Developing comprehensive guidance to drive the use of RWE for decision-making

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RWE4Decisions Webinar
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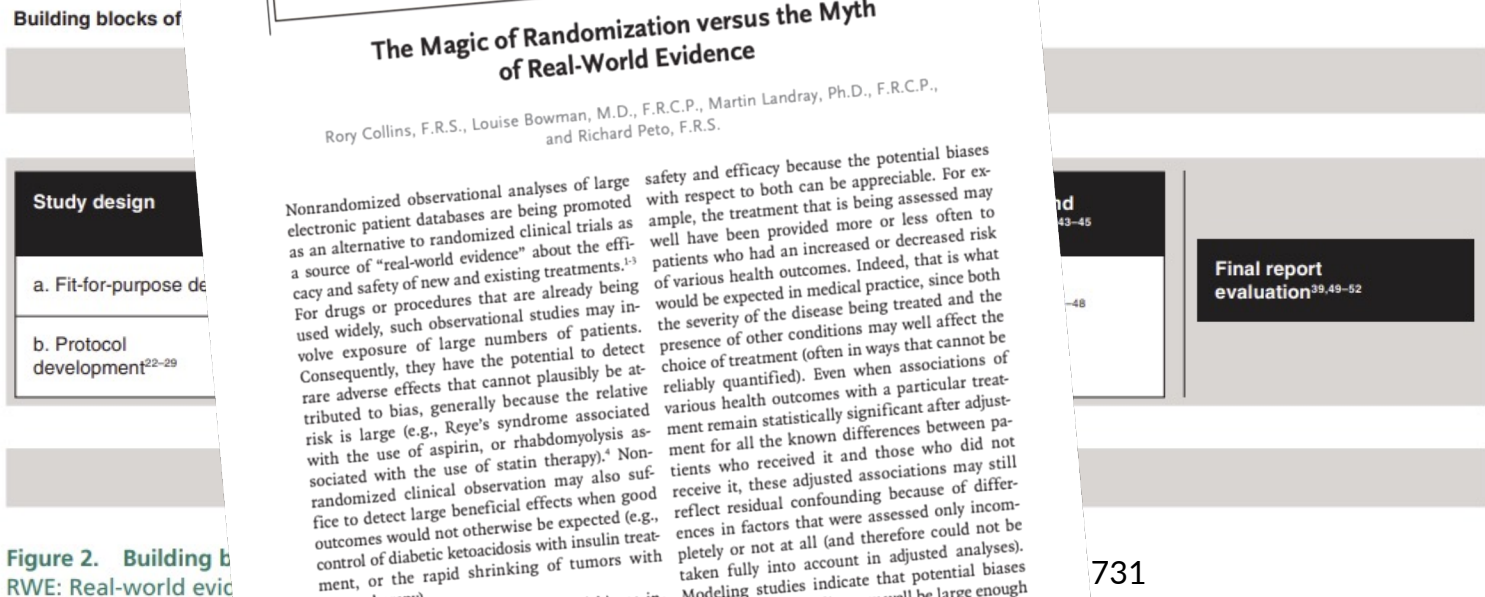
NICE National Institute for Health and Care Excellence

RWE: We're (still) on a journey



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The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P., and Richard Peto, F.R.S.

Nonrandomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of "real-world evidence" about the efficacy and safety of new and existing treatments.[1-3] For drugs or procedures that are already being used widely, such observational studies may involve exposure of large numbers of patients. Consequently, they have the potential to detect rare adverse effects that cannot plausibly be attributed to bias, generally because the relative risk is large (e.g., Reye's syndrome associated with the use of aspirin, or rhabdomyolysis associated with the use of statin therapy).[4] Nonrandomized clinical observation may also suffice to detect large beneficial effects when good outcomes would not otherwise be expected (e.g., control of diabetic ketoacidosis with insulin treatment, or the rapid shrinking of tumors with chemotherapy).

