Welcome to the Sentinel Innovation and Methods Seminar Series

The webinar will begin momentarily

Please visit www.sentinelinitiative.org for recordings of past sessions and details on upcoming webinars.

Note: closed-captioning for today's webinar will be available on the recording posted at the link above.

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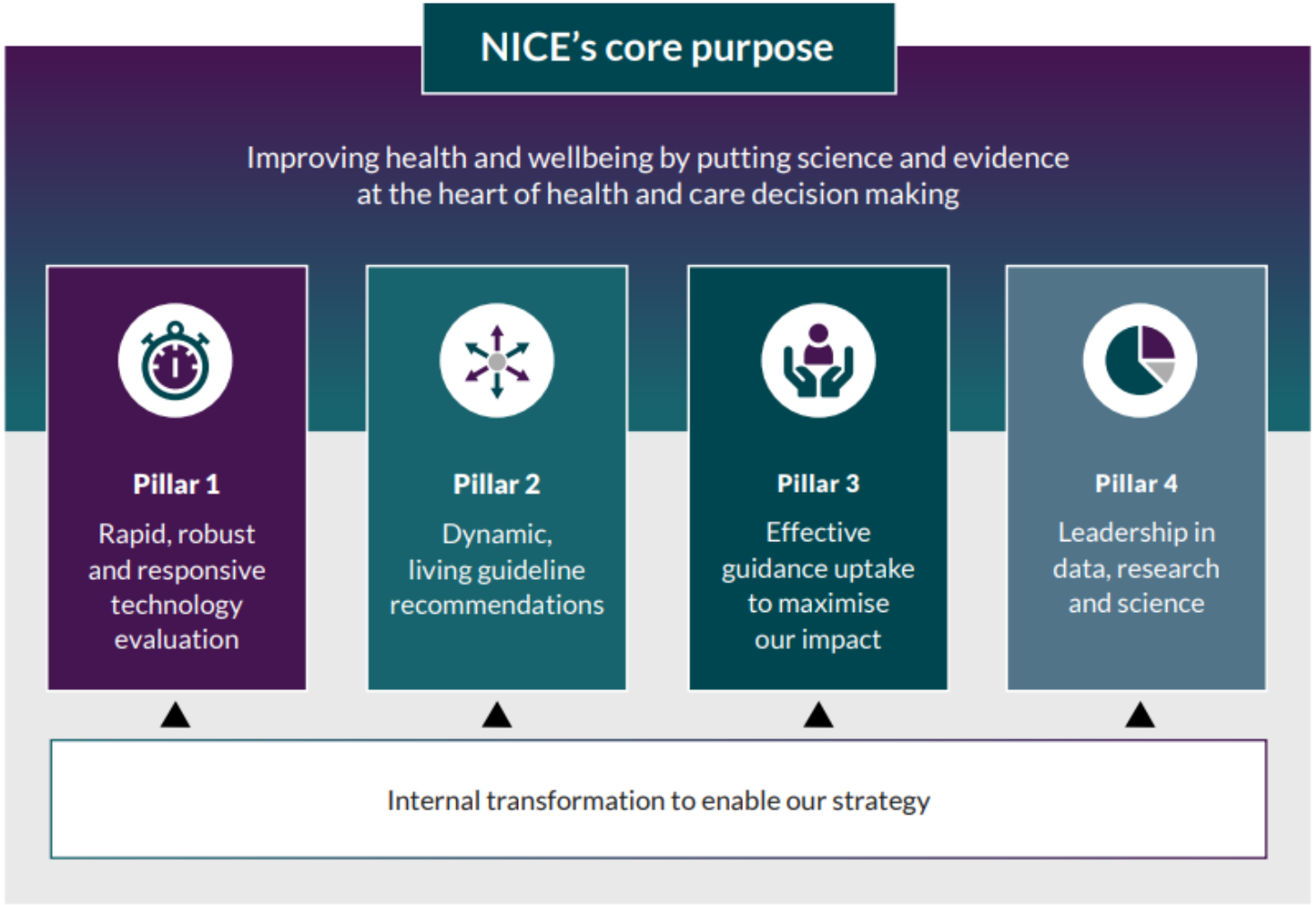
Advancing the use of real-world evidence for health technology assessment

Seamus Kent, NICE

11 August 2022

NICE National Institute for Health and Care Excellence

NICE's RWE ambition



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What is health technology assessment?

