Use of Real World Evidence by NICE

17 November 2024

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NICE National Institute for Health and Care Excellence

Where NICE uses Real World Evidence

NICE 3

Case Study 1:
CAR-T in the CDF

TA554 Tisagenlecleucel
TA567 Tisagenlecleucel
TA559 Axicabtagene ciloleucel
TA677 Brexucabtagene autoleucel

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Case Study 2:
Gene therapies for blood conditions in the IMF

TA989 Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B

TA1003 Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over

NICE National Institute for Health and Care Excellence 13

Case Study 3
Early rare disease MA topic

HST12 - Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

NICE 16

Case study 4
The RWE framework in action

TA850 - Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy

NICE 19

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Any questions

23

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Where NICE uses Real World Evidence

NICE has a Real World Evidence Framework

Real-world data is widely used to inform NICE guidance to, for example:

design, populate and validate economic models (including estimates of resource use, quality of life, event rates, prevalence, incidence and long-term outcomes)

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.

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RWE is also used as part of the Evidence Generation for topics in Managed Access

- **Two Managed Access Funds Cancer Drugs Fund (CDF) and Innovative Medicines Fund (IMF)**
- **A Managed Access Agreement (MAA) (type of MEA) is a time-limited arrangement to:**
  - Enable patient access while further data is collected to address the key clinical uncertainties
  - Can require RWE which is defined in a Data collection Agreement (DCA)
  - Ensure the NHS still pays a cost-effective price, through a commercial access agreement (CAA)
  - Evidence Generation in Managed Access is governed by a set of Principles

Evidence Generation in Managed Access is governed by a set of Principles

Equal opportunity for cancer & non-cancer

Targets the most promising medicines with significant remaining resolvable uncertainty

Plausibly cost effective

Priced responsibly during managed access

Shortest time necessary to resolve uncertainties – maximum of 5 years

Entire eligible population can access treatment during managed access

Guidance update by NICE at the end of managed access

All patients can continue treatment in the event of negative re-evaluation

Funds should never have to close to new entrants

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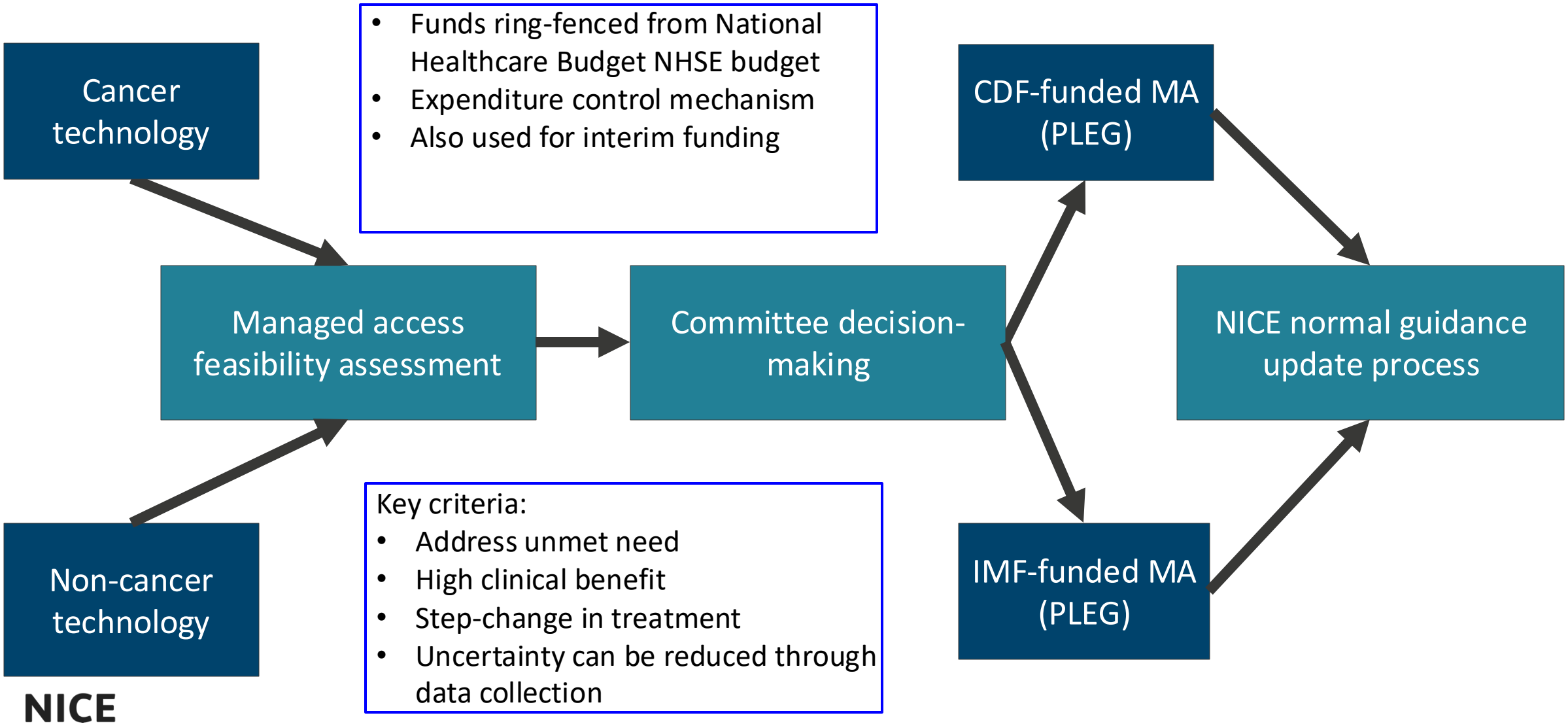
https://www.england.nhs.uk/publication/the-innovative-medicines-fund-principles/