However, because of the potential biases inherent in observational studies, such studies cannot generally be trusted when — as is often the case — the effects of the treatment of interest are actually null or only moderate (i.e., less than a twofold difference in the incidence of the health outcome between using and not using the treatment).[4-6] In those circumstances, large observational studies may yield misleading associations of a treatment with health outcomes that are statistically significant but noncausal, or that are mistakenly null when the treatment really

are generally required to ensure that ally
ate benefits or moderate harms of a treatment are
assessed reliably enough to guide patient care
appropriately (Box 1).[5-7]

safety and efficacy because the potential biases with respect to both can be appreciable. For example, the treatment that is being assessed may well have been provided more or less often to patients who had an increased or decreased risk of various health outcomes. Indeed, that is what would be expected in medical practice, since both the severity of the disease being treated and the presence of other conditions may well affect the choice of treatment (often in ways that cannot be reliably quantified). Even when associations of various health outcomes with a particular treatment remain statistically significant after adjustment for all the known differences between patients who received it and those who did not receive it, these adjusted associations may still reflect residual confounding because of differences in factors that were assessed only incompletely or not at all (and therefore could not be taken fully into account in adjusted analyses). Modeling studies indicate that potential biases in observational studies may well be large enough to lead to the false conclusion that a treatment produces benefit or harm, with none of a range of statistical strategies capable of adjusting with certainty for bias. Those findings are consistent with findings from reviews that compared estimates of treatment effects from observational studies with estimates from randomized trials, with examples in which results for the same intervention were similar but also many in which the results were importantly different.[8-12]

Such discrepancies are illustrated by a data-
analysis involving the entire Danish popu-
from cancer was
interval, 13 to 18) among patients who had
taken statin therapy for only a few years than
among those who had not taken statin therapy,
adjustment for what was

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Perspective

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Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance

Journal of Comparative Effectiveness Research

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Decision-makers have become increasingly interested in incorporating real-world evidence (RWE) into their decision-making process. Due to concerns regarding the reliability and quality of RWE, stakeholders have issued numerous recommendation documents to assist in setting RWE standards. The fragmented nature of these documents poses a challenge to researchers and decision-makers looking for guidance on what is 'high-quality' RWE and how it can be used in decision-making. We offer researchers and decision-makers a structure to organize the landscape of RWE recommendations and identify consensus and gaps in the current recommendations. To provide researchers with a much needed pathway for generating RWE, we discuss how decision-makers can move from fragmented recommendations to comprehensive guidance.

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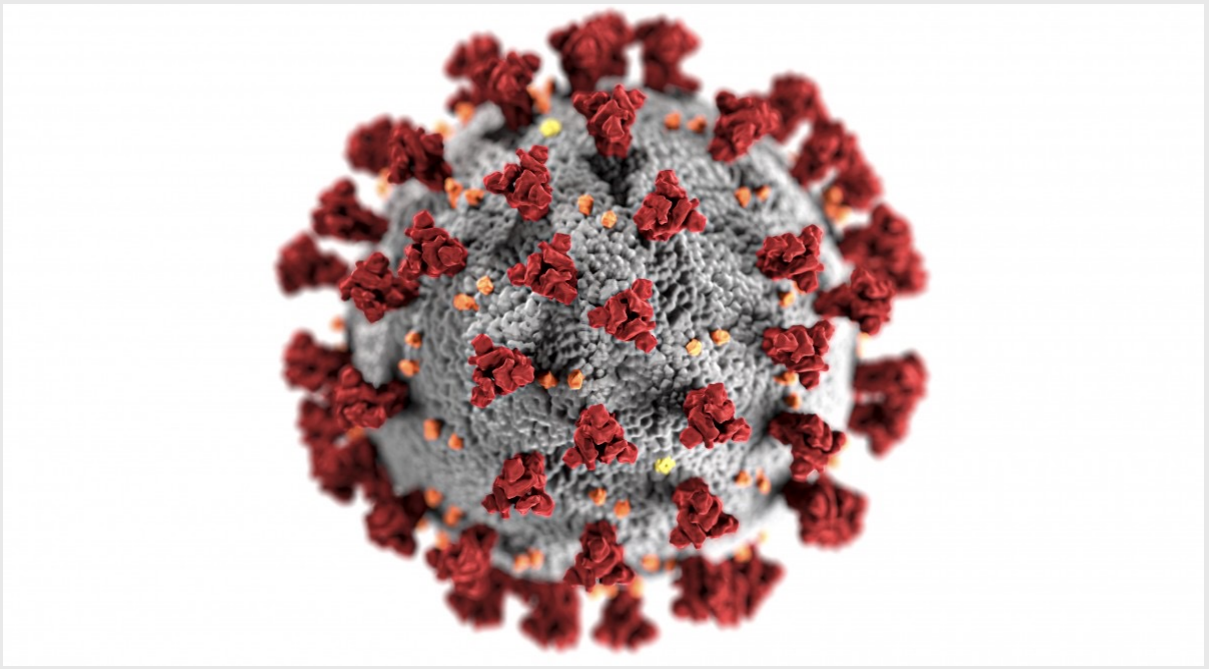
Keywords: decision-making • health technology assessment • methodology • observational research • real-world evidence • regulatory approval