- Health technology assessment bodies and payers make decisions about the coverage and reimbursement of health technologies
- Most do this based on comparing new technologies against **local standard of care**, considering:
    - **Clinical effectiveness** – effects on…
        - Patient outcomes – how a patient functions, feels, or how long they survive
        - System outcomes – resource use, costs, etc.
    - **Cost-effectiveness**
        - At NICE, incremental cost per quality adjusted life year (QALY) over patient lifetime
        - Usually informed by economic modelling
    - Other attributes – e.g., unmet need, severity, societal impact, uncertainty, safety, etc.

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Key differences vs. regulation

- Standard of care
- Interest in treatment policy
- Effectiveness vs. efficacy
- Effect size estimation vs. hypothesis testing

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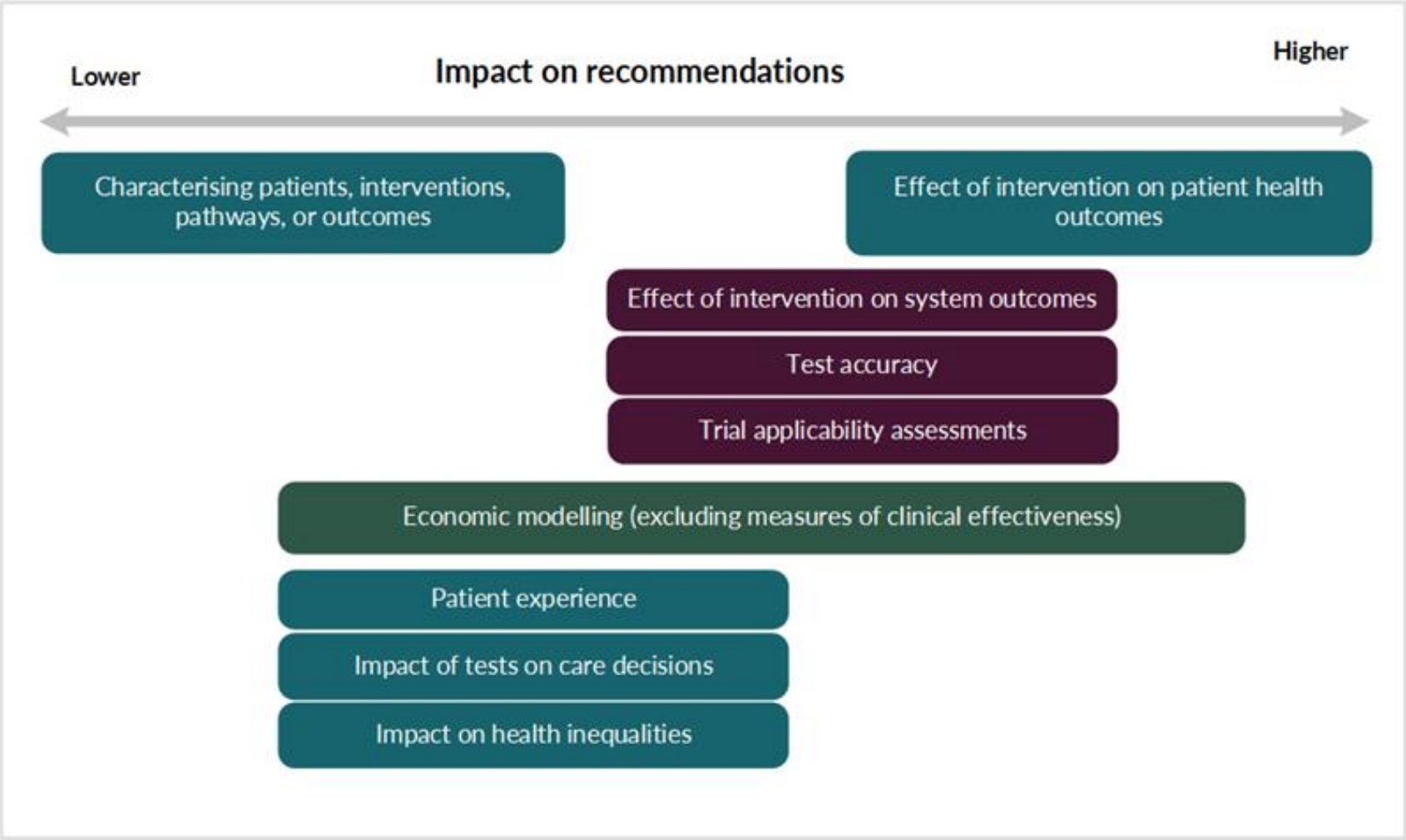
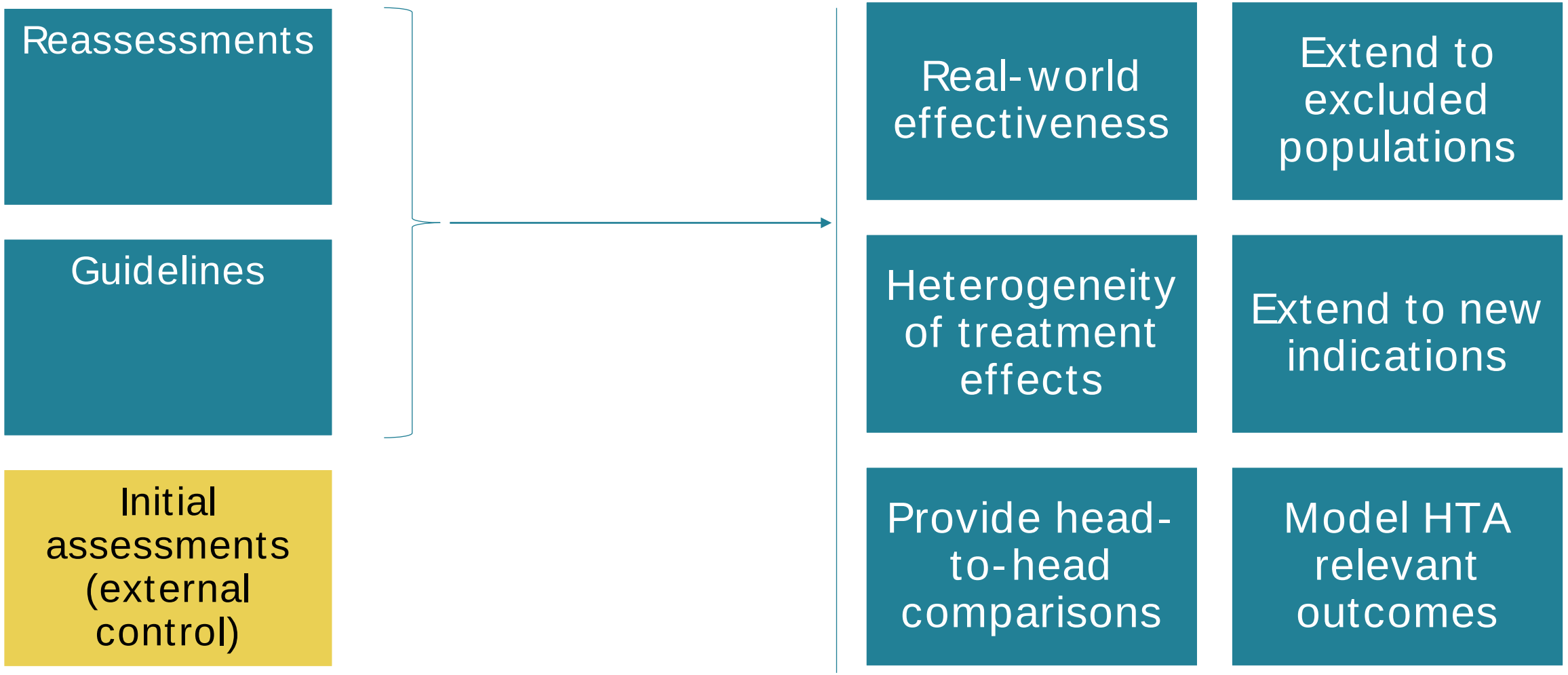
What are our evidence needs?



