National Institute for Health and Care Excellence

Real-World Evidence Framework Update

This report gives details of the Real-World Evidence Framework (version 1) developed by the Data & Analytics team.

The Board is asked to:

* Approve the plans for consultation on the RWE Framework
* Discuss our plans for further developing the framework and implementation

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Introduction

NICE first outlined its ambitions to make greater use of real-world data in a Statement of Intent published in January 2020. This ambition has since been strengthened by the NICE Strategy 2021 to 2026 which recognised that real-world data underpinned NICE’s strategic ambitions including: rapid, robust, and responsive technology evaluations; dynamic, living guideline recommendations; effective guidance uptake; and, leadership in data, research and science.

The Data & Analytics team at NICE was asked by the NICE board to develop a framework for the use of data and analytics in NICE guidance development (the real-world evidence [RWE] framework). The primary objective of the framework is to encourage the best use of available data for informing NICE guidance in a timely, robust, and transparent manner. The board approved a two-year programme of work to develop this framework in January 2021. This became a priority strategic objective following the publication of the NICE Strategy in April 2021.

We have developed the first version of the RWE framework and received positive feedback from a wide range of external stakeholders including NICE committee members and external academic groups, patient representatives, the life sciences industry, data custodians, and UK healthcare bodies including the MHRA.

This paper describes the purpose and scope of the framework, its content, its development, and discusses the next steps to ensure the successful implementation and continued relevance of the framework.

Purpose and scope of the RWE framework

The framework clearly describes where real-world evidence could inform guidance and signals best practice around the planning, conduct, and reporting of real-world evidence studies.

The framework is intended to inform guidance development across NICE but is not positioned as formal methods guidance. The framework is referenced in the updated health technology evaluations manual (paragraph 3.3.14). We are currently working on its integration into the developing NICE guidelines manual.

The framework is aimed primarily at those developing evidence for use in NICE guidance. This includes manufacturers, third parties, and NICE staff or collaborators, but will also support those reviewing evidence. The framework will help ensure that real-world studies are undertaken with integrity and reported transparently, following best practice methods. This will improve both quality of real-world evidence studies and consistency in their evaluation.

The framework does not impose minimum standards for real-world evidence studies. We recognise that the acceptability of a specific study will depend on the use case, the NICE programme, and a range of other contextual factors such as decision uncertainty.

The framework will be updated periodically to reflect user feedback on this first version, developments in real-world evidence research, and to extend its scope to include additional guidance on priority topics

Summary of RWE framework content

The first version of the framework focuses on the primary analysis of real-world data sources for informing NICE guidance with an emphasis on quantitative research.

We define the following principles which should be followed to generate high-quality and trusted real-world evidence across use cases:

* Ensure data is of demonstrable 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 currently consists of the following sections:

* Personas – provides examples of how different users can engage with the framework and the benefits it offers (Appendix A).
* Overview – provides a short, accessible overview of the framework that summarises key considerations for developing real-world evidence (Appendix B).
* Introduction – provides background material on real-world data and real-world evidence, discuss its strengths and weaknesses, and summarises current and potential uses within NICE guidance.
* Study conduct – describes best-practices for the planning, conduct, and reporting of primary real-world evidence studies across use cases.
* Assessing data suitability – describes the information needed to assess data provenance and its fitness for purpose for specific research questions; we developed the Data Suitability Assessment Tool (DataSAT) to support structured and consistent reporting of data suitability.
* Methods for studies of comparative effects – provides detailed recommendations and considerations for the conduct of non-randomised studies using real-world data; this builds on the Technical Support Document 17 concerning statistical methods for confounding control in observational data with additional guidance on study design (drawing on the target trial approach), sensitivity and bias analysis, and reporting.
* Appendices – presents reporting tools and case studies.

Framework development

## Overview

Our initial plans for the real-world evidence framework were approved by the NICE board in January 2021. We presented progress and plans to the Data & Analytics oversight group meetings every two months starting in April 2021. Progress reports were presented to the Pillar 4 strategy board every month.

The framework content was developed in an iterative fashion consisting of:

* Development of plans for each section of the framework (April to July 2021).
* General and targeted literature reviews supported by Information Services (August – November 2021).
* Initial framework and tool development (July – November 2021); including development of a [preliminary RWE framework](https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/nice-guidance/chte-methods-and-processes-consultation/appendix-real-world-evidence-framework.docx) for the update of the CHTE methods manual.
* Internal workshop on data suitability assessment (September 2021).
* External workshop on data suitability assessment (November 2021).
* Full draft version of framework shared with internal NICE teams (including all guidance and advice producing teams) and feedback meetings held (November – December 2021).
* Revision to draft shared with external stakeholders (December 2021 – January 2022).
* External stakeholder workshops and reviews (January 2022).
* Final framework development (January 2022 – February 2022).

We invited comment and hosted workshops with a large number of varied stakeholders including:

* UK system partners (MHRA, NHS England, Academic Health Science Networks, Health Data Research UK).
* International HTA bodies (Scottish Medicines Consortium, All Wales Medicines Strategy Group, Pharmaceutical Benefits Advisory Committee, Canadian Agency for Drugs and Technologies in Health).
* Life sciences industry (including Association of the British Pharmaceutical Industry, Association of British HealthTech Industries).
* Patient groups and lay experts (with support from the NICE Patient and Public Involvement Team).
* Health charities.
* Data and analytic companies and organisations.
* Academic experts in real-world data.
* NICE expert collaborating groups (including the NICE decision support unit, evidence review groups, external assessment centres, and the guideline support unit).