Background

Health technology assessment (HTA) agencies and regulators, including the National Institute for Health and Care Excellence (NICE), the US FDA and the European Medicines Agency (EMA) have recently committed to evaluating opportunities to increase the use of real-world evidence (RWE) in their decision-making processes [1–3]. With the Coronavirus disease 2019 (COVID-19) pandemic, regulators and HTA agencies have an increased sense of urgency to use RWE, alongside randomized control trials (RCTs), to evaluate the effectiveness of treatment and vaccines under compressed timelines [4].

Across the healthcare ecosystem, however, there are concerns over wider adoption of RWE in regulatory and reimbursement decision-making. Critics are concerned that researchers will be disincentivized from conducting RCTs and healthcare decision-makers could be forced to rely on 'inferior' evidence [5]. Several high-profile 'disasters,' including recent retractions of a COVID-19 RWE study from major journals [6,7], have solidified the concern that RWE could lead to inaccurate results and poor patient outcomes [8]. Critics also fear that, if allowed to do so, industry will prefer RWE instead of RCTs because RWE is cheaper. Critics thus propose continued adherence to the current paradigm of traditional evidence hierarchies, which display RCTs at the pinnacle and non-randomized studies as inferior [9,10].

A tale of two disruptors



New regulatory and access initiatives

- Closer collaboration between UK's regulator and HTA: Innovative Licensing and Access Pathway (ILAP)
- Project Obis (USA + Australia, Canada, UK, Singapore, Switzerland, Brazil)
- ACCESS Consortium (UK, Australia, Canada Switzerland, Singapore)