Introduction to Managed Access Funds



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Examples of data sources

Ongoing / Planned clinical trials	• Preferred source, where outcomes reflect evidential uncertainties • Minimal additional impact on NHS services for data collection or clinician care
NHS data collection	• NHS Digital Systemic Anti-Cancer Therapies (SACT) • NHS England's High Cost Drug and Cancer Drug Prior Approval (Blueteq) • NHS England's National Haemoglobinopathy Register
Academic networks	• NorthStar Registry • Spinal Muscular Atrophy(SMA) Reach UK
Company commissioned	• Third parties commissioned to collect and process patient data
Patient groups	• Cystic Fibrosis Trust • Rare Diseases Research Partnership

Feasibility Assessment for Managed Access: RWE considerations

- Existing, adapted, or new data collection
- Prior experience with managed access
- Relevance of existing data items
- If required, ease that new data items can be created / modified
- How quickly could the data collection be implemented
- Population coverage
- Data completeness
- Data accuracy
- Data timeliness
- Quality assurance processes
- Data availability lag
- New data sharing arrangements required?
- New data linkages required?
- If yes, has the governance of data sharing been established
- Lawful basis for data collection
- Privacy notice & data subject rights
- Territory of processing
- Data protection registration
- Security assurance
- Existing relevant ethics/research approvals
- Patient consent
- Existing funding
- Additional funding required for MA
- If yes, has additional funding been agreed in principle
- Does data collection through registry require any change from normal treatment or service standards?
- Is the study designed to produce generalisable or transferable findings?
- Are the clinical assessments and data collection comparable to current clinical practice data collection?
- Expected overall additional patient burden from data collection?
- Expected overall additional system burden from data collection?
- Do stakeholders consider any additional burden to be acceptable
- Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access

