# **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

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| --- | --- | --- |
| **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 | Data  Methods |
| [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 | Methodology  Data (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 | Methods  Data  Trust 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 transparency  Methods  Data |
| [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 | Methods  Data  Policy and partnerships |
| [Berger *et al*. (2017)](https://pubmed.ncbi.nlm.nih.gov/28964430/) (10) (ISPOR/ISPE special taskforce) | * Data dredging * Publication bias * Cherry picking | Data  Trust 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  Data  Methods |
| [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  Data  Expertise 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 | Data  Trust 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.