Appendix B – Overview of Real-World Evidence Framework

## Key messages

The [NICE Strategy 2021 to 2026](https://www.nice.org.uk/about/who-we-are/corporate-publications/the-nice-strategy-2021-to-2026) states our ambition to use real-world data to resolve gaps in knowledge and drive forward access to innovations for patients. Real-world data is essential to enabling rapid, robust, and responsive technology evaluations and dynamic, living guidelines.

* We have developed the Real-World Evidence Framework to help deliver on this ambition. It does this by:
* identifying where real-world data can be used to reduce uncertainties and improve guidance
* clearly describing best-practices for the planning, conduct, and reporting of real-world evidence studies to improve the quality and transparency of evidence.
* The body of the framework provides in-depth guidance and tools to support the implementation of these core principles across real-world evidence use cases and is structured as follows:
* In the [Introduction](#_Introduction_to_real) we provide background material on real-world data and real-world evidence, discuss its strengths and weaknesses, and summarise current and potential uses within NICE guidance.
* In [study conduct](#_Conduct_of_quantitative_1) we describe expectations for the planning, conduct, and reporting of real-world evidence studies, recognising that acceptability of evidence will depend on the type of evidence and other contextual factors.
* In [assessing data suitability](#_Assessing__data) we describe the information needed to assess data provenance and its quality and relevance for addressing specific research questions
* In methods for [real-world studies of comparative effects](#_Methods_for_real-world_1), we provide more specific recommendations for the conduct of non-randomised studies. This includes traditional observational studies as well as clinical trials using real-world data to form an external control.
* The following core principles should be followed to generate high-quality and trusted real-world evidence, while [Table 1](#Table1) provides a summary of key considerations when conducting real-world evidence studies:
* Ensure data is of good provenance and is relevant and of sufficient quality to answer the research question.
* Generate evidence in a transparent way and with integrity from study planning through to study conduct and reporting.
* Use analytical methods that minimise the risk of bias and characterise uncertainty.
* The framework is a living framework that will be updated periodically to reflect user feedback, learnings from implementation including exemplar case studies, developments in real-world evidence methodology, and to extend its scope to include additional guidance on priority topics.
* We encourage companies planning to use real-world data in their submissions to NICE to engage early with [NICE Scientific Advice](https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice) on how to make best use of real-world data as part of their evidence generation plans.

Table 1. Summary of key considerations in the planning, conduct and reporting of real-world evidence studies

| Stage of evidence generation | Key considerations |
| --- | --- |
| [Planning](#_Study_planning_1) | * Clearly define the research question including, as relevant, definitions of population eligibility criteria, interventions, outcomes, and the target quantity of estimation * Plan the study prospectively and make protocols publicly available * Choose data that is of good provenance and of sufficient quality and relevance to address the research question * Justify the need for further primary data collection weighing up the burden on patients and healthcare professionals against the value of additional data * Use data in accordance with local law, governance processes, codes of practice, and the requirements of the data owner |
| [Conduct](#_Study_conduct_2) | * Use a study design and statistical methods appropriate to the research question considering the key risks of bias * Use sensitivity and/or bias analysis to assess the robustness of studies to key risks of bias and uncertain data curation or analytical decisions * Undertake quality assurance to ensure the integrity and quality of the study |
| [Reporting](#_Study_reporting) | * Report study design and analytical methods in sufficient detail to enable independent researchers to fully understand what was done and why, critically appraise the study, and reproduce it * Reporting should also cover:   + The provenance, quality, and relevance of the data (see [assessing data suitability](#_Chapter__))   + Data curation   + Patient attrition from initial data to the final analyses   + Characteristics of patients (including missing data) and details of follow-up overall and across key population groups   + Results for all planned and conducted analyses (clearly indicating which analyses which were not pre-planned)   + Assessment of risk of bias and generalisability to the target population in the NHS |

## Real-world data and its role in NICE guidance

* Real-world data refers to data collected outside of highly-controlled trials, and can come from many different sources including patient health records, administrative records, patient registries, surveys, observational cohort studies, and digital health technologies.
* Real-world data is already widely used to inform NICE guidance, for instance to:
* Characterise health conditions, interventions, care pathways, and patient outcomes and experiences
* Design, populate, and validate economic models (including estimates of resource use, quality of life, event rates, prevalence, incidence, long-term outcomes)
* Develop or validate digital health technologies
* Identify, characterise, and address health inequalities
* Understand the safety of medical technologies including medicines, devices, and interventional procedures
* Assess the impact of interventions (including tests) on service delivery and decisions about care
* Assess the applicability of clinical trials to patients in the NHS
* Real-world data that represents the population of interest should be the preferred source of evidence for most of these applications. While such data is regularly used for these purposes in NICE guidance, its use could be more commonplace, especially of routinely collected data.
* Randomised controlled trials are the preferred source of evidence on the effectiveness of interventions. Randomisation ensures that any differences in baseline characteristics between groups is due to chance and blinding (where applied) prevents knowledge of treatment allocation from influencing behaviours. However, randomised trials are sometimes unavailable or are not directly relevant to decisions about patient care in the NHS.
* Randomised trials may not be available for several reasons including:
* randomisation is considered unethical or infeasible (for instance, for some rare or severe diseases with unmet need)
* technical challenges that make randomisation impractical, which are most common for medical devices and interventional procedures
* absence of funding for a trial (for instance, when the intervention is already in routine practice).
* Even where randomised evidence is available, it may not be sufficient for decision-making in the NHS for several reasons including:
* The comparator does not reflect standard of care in the NHS
* Relevant population groups are excluded
* There are major differences in patient behaviours, care pathways, or settings that differ from implementation in routine practice
* Follow-up is limited
* Unvalidated surrogate outcomes are used
* Learning effects are present
* Trials were of poor quality
* Non-randomised studies are already widely used to estimate the effects of medical devices and procedures and public health interventions, where trials are less common. They are becoming more widely used in the initial assessments of medicines as more medicines are granted regulatory approval based on uncontrolled single-arm trials. Finally, the increased focus on the lifecycle of technologies and lived experiences of patients relies on non-randomised studies after initial approvals. The most common non-randomised studies using real-world data to assess comparative effects are observational cohort studies and single-arm trials with real-world external control.
* While real-world data could be used to a greater extent to fill evidence gaps and speed up patient access, there are several important barriers to its use including:
* Challenges in accessing high-quality data in a timely manner
* Concerns about data provenance and quality
* Risk of bias from information limitations, selection into or exit from studies, and confounding by indication in comparative studies evidence
* Limited trust in the integrity of some real-world evidence studies given the complexity of evidence generation and opportunity to cherry-pick results
* It is important that NICE communicates its expectations for the conduct of real-world evidence studies to ensure that is generated transparently and is of good quality. This is essential to improving trust in real-world evidence studies and their use in decision-making.