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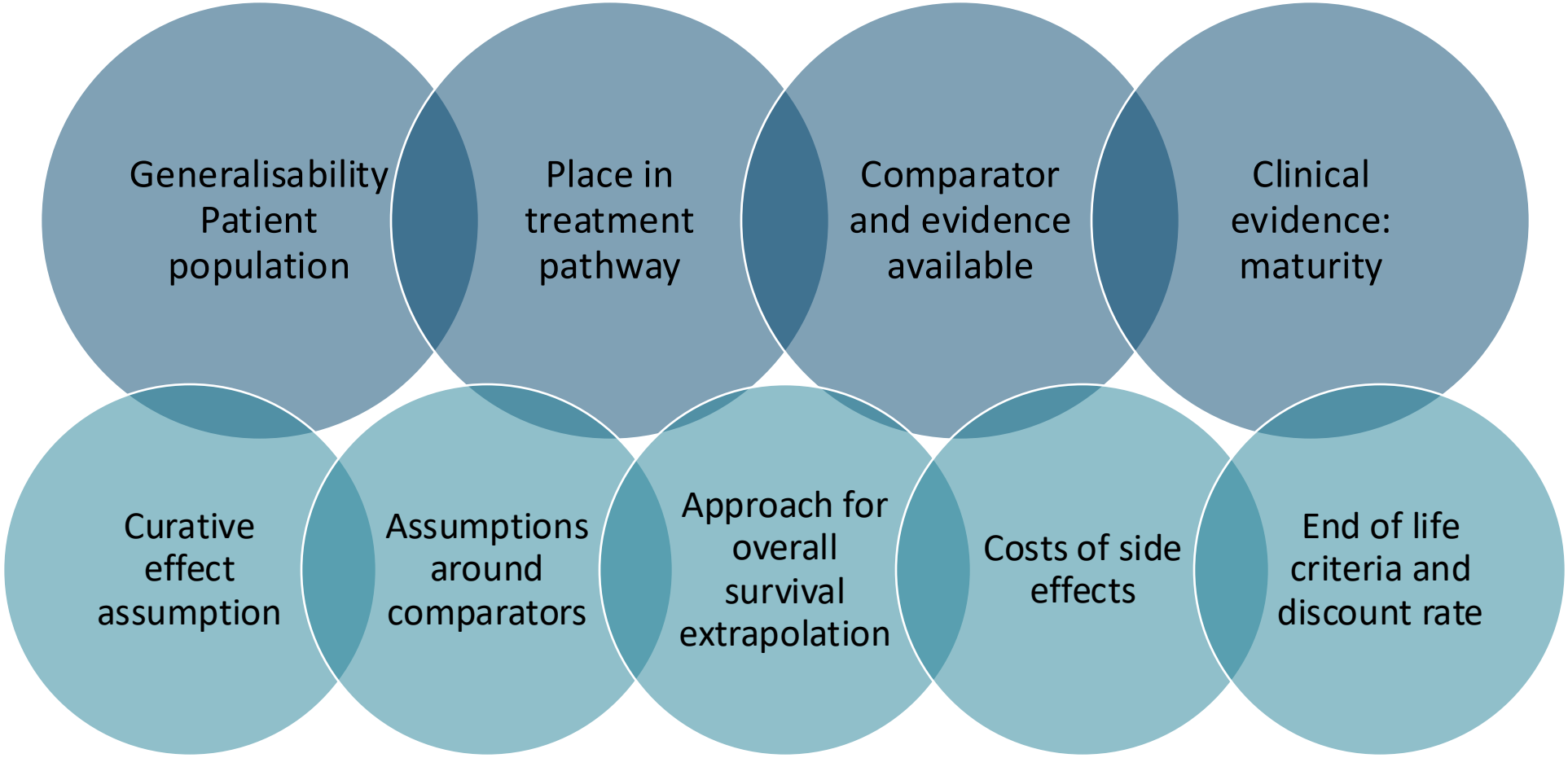
CDF:

SACT data collection

- Mandated data collection for
  - Baseline patient characteristics (Linked to NHS Blueteq data)
  - Treatment duration
  - Overall survival (Linked to Personal Demographics Service)
  - Previous and subsequent treatments
  - Basic retrospective data collection (completed by clinician using Blueteq)
  - Other data inputs – Stem cell transplants, response rate, testing data etc.
- Additional data items considered
- Low burden

Key issues in clinical and cost effectiveness in CAR-T cell appraisals



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IMF:

Real-world evidence

- Wide-range of conditions
- No single repository of registries and databases
- No mandated data collection
- Relies on existing registries
- Avoid setting up new databases
- Engagement with company and registries before and after committee meetings