Potential role for RWE in assessing effectiveness



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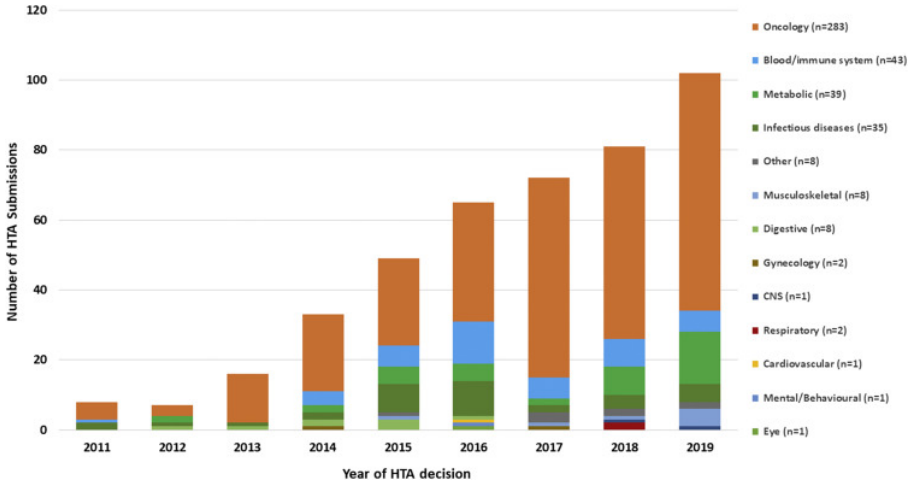
External control arms for single-arm trials

- There has been a large increase in the number of drugs presenting information from only uncontrolled studies, especially in rare diseases and oncology
- (Sometimes, the comparator from an RCT is not relevant to UK clinical practice)
- Most external control studies have used previous clinical trials but increasingly RWD is used
- The quality of external control studies is often poor
    - Majority of studies are naïve comparisons
    - Little, if any, consideration given to study design challenges (incl. definition of time zero)
    - Insufficient or uninformative sensitivity analyses
    - Limited transparency
    - Incorrect estimands (or analytical methods given estimand)



Source of comparator data*, n (%)	Method of comparison			Total
	Adjusted ITC	Naïve ITC	Unclear/No EC	
Prior clinical trial	32 (31%)	62 (60%)	10 (10%)	104
Undefined RWD study	8 (22%)	23 (62%)	6 (16%)	37
Prior CT & RWD study	12 (34%)	20 (57%)	3 (9%)	35
Registry	4 (17%)	17 (71%)	3 (13%)	24
Database study	7 (30%)	15 (65%)	1 (4%)	23
Chart review	3 (100%)			3
Grand Total	66 (29%)	137 (61%)	23 (10%)	226

Patel et al. 2021. Combines data from NICE (England), CADTH (Canada), G-BA (Germany), HAS (France), and PBAC (Australia)

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Challenges in making greater use of RWE

Trust	Data quality	Risk of bias	Limited transparency
Data access	Processes & timelines	Expertise and capacity	Absence of clear guidance