Increased responsiveness to new data

- Greater reliance on emerging data
- Development of living clinical guidelines

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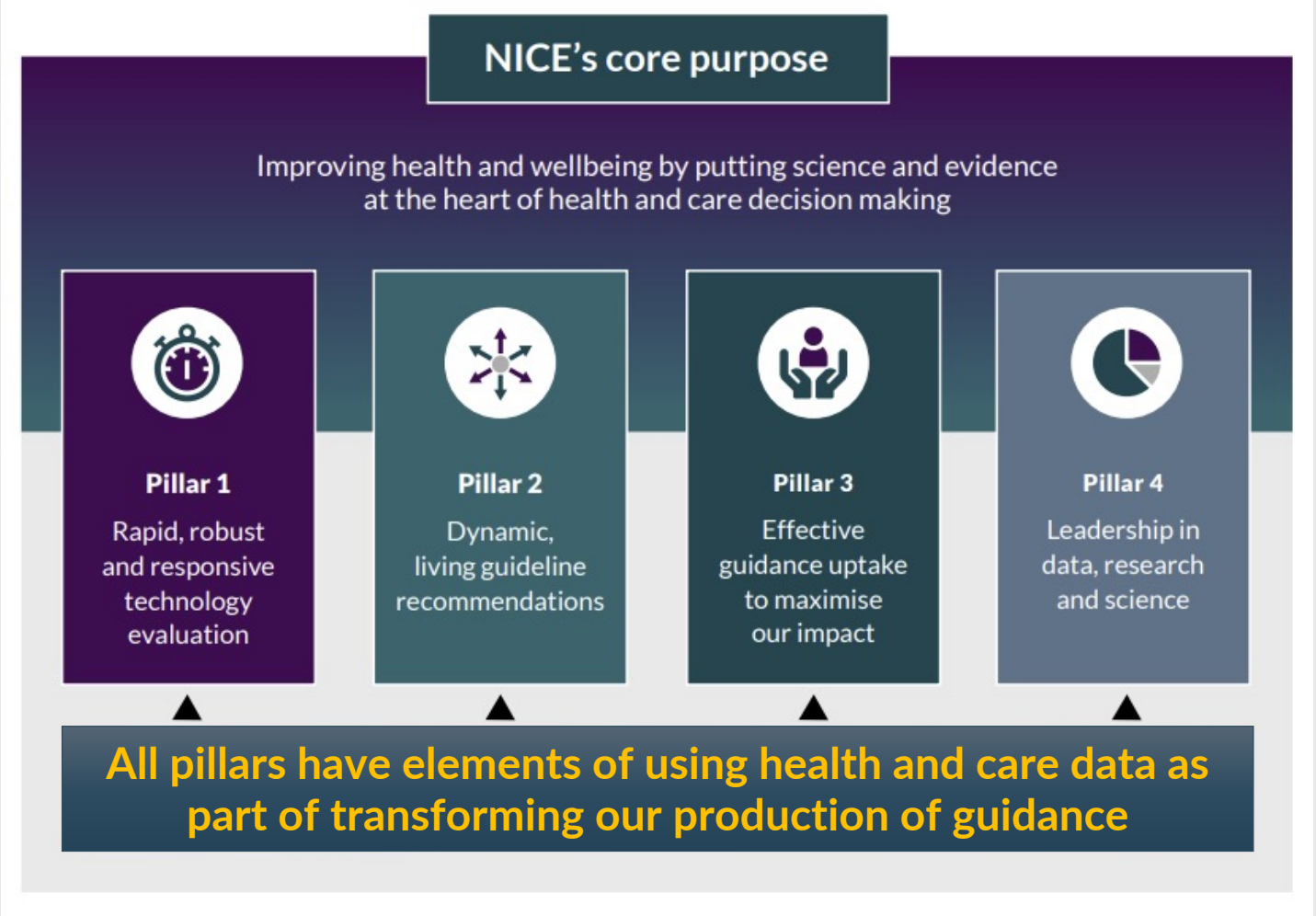
RWE: NICE's strategy 2021-2026

> *The ability to link real-world evidence with evidence-based practice will drive a shift from recommendations being produced at a single 'static' point in time to more dynamic, living guidance, and from health technology assessment to health technology management.*

> *[we will] develop world-leading capabilities and standards for routinely using real-world data to inform all aspects of our work, by working with partner organisations.*



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RWE: What is NICE currently doing?

RWE framework

- Ensure that we are using real world (i.e. observational) data where it offers value (i.e. can improve decision-making)
- Improve the quality of the evidence submitted by providing clear expectations around study conduct and reporting
- Support the ability of review groups and committees to better understand the quality and relevance of evidence for a given submission
- Initial output planned for March 2022

Research and demonstration projects

- Testing suitability and robustness of new data and analytics in the context of NICE guidance
- OpenSAFELY, demonstration projects with industry and academia, CPRD, EU Horizon Europe funded-work…

Engagement with systems partners

- Government, regulator, payer, NHS, life sciences partners *(DHSC*, *NHSX*, *NHSD*, *MHRA*, *OLS*, *AAC*, *AHSNs…)*

Access to data

- Trusted Research Environments (TREs)
- Alternative sources (e.g. for medtech and digital health)