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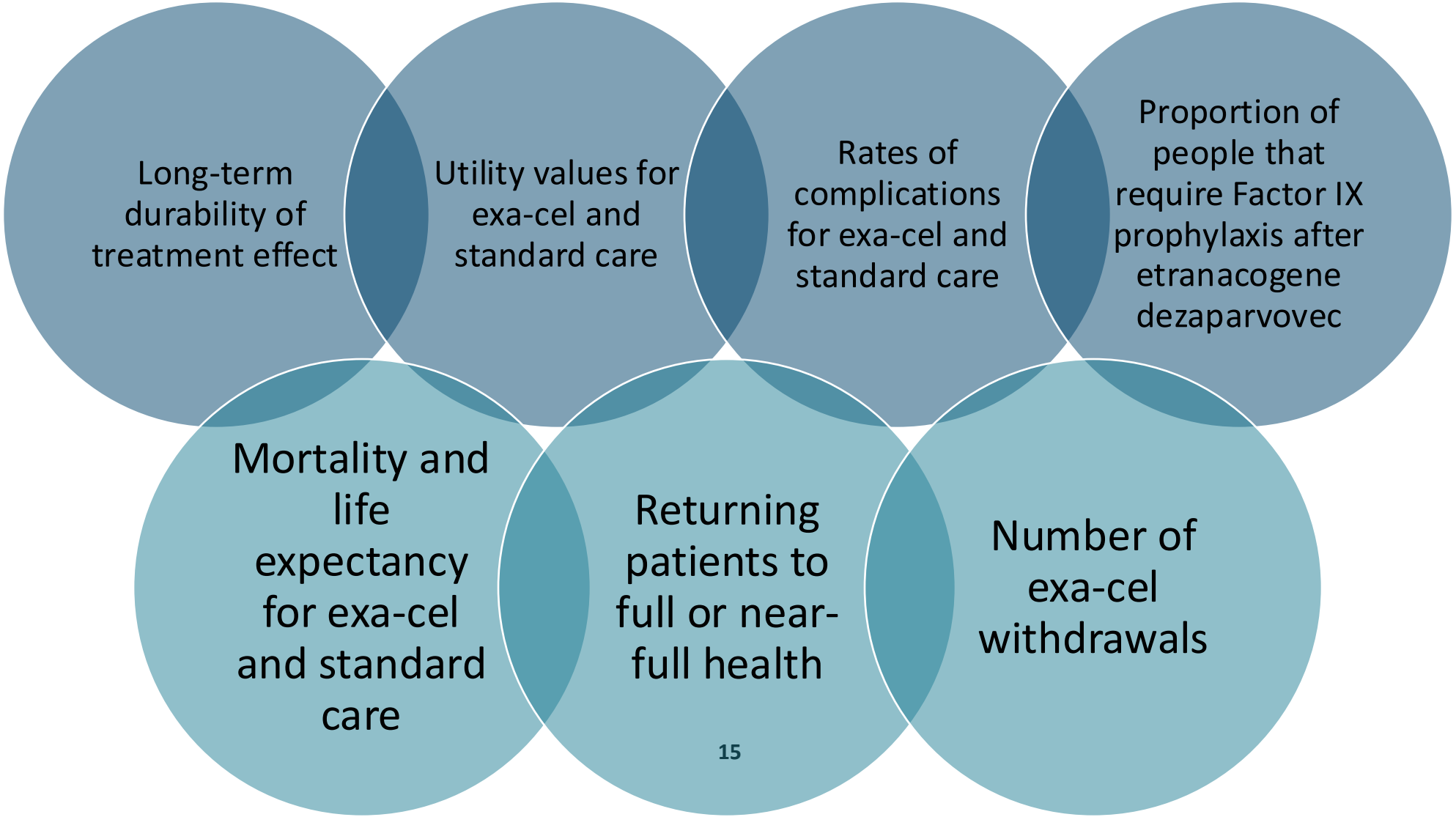
Key issues in clinical and cost effectiveness in blood conditions appraisals