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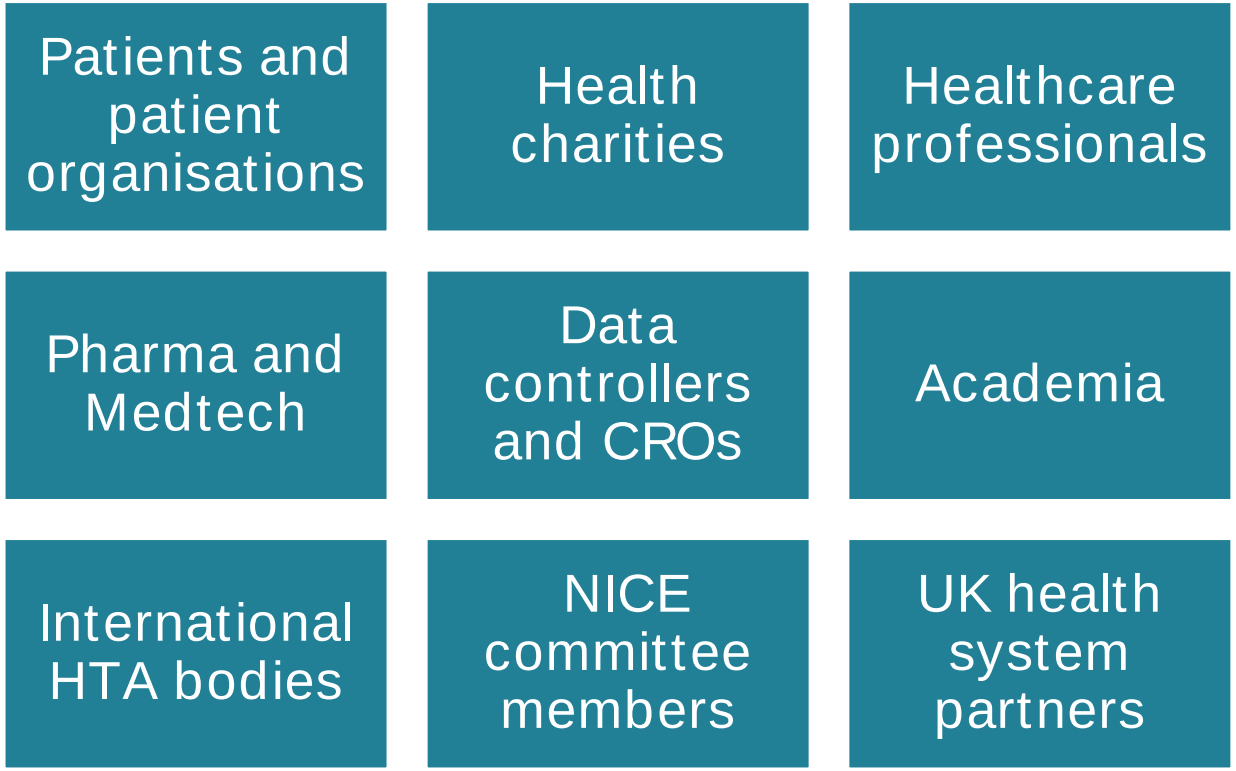
NICE's Real World Evidence Framework

- NICE published its real-world evidence framework in June 2022
- It aims to:
  - Encourage the use of RWE to fill evidence gaps and improve recommendations
  - Improve the quality and transparency of RWE studies that inform guidance
  - Enable informed critical appraisal of RWE studies and engender trust in high-quality studies
- It does this by clearly describing
  - Where RWE can be used to improve recommendations
  - Best-practices for planning, conducting, and reporting RWE studies

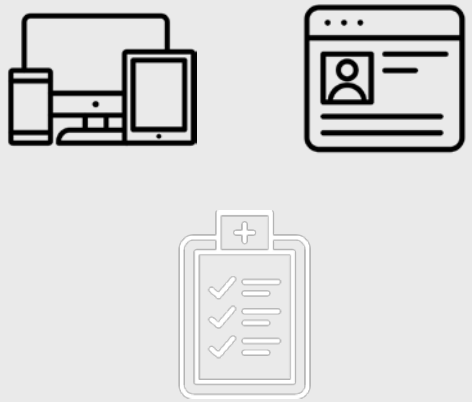
How we developed the framework

- Framework informed by existing best-practice guidance for using real-world data
- Series of multistakeholder workshops in November 2021 and January 2022
- Open consultation in April 2022



What is real-world data?

Real-world data is data relating to patient health or experience or care delivery collected outside of clinical trials



Data from service evaluations or audits or generated from patient devices

Routinely collected data: patient health records, health service administrative records

Data collected for specific research projects: patient registries, cohort studies, surveys

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Principles of evidence generation

1 Transparency

Generate evidence in a transparent way and with integrity from study planning through to study conduct and reporting.

2 Data suitability

Ensure data is trustworthy, relevant and of sufficient quality to answer the research question.

3 Methods

Use analytical methods that minimise the risk of bias and characterise uncertainty.