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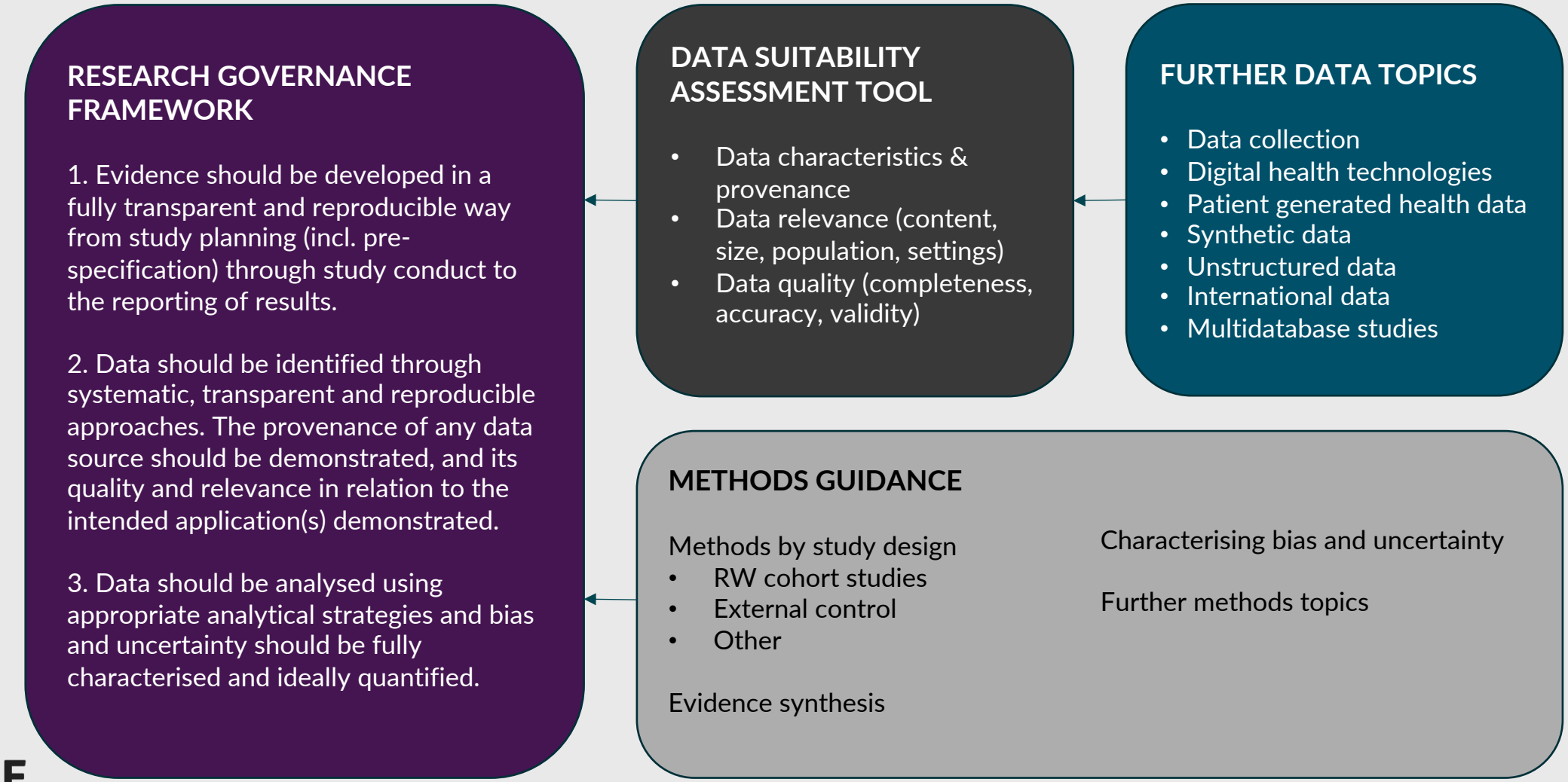
NICE's RWE framework (in development)



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Data suitability assessment tool: DataSAT

Purpose

- Provide structured information on data source(s), their provenance, and quality and relevance in relation to intended application(s)
- Completed by evidence developers, informing reviewers and committees
- Applicable across wide range of RWD sources (e.g., EHR, patient registries, administrative data, health surveys) and applications (comparative effects, population economic models, disease characterisation)

Uses

- Help evaluate RWE submissions in guidance development
- Support choice of appropriate data source(s) for a given application
- Provide guidance on NICE's expectations around data provenance and quality

