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Improving healthcare decisions

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Real-world evidence framework feedback

ISPORs Response to the NICE real-world evidence framework is as follows:

Your views on whether the framework supports NICE's ambitions in real-world evidence

Overall, how strongly do you agree or disagree with the following?

NICE's Real-world evidence framework…

	Agree strongly	Agree	Neither agree nor disagree	Disagree	Disagree strongly	Unsure/Don't know
Has a clear purpose	○	◉	○	○	○	○
Signals NICE's view as to what high-quality real-world evidence looks like	○	◉	○	○	○	○
Is useful for informing evidence generation plans	○	○	◉	○	○	○
Will improve the quality and transparency of real-world evidence considered in NICE's work	○	◉	○	○	○	○
Will improve trust in high-quality real-world evidence studies	○	○	◉	○	○	○
Will help committees better evaluate real-world evidence studies	○	◉	○	○	○	○
Highlights potential uses for real-world evidence in NICE guidance	○	◉	○	○	○	○
Accurately describes best-practice for planning, conducting, and clearly reporting these studies	○	◉	○	○	○	○

Your views on the key sections of the Real-world evidence framework

The Real-world evidence framework consists of three key sections about conduct, data suitability and methods. We invite you to share your views on each of the sections below. If you would like to remind yourself of the content of the Real-world evidence framework, please click this link to take you to the consultation page which will open in a new browser.

Alternatively, paste the link directly into your browser https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

The sections can be located at the following page numbers:

'Conduct of quantitative real-world evidence studies' (p18-25)
'Assessing data suitability' (p26-33)
'Methods for real-world studies of comparative effects' (p34-50)

Please confirm which of the sections of the Real-world evidence framework you would like to comment on:

Please select all that apply

- ☑ Conduct of quantitative real-world evidence studies
- ☑ Assessing data suitability
- ☑ Methods for real-world studies of comparative effects
- ☑ I would like to comment on another part of the framework

Conduct of quantitative real-world evidence studies

It seems too ambitious to repeat or condense the very good work that is done elsewhere. Attempts to condense it may go too far and end up making it inaccurate (example: selection bias portion). Some things are too complicated to cover well in a paragraph or a few sentences, so there is a risk of misunderstanding. The intention is good, but there should be instead more emphasis on identifying the issues of importance, and which reference(s) offer descriptions and solutions for which concern(s). Where there are controversies, acknowledge them and (where possible) take a position on where NICE generally lands in decision-making and where exceptions might apply.

Page 20, Center: various options for registering studies are listed. The open science foundation collaboration with ISPOR is specifically suited for real world studies, where sites like clinical trials.gov are less well-suited. The specific website for the RWE Registry is https://osf.io/registries/rwe/discover. Some mention of suitability for real world studies should be included.

Page 22 through 24: it is very helpful and useful to have the links to tools and resources as is done here throughout.

We would also recommend specifying validated subgroup categories so that, e.g., if meta-analysis is being done, the analyst can be sure that consistent subgroup definitions have been used.

Under "Reporting on data sources," it should also be disclosed that if synthetic data was used, one should include the rationale for its use.

Assessing data suitability

Page 27: it seems the part about data linkage may fit better under "data collection"

Page 28: missing a bullet point before "transformations performed on the data..."
There was no discussion of synthetic data sources and their potential uses (e.g., for modeling parameters), as well as caveats.

It was positive to see a reference encouraging sharing of source data. There was also a good discussion of potential data challenges.

Methods for real-world studies of comparative effects

Page 37, heading “self – controlled studies“: Is this the same as within-subject Designs? If so, please state. There is also mixed method with between - and within - subject analyses.

Other parts of the draft Real-world evidence

Comments on Overview section

If NICE believes there are important ways in which this framework differs from other RWE frameworks, guidances or good practices (e.g, FDA RWE framework, ISPOR/ISPE good practices), it would useful to call them out with reasons for those differences.

A general comment: there is generally greater emphasis on secondary use of existing data vs primary data collection. Indeed, most of study conduct and reporting aspects are more applicable to healthcare database analyses than primary data collection approaches. However, this may highlight an opportunity for guidance on the specificities of primary data collection when designing RWE. Early Access programs are also not mentioned at all, whereas it is supposed to provide early RWE and potentially inform NICE decisions.

Page 2, Table 1: Under Planning, the first bullet says “target quantity of estimation“ – is "estimand" meant here? If not, please clarify. Calling out the specific unit of analysis, along with any relevant nesting, would be important here. Also under "Planning," where it states "Use data in accordance with local law, governance processes, codes of practice and the requirements of the data owner": The term "data owner" is a subjective term given the existing tension between data owners and data subjects. Ownership denotes property and this contention is not fully resolved among legal experts, including the court of law. Consider changing the term "data owner" to "owner of the data system." Under "Conduct," consider changing the following phrase from "Do quality assurance to ensure the integrity and quality of the study" to "Create and implement quality assurance standards and protocols to ensure the integrity, quality, and repeatability of the study". Under Reporting, while it is important to focus on "characteristics of patients (including missing data)," it is also important to understand the characteristics and limitations of data systems (including how these limitations can contribute to interpretations of or around missing data).

Page 2, Table 1. It is important to include the validation of real-world endpoint/outcome data during the planning process; it may be worth including this point in table 1. Similarly, transforming data from secondary data sources such as claims data or electronic health records into "research-ready" data is a major challenge. Therefore, suggest to include ensuring robust data curation processes are in place to generate "research-ready" from secondary data sources in table 1.