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Planning studies

- Clear definition of the research question
- Pre-specified protocols – publish on a publicly accessible platform
- Selecting fit for-for-purpose data
    - Systematic and transparent search – recognising data identification and access challenges
    - Selecting a data source – see ***assessing data suitability***
- Data collection
- Follow national laws, regulations, and codes of practice for data collection and use – in the UK consult the Health Research Authority

Conducting studies

- Choose appropriate study design and analytical methods
    - Should be relevant to the research question and reflect the characteristics of the data
    - Minimise risk of bias from selection and information bias and confounding
    - Use diagnostic checks to assess the validity/reliability of the methods used
- Assess the robustness of study results to key causes of uncertainty including:
    - Data curation
    - Study design
    - Statistical models
    - Data limitations
- Use proportionate quality assurance processes

Reporting studies

- Reporting should be sufficient to enable an independent researcher with access to the data to reproduce the results, interpret the results, and fully understand its strengths and weaknesses
- Reporting should cover at a minimum:
    - Data sources – see ***assessing data suitability***
    - Data curation and analysis
        - Sufficient to understand what was done and how it may impact on results
        - Ideally share analytical code and data – But, what is possible (e.g. unstructured data) and what can we do with that code?
        - Audit trails
    - Methods
        - Study design – operational definitions, index date, anchored time windows, etc.
        - Statistical methods – what was done and why
    - Results
        - Patient flow diagrams
        - Patient characteristics and details of follow-up
        - Point estimates and measures of precision
        - Results for all analyses conducted, whether planned or post-hoc
- We encourage the use of reporting checklists and tools including START-RWE

Assessing data suitability

Data provenance

- What was the purpose of data collection?
- What data was collected, in what settings, how and by whom?
- Data documentation and quality management
- Data governance arrangements

Fitness for purpose

Quality

- How much data is missing on key study variables (see PICO)? Why is data missing?
- How accurately is data recorded?
- How was accuracy assessed?

Relevance

- Does the data source contain all relevant study variables?
- Is the population similar to the intended population for the technology?
- Are the care settings relevant to patient care in the NHS
- Are the sample size and follow-up sufficient to generate reliable results?

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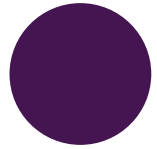
We developed the Data Suitability Assessment Tool (**DataSAT**) to support the consistent and structured reporting of this information

Real-world evidence studies of comparative effects

Real-world evidence can be used in the absence of trial evidence or to complement it to answer a broader range of questions about the effects of interventions in routine settings.

Here we present best-practices for cohort studies (including trials using real-world data to form external control). Other study designs including quasi-experimental designs might be most appropriate for some interventions.



Design studies to emulate the preferred randomised controlled trial – use a “target trial approach”

Identify potential confounders and address these considering observed and unobserved confounding

Consider the impact of bias from informative censoring, missing data, and measurement error – address appropriately where required

Use sensitivity and bias analysis to assess the robustness of study findings

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Dimensions of the target trial and HTA considerations

Eligibility criteria	Treatment strategies	Outcomes	Causal effect of interest
• Reflect clinical pathways and patients seen in routine care in the NHS • For ECAs should mimic SAT eligibility criteria	• Comparator should be local standard of care • Strategies should reflect local care pathways • New-user, active comparator designs where feasible and relevant • Data from similar time period	• How a patient functions, feels, or how long they survive • Surrogate outcomes (e.g., PFS/ORR) need good evidence that they are causally associated with changes in final outcomes	• Of primary interest is a **treatment policy** estimand, reflecting UK clinical practice after initial treatment • Other estimands may also be of interest or necessary for valid causal estimates (and for safety studies) • Trials do not always estimate the estimand needed for HTA • ATE of interest, but ATT or ATO common

Sensitivity analysis

- Sensitivity analysis including probabilistic and deterministic analyses are a central component of HTA
- They should be widely used to explore uncertainties in RWE studies
- Quantitative bias methods can be used to
    - Understand the extent to which bias would have to present to change study conclusions or reimbursement decisions
    - Estimate the impact of bias on estimates of clinical- and/or cost-effectiveness
- NICE is involved in research projects – Q-BASEL and T-BASEL – about the use of QBA for external control arm studies

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A living framework

Ensure up-to-date

Extend for priority topics

Implementation

Measurement of benefits

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Key remaining areas of uncertainty

- Minimum evidentiary standards
- Unstructured data
- Sharing analytical code incl. AI/ML
- Validity of causal estimates – external control arms
- ATE/ATT – which PS models?
- Small populations (e.g., rare disease)
- Evidence synthesis (randomised and non-randomised studies)
- MedTech
- Patient generated health data
- International data and transportability
- Simple to use tool for study evaluation

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Thank you.