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Case Study 3

Early rare disease MA topic

HST12 - Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

November 2019

MA Entry

(HST12)

- Cerliponase alfa received a positive recommendation by NICE within the context of a MAA
- The previous appraisal identified several issues that meant that a MAA was needed. These included limited evidence and uncertainties in the following areas:
  - CLN2 Clinical Rating Scale scores over time and whether there was long-term stabilisation of disease
  - improvements over time in motor and language score at time of treatment initiation,
  - the frequency and severity of tonic-clonic seizures
  - myoclonus and dystonia control, impact on visual acuity (VA)
  - and measures of QoL

June 2024

MA-review

- Review of HST currently in process using the following evidences sources:
  - long-term effectiveness data from study 190-202 (which is an extension of study 190-201)
  - new sources of clinical effectiveness evidence from the MAA and from study 190-203
  - three long term safety studies
  - and two supplementary studies

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Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; HST, Highly specialised technology; MA, Managed access; MAA, Managed access agreement;

Challenges experienced during Cerliponase alfa Managed Access

No exit clause

No funding route for drug in the event of negative recommendation at reappraisal

Anxiety for patients and parents

Poorly defined data collection period

Confusion when final reports due

Confusion around when MAA was applicable

Poorly defined clinical uncertainties

Large amount of data collected

Lacked specificity

Likely occurred because uncertainty prevalent throughout evidence

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Case study 4

The RWE framework in action

TA850 - Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy

Case study: Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy

Study component	Amivantamab TA850
Trial design	• Single arm phase 1b • 114 patients (efficacy pop)
Outcomes	• Progression free survival: median 6.7 months • Overall survival: median 22.8 months
Comparator data	• No prior clinical trials in EGFR Exon 20 insertion-positive population • US RWD combined from Flatiron, ConcertAI, and COTA (n=206) • UK data (n=16) - NCRAS with additional molecular data to identify subgroup • Used a blended comparator
Methods	• Adjusted indirect comparison • Pre-defined list of confounders • Complete case analysis • Propensity score weighting
Results	• Substantially higher OS & PFS for experimental drug

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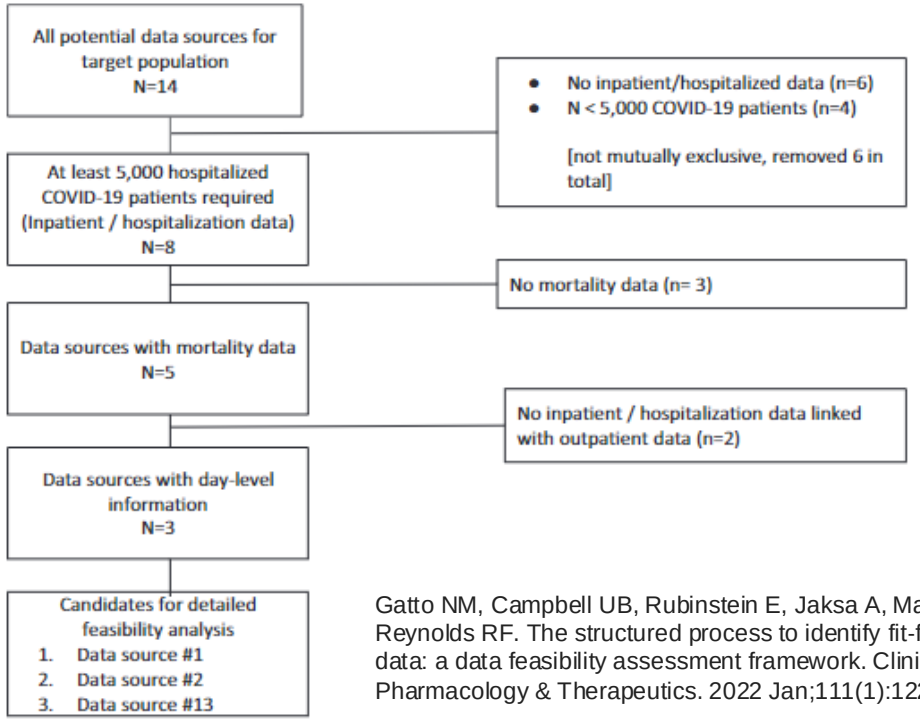
Committee concerns – suitability of RWD sources

- How were datasets selected/prioritised?
- Are the data sources relevant to UK context?
- Is it appropriate to pool the three sources of US RWD?
- How were patient selected into this pooled database?
- Was the case-mix of comparator treatments and subsequent therapies relevant to the UK?
- Were relevant confounders captured and how much missing data? (e.g., ECOG)?



