# **Supplementary materials**

## ***Pragmatic literature review – methodology***

A pragmatic literature search of peer reviewed, articles on the HTA body and payer perspectives of barriers to RWE use, including a ‘review of reviews’ was undertaken. This approach was used to ensure the evidence identified built on the extensive RWD/RWE body of work published to date. Searches were restricted to EU, UK, Canada, and USA. Stakeholders of interest included regulators, HTAs, payers, multi-stakeholder initiatives, and academic/scientific institutions (if overlapping).

Further targeted literature reviews were undertaken to identify solutions to barriers such as methodological papers. This included a search of key RWD/RWE initiatives, HTA/regulatory websites, EUnetHTA, Google, and PubMed, this included: HTA bodies (NICE, HAS, IQWiG, TLV, CADTH) + PCORI; multi-stakeholder groups involved in RWE initiatives (GET REAL RWE-navigator, ISPOR, ISPE), and regulatory bodies (FDA, EMA).

Key information was extracted for each document.

The six key papers identified in the pragmatic literature review are shown in **Table 1**. The remaining papers are outlined in **Table S1**.

## ***Targeted literature review – methodology***

A targeted literature reviews was undertaken to identify solutions to barriers and had a focus on seeking out methodological papers of interest. This included a search of key RWD and RWE initiatives, HTA/regulatory websites, EUnetHTA, Google, and PubMed.

**Table S1.** Remaining papers identified in the pragmatic and targeted literature reviews and the issues reported related to RWD and RWE

|  |  |  |
| --- | --- | --- |
| **Reference** | **Issues reported** | **Themes** |
| [Makady *et al*. 2017b](https://pubmed.ncbi.nlm.nih.gov/28857631/) | * Availability/accessibility of RWD-IPD
* Varying definitions of outcome measures
* Lack of trust in the robustness of data and findings compared with RCT
* Lack of experience with using RWE in currently available methods to address questions relating to (comparative) drug effectiveness
* Lack of clarity, undisclosed contracts in registry set up-need for transparent governance
 | DataMethods |
| [Polisena and Jayaraman 2020](https://pubmed.ncbi.nlm.nih.gov/33161916/) (16) | * Leadership: regulatory and HTA bodies must explicitly communicate the purposes for which RWD will be collected and how RWE generated will be used for regulatory decisions and HTA recommendations
* Need for framework (from Health Canada) and guidance on RWE use, identify relevant outcomes for data collection
* Criteria for data quality
* Need to conduct post-market surveillance more systematically
* Partner with HTA organizations to develop methods for RWE generation
* Robust scientific methods for RWE generation critical to ensure that relevant questions asked, and rigorous statistical analyses done
* Patient privacy, patient participation based on usage
 | MethodologyData (governance)Policy and partnerships |
| [Hampson *et al*. 2018](https://pubmed.ncbi.nlm.nih.gov/30411972/) (12) | * Bias and confounding
* Obsolete evidence hierarchies
* Lack of investigator expertise, methods guidance
* Lack of common methods standards
* Data access
* Data mining
* Incomplete data
 | MethodsDataTrust and transparency |
| [Malone *et al*. 2018](https://pubmed.ncbi.nlm.nih.gov/29566840/) (13) | * Timeliness of results
* Resources and skills to evaluate/conduct studies
* Lack of transparency in methods
* Relevance of study/study endpoints
* Data quality
* Methods, confounding
 | Trust and transparencyMethodsData |
| [Clausen *et al*. 2020](https://pubmed.ncbi.nlm.nih.gov/33234584/) (14) | * Lack of expertise in methods
* Lack of universal methods standards
* Challenges for data access
* Bias, confounding, use instead of RCT to establish efficacy
* Inadequate data infrastructure
* Lack of resources
* Siloed working
 | MethodsDataPolicy and partnerships |
| [Berger *et al*. (2017)](https://pubmed.ncbi.nlm.nih.gov/28964430/) (10) (ISPOR/ISPE special taskforce) | * Data dredging
* Publication bias
* Cherry picking
 | DataTrust and transparency |
| [ICER 2018](https://icer.org/wp-content/uploads/2020/11/ICER-RWE-Framework-Companion-White-Paper-03282018.pdf) (11) | * Don't want to incentivize RWE in place of RCT
* Bias and confounding
* Incomplete data
* Data mining
* Access to data
* Lack of universally accepted methodological standards
 | Trust and Transparency DataMethods |
| [Bullement *et al*. 2020](https://pubmed.ncbi.nlm.nih.gov/32646531/)(17) | * Specific data sources and the applicability of these to the decision problem
* Comparability of real-world cohorts to the clinical trial patients
* Relevance of RWE patient cohorts to contemporary practice
* Difficulties in collecting baseline health-related quality of life data and patient consent
* Securing adequate funding to maintain a database and support staff, information technology issues
* Lack of a clear control group
 | Methods Data |
| [NICE 2016](https://nicedsu.sites.sheffield.ac.uk/tsds/observational-data-tsd) (21) | Interviews: * RG skill sets vary – many skilled in systematic review and meta-analysis using RCT data, but lack expertise to critically assess the quality of observational studies or perform a statistical analysis on patient-level observational data
* Limited guidance on combining RCT evidence with observational evidence, single arm evidence, and assessing the uncertainty surrounding treatment effects
* Earlier assessment comes greater uncertainty, therefore managed entry agreements required but further guidance needed on design and methods
* MEAs: risk of bias if attrition or discontinuation differs by prognostic factors

Case studies: Selection bias, lack of adjustment for confounding factors in design and analyses, unmeasured confounding, single source RWD | Methods DataExpertise and resources |
| [Lee *et al*. 2021](https://pubmed.ncbi.nlm.nih.gov/33377439/) (18) | * Reference Malone *et al*. (2019) on payer barriers to RWE use. Additional barriers noted were:
	+ Lack of awareness and underutilization of quality assessment tools for RWE
	+ Underutilization due to the time required to generate RWE
	+ Difference in sample sizes, data sources, study designs, and critically, few preregistered RWE studies (reference made to ISPE and ISPOR RWE Transparency Initiative) led to variability in ICER acceptance
 | DataTrust and transparency |
| [Chan *et al*. 2020](https://bmjopen.bmj.com/content/10/1/e032884) (15) (CanREValue) | * Challenges to survival estimation for comparative treatment effectiveness
* Baseline confounding
* Time-varying confounders
* Appropriate study design and methods to adjust for selection bias and the effects of confounding
* Data availability and quality, operationalization, and implementation
* Endpoints (PFS) not well defined in health administrative databases
* Immortal time bias and left truncation
 | Data Methods  |

**Abbreviations:** HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; ISPE, International Society for Pharmacoepidemiology; ISPOR, The Professional Society for Health Economics and Outcomes Research; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; RCT, randomized controlled trial; RWD, real-world data; RWE, real-world evidence.