Development process

Develop conceptual model based on needs assessment

Literature review including policy documents

Mapping literature to conceptual model

Iterative development of tool

Workshops – internal and external

Consultation

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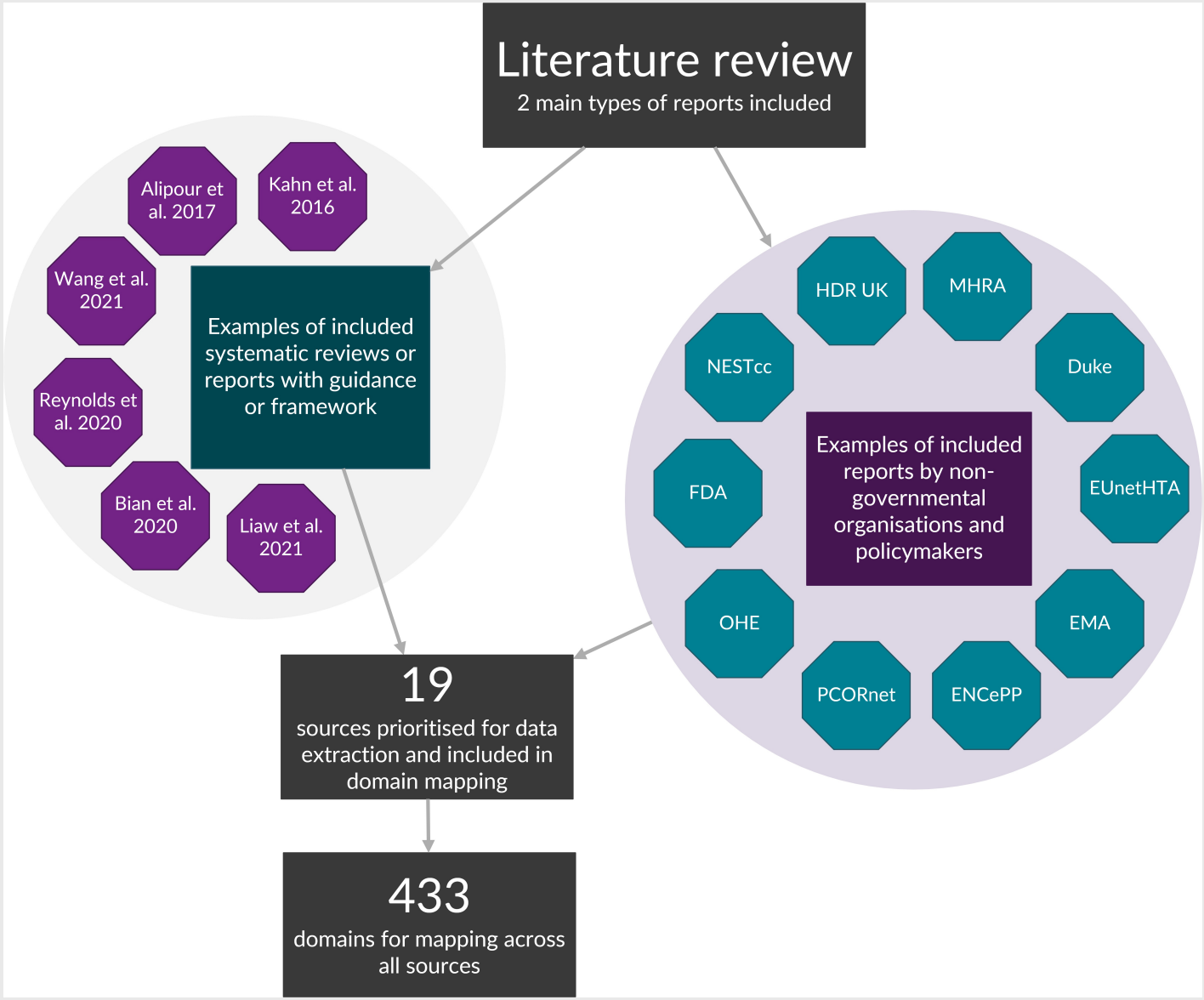
Data suitability assessment tool



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Multi stakeholder engagement

2013-2017

Original project
30+ scientific papers
Tool development
RWE Academy

June 2018 – April 2021

Refine and promote outputs
Think Tank
Sustainability planning

Innovative Medicines Initiative (IMI) Programmes

28 April 2021

Independent, member-led non-profit Institute

The multi-stakeholder hub for collaborative development and implementation of solutions to *put RWE into practice* in Europe

The GetReal Institute

Mission: Facilitate the adoption and implementation of RWE in health care decision-making in Europe