Gatto NM, Campbell UB, Rubinstein E, Jaksa A, Mattox P, Mo J, Reynolds RF. The structured process to identify fit-for-purpose data: a data feasibility assessment framework. Clinical Pharmacology & Therapeutics. 2022 Jan;111(1):122-34.

Appendix 1 – Data Suitability Assessment Tool (DataSAT)

DataSAT assessment template

DataSAT - case study

See tools and resources for a downloadable DataSAT assessment template.

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Committee concerns – methods

- Was choice of confounders appropriate? Are there key missing confounders?
- What was the choice of propensity score model (i.e., weighting) appropriate?
- Was a complete case analysis appropriate (i.e., was data 'missing completely at random'?)
- Were best-practice study design principles followed?
    - Did the External Control Arm (ECA) match eligibility criteria to the Single Arms Trial (SAT)?
    - Is the start of follow-up the same for the SAT and ECA?
- Were the results robust to residual biases from unmeasured confounding, missing data, and measurement error?

Methods for real-world studies of comparative effects

Key messages

- Non-randomised studies can be used to provide evidence on comparative effects in the absence of randomised controlled trials or to complement trial evidence to answer a broader range of questions about the effects of interventions in routine settings.
- The recommendations presented here focus predominantly on cohort studies including those using real-world data to form external control arms.
- Study design
    - Design studies to emulate the preferred randomised controlled trial (target trial approach).
    - Avoid time-related biases due to differences between patient eligibility criteria being met, treatment assignment, and start of follow-up.
    - For studies using external control, select and curate data to minimise differences between data sources including availability and operational definitions of key study variables, data collection processes, patient characteristics, treatment settings, care pathways, and time periods, and consider the implications for study quality and relevance.
- Analysis
    - Identify potential confounders (including time-varying confounders) using a systematic approach and clearly articulate causal assumptions.
    - Use a statistical method that addresses confounding considering observed and unobserved confounders.
    - Consider the impact of bias from informative censoring, missing data, and measurement error and address appropriately if needed.
    - Use sensitivity and bias analysis to assess the robustness of results to main risks of bias and uncertain data curation and analysis decisions.
- Reporting
    - Justify the need for non-randomised evidence.
    - Provide a study protocol and statistical analysis plan before performing final analyses.
    - Report studies in sufficient detail to enable independent researchers to reproduce the study and understand what was done and why.
    - Assess the risk of bias and relevance of the study to the research question.
- The acceptable quality of evidence may depend on the application and various contextual factors.

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Any questions

RWE use through Cancer Drugs Fund: SACT

Comparison of Outcomes (Trial vs SACT)

TA796 Venetoclax for treating chronic lymphocytic leukaemia	SACT data used in preference to trial for OS or PFS estimate	**TA795** Ibrutinib for treating Waldenstrom's macroglobulinaemia
TA736 Nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy	SACT data used in scenario analysis but not in final model	
TA655 Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy	SACT data provided reassurance regarding trial OS	**TA798** Durvalumab for unresectable NSCLC after platinum-based chemoradiation

Other uses

TA802 Cemiplimab for treating advanced cutaneous squamous cell carcinoma	Baseline characteristics adjusted to reflect SACT data in the updated model
TA524 Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma	Estimating rate of subsequent therapies (stem cell transplant)
TA770 Pembroliz. with carboplatin + paclitaxel for untreated metastatic squamous NSCLC	Reweighting results from trials to reflect characteristics of all eligible patients