report which only aims to provide a review of policies and perspectives on RWD. The authors acknowledge, however, that this is an important point to be discussed by the GetReal consortium. Therefore, no subsequent changes to the text were made.</th>
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<tbody>
<tr>
<td>PA</td>
<td>ZIN</td>
<td>General</td>
<td>Summary table overview needed to present results of main recurrent themes per sub-heading</td>
<td>The authors agree that readers would benefit from a summary table. Please see lines 263-265, 809-811 and tables 6 &amp; 9 for the subsequent changes made.</td>
</tr>
<tr>
<td>PA</td>
<td>ZIN</td>
<td>Section 3.6</td>
<td>Last paragraph not very clear; confusion regarding the availability of RWD</td>
<td>The authors believe that the confusion referred to here is a result of the reader's interpretation. However, the context within which the availability of RWD is mentioned has been checked to ascertain that it can be clearly interpreted by readers. Therefore, no subsequent changes to the text were made.</td>
</tr>
<tr>
<td>PA</td>
<td>ZIN</td>
<td>Sections 3.7/3.9</td>
<td>Is it possible to merge the sections on practical obstacles and procedural considerations, given they complement/ repeat one another?</td>
<td>The authors agree with the reviewer on the overlap between issues exhibited in the sections on practical obstacles and procedural considerations. However, these cannot be combined into one section, as that on practical obstacles demonstrates the real-life problems encountered while collecting and using RWD, whereas procedural consideration provides reflections on how to potentially incorporate RWD in decision-making. Therefore, the authors decided to keep both sections separate.</td>
</tr>
<tr>
<td>PA</td>
<td>ZIN</td>
<td>Section 3.8</td>
<td>Consider changing the heading from political considerations to governance considerations</td>
<td>By using the term political, the authors incorporate aspects of both law-making as well as decision-making. However, by referring to governance, the authors believe they would set the focus on the methods for exercising the administration of law-making and decision-making. In accordance with the scope of this section, the authors thus chose to stick with the term political considerations.</td>
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