## Demonstration projects

In parallel we participated, with external partners, in several demonstration projects and other research initiatives which informed the development of the framework. These include:

* Flatiron Health – we explored the role of US oncology data from electronic health record in reducing decision uncertainties at initial technology evaluations and at reassessments (manuscript in development).
* Aetion – we performed a head-to-head comparison of different direct oral anticoagulants (DOACs) for stroke prevention in patients with atrial fibrillation using UK primary data (a full [protocol](https://www.encepp.eu/encepp/viewResource.htm?id=45074) was published prospectively on EU-PAS registry; the final manuscript is in development).
* BHF-CVD-COVID UK – we worked with British Heart Foundation CVD-CVOID-UK consortium to use linked national UK health data to explore the impact of the COVID-19 pandemic on delayed initiation of treatment for people with hypertension (paper under review).
* Quantitative bias analysis – we wrote an introductory paper to bias analysis in health technology assessment in collaboration with an academic at Leiden University, PHMR Ltd, and Roche (manuscript under review).
* NICE Science Policy & Research (SP&R) projects – we contributed to European projects led by SP&R relating to real-world evidence including IMPACT-HTA ([Kent et al. 2021](file:///C:\Users\SKent\AppData\Roaming\Microsoft\Word\The%20use%20of%20nonrandomized%20evidence%20to%20estimate%20treatment%20effects%20in%20health%20technology%20assessment)) and EHDEN ([Kent et al. 2021](https://pubmed.ncbi.nlm.nih.gov/33336320/)).

## Review comments

Overall the RWE framework was positively received. The purpose of the framework and the clarity of the guidance were thought to be clear and struck a reasonable balance between the need for rigorous analysis and transparent reporting of studies and the burden on evidence developers and reviewers.

The main comments for developments to the framework were:

* The need for further work to improve the accessibility of the framework to non-experts in data or epidemiological research (‘accessibility layer’).
* Recognition of the additional challenges in generating the highest-quality real-world evidence for some interventional procedures and medical devices, including diagnostics and digital health technologies.
* How small patient organisations can be supported to fully participate in evidence generation and appraisal.
* The importance of successful implementing of the framework such that it improves the accessibility of high-quality real-world evidence and supports decision making.
* Need for additional expertise in review groups and committees to evaluate real-world evidence.
* The need for greater transparency in how real-world evidence informs recommendations and consistency in evaluation.
* Additional guidance would be valuable on other priority real-world evidence use cases; key topics mentioned included: patient experience and other qualitative data, extrapolation of long-term outcomes, trial applicability assessments, and synthesis of randomised and non-randomised evidence.

Ongoing activities and further initiatives

## Accessibility

We have added additional content from the previous version of the framework to improve accessibility and address reviewer comments. This includes:

* Personas which provide examples of how to engage with the framework and the benefits it offers to different users (Appendix A).
* An overview of the framework which includes a summary of recommendations (Appendix B).
* Key messages for each section of the framework.

This content will be used to develop further materials to improve accessibility including figures, infographics and interactive material. We will also further develop case studies to illustrate high-quality evidence generation in practice. This will focus particularly on providing content for developers in MedTech.

## Implementation

We will continue to work closely with guidance and advice producing teams across NICE to embed the use of the framework in methods guidance and in decision making. Members of the Data & Analytics team are involved in the update to the guideline methods manual including co-leading a workstream on data and analytics and through membership of the steering group.

We are developing training and educational materials to help support upskilling of NICE technical staff and committee members in data and analytics. We will contribute to ongoing training initiatives through the Centre for Health Technology Evaluations and the Centre for Guidelines as well as running a series of technical seminars within NICE.

We are working with the Transformation Team within NICE to clearly articulate and measure the benefits of the programme. This may include metrics such as the following:

* Uses of the RWE framework in advice programmes (such as NICE scientific advice or the Innovative Licensing and Access Pathway [ILAP]).
* The uses of real-world evidence in NICE guidance, its impact on decisions, and whether the real-world evidence framework supported committees in making recommendations.

This would require a formal process for prospectively identifying topics in which RWE is being used and qualitative research to understand its impact on decisions and the value of the framework.

## Further development of the Framework

We plan to publish version 1 of the RWE Framework as a beta-version in April 2022 with consultation open for 4 weeks. The framework would be revised based on this feedback and published in Summer 2022. In parallel to this we will:

* further develop accessible materials to support the implementation of the framework
* collect exemplar case studies

Stakeholders emphasised the importance of maintaining the framework over time to reflect learnings from the use of RWE in NICE guidance and advances in research methods. This may involve establishing a prospective surveillance system for uses of RWE in NICE guidance and qualitative research on its impact on recommendations.

We will continue to engage with methods teams from across NICE and with external stakeholders to identify priorities for the further development of the framework and implement these internally or, where appropriate, with external partners.

We will continue to collaborate with external partners on research projects to further improve our understanding of real-world evidence and build useful tools. Confirmed research collaborations for 2022/23 include:

* Developing a simple tool for reviewers to critically appraise comparative effectiveness real-world evidence studies; the development of the tool is being funded by the International Society for Pharmacoepidemiology (ISPE) and led by Havard Medical School.
* Methods for comparative effectiveness using single arm trials and bias analysis; the research involves collaborators from academia and industry.

We are working with colleagues in SP&R to support bids for funding from Horizon 2020 to develop methods and tools for the generation and evaluation of real-world evidence with European collaborators.

Conclusion

The Real-World Evidence Framework (version 1) clarifies what good quality real-world evidence looks like and how it can be generated. This will provide useful guidance to developers and help deliver on NICE's ambition to make greater and better use of real-world data.

Issues for decision

The Board is asked to:

* Approve our plans for consultation on the RWE Framework
* Discuss our plans for further developing the framework and implementation

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