Page 3, line 48. It would be good to state explicitly here whether NICE considers pragmatic clinical trials to be in scope here (the FDA considers them RWD), or whether you consider RWD to be limited to designs not using formal randomization. We do see they are mentioned on p. 12. However, most of the document is directed at non-randomized designs.

Page 3 line 67: uses the word "effectiveness" as the outcome from randomized controlled trials – we believe that this should say efficacy instead. Similarly, page 3 line 67 says RCTs are the

preferred source of evidence on the "effectiveness" of interventions. Again we believe this should say "efficacy"; RWD is probably the only source of evidence on effectiveness per se.

Page 4, lines 102-105 104: Considering removing or modifying these sub-bullets, because they are not limitations that are limited to real-world studies. Clinical studies can also be highly complex and risks of biases due to information limitations and have results that are cherry picked. In fact, many other bullets in this section beginning on line 98 could also be applied to clinical trials. Perhaps the only one that is unique to real-world data and not clinical trials is the second bullet, concerns about data provenance and quality. But other issues such as timeliness, risk of bias, etc. are all equally relevant for clinical trials. Instead, it would be good to add a limitation of understanding the purpose and context of the original data collection, since it was not often for research purposes. For example, if the primary purpose of data collection was to reimburse for products or services, there is no direct assessment of intent or outcome. The limitation is that these focuses of study must be inferred since they were not directly measured. This would be a limitation unique to real world data that is distinct from the data within prospective trials.

Page 6, Table 2, the definitions of patient and consumer should be somehow reconciled given that the data type included in this definition is arguably health consumer data versus patient-generated health data (the term "patient-consumer" has been used in the past, which might be helpful as you consider this comment: https://fpf.org/blog/fpf-presents-rightscon-2020-frontiers-in-health-data-privacy-navigating-blurred-expectations-across-the-patient-consumer-spectrum/.

Page 6, Table 2. It is worth noting that some of these methods also are commonly used in market research as well as scientific research. If RWD has already been collected as part of market research, under the standards/rules governing market research (which can be less restrictive), would they be permissible for the nature of evidence covered in this guidance?

Page 6, Table 2. Patient-reported outcome and observer-reported outcome measures are important examples of patient/carer generated data commonly used to generate RWE; we suggest including as examples in table 2.

Page 10, section beginning l. 235. Should this section be renamed something like "Limitations of randomized controlled trials", given its content? (and on l.237, "effectiveness" is used rather than "efficacy".)

Page 12, Line 279-280. The sentence ends by mischaracterizing the reference it provides. The text says “guidance on producing real world evidence from randomized controlled trial‘s“ but the linked guidance article is about using real world data to inform trial design in support of regulatory decisions. The direction of evidence in the article (production of a high-quality trial using real world data) is the reverse of what is stated in the sentence (producing real world evidence from randomized trials).

Page 14, Table 3, consider changing the parenthetical for "clinical equipoise" to "(or treatment choice uncertainty)" to make this definition clearer to public audiences. Under "Other forms of bias," it might be helpful to discuss length time bias for longitudinal studies assessing survival time using RWD

Page 15, Table 3 Very complicated methodological issues, and makes comparisons relative to trials but seemingly pro/con per row also when it's actually comparable bias in both settings (or reverse to what is shown). First row on the top of the page: self-reported outcomes are listed as a generally higher risk of bias, but it should be noted that in some cases there is literally no better outcome, for example, pain or sleep quality. These concepts are defined entirely by patient report and may in fact be primary outcomes of interest. Also, it bears noting that placebo effects are often measured in objective clinical and laboratory values. This does not mean that the physical and objective effects are not real, it just means that they are not explainable by the intervention. In addition, since this table is in reference to the relative bias between clinical and non-randomized studies, self-reported outcomes may have higher validity when there is no pressure to please an experimenter or a clinician. These outcomes would be recorded presumably for no other purpose them for the patients benefit. In other words, there is a little incentive to alter a score for the sake of pleasing an experimenter.

Page 16, line. 425, In comparative studies, biases in general and selection biases in particular can be systematic (both arms) or differential (one arm only) and these have different consequences. A difference of representativeness between arms can be an issue in comparative studies. Therefore, a recommendation is to remove the sentence on selection bias and representativeness in comparative studies which is too general and does not capture the complexity of bias assessment and management.

Glossary: Can add "Data governance"

What do you think our priorities for further development should be?

More attention to specific requirements for data validation and for prospective observational studies

Are there any additional materials that would support you in using the framework?

Perhaps a checklist for the fundamental aspects of the Framework, as a ready reference for researchers planning studies, would be useful.

Are you able to recommend any exemplar case studies (these can cover different uses of real-world data for different types of intervention)?

CanRevalue work in Canada provides example of collaborative work across jurisdictions to evaluate oncology agents in the real-world setting.

About you

Which of the following best describes you/your organisation:

- ( ) Academic body
- ( ) Charity
- ( ) Data company or data owner
- ( ) Life sciences consultancy
- ( ) MedTech developer
- ( ) MedTech industry body
- ( ) NHS organisation
- ( ) Patient organisation
- ( ) Pharmaceutical developer
- ( ) Pharmaceutical industry body
- (x) Professional organisation
- ( ) Public/individual
- ( ) NICE committee member
- ( ) NICE staff
- ( ) Other (please specify)

Please tell us your name/role and organisation (OPTIONAL)

This will help us better understand the needs and perspectives of different stakeholders.

Name/role	Richard Willke
Organisation	ISPOR