four situations in which RCT evidence may not be feasible or practical for informing regulatory and HTA decisions. These situations are illustrated in Figure 1.

An Evaluation of Non-Randomized Evidence (NRE) Used in HTA Decision-Making: A Case Study Review

RWD119

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Background

Randomised controlled trials (RCTs), and meta-analyses of RCTs, are considered the 'gold standard' in the hierarchy of clinical evidence (Murad et al., 2016). RCTs are valued for their high degree of internal validity, or the extent to which observed differences between groups can be attributed to the intervention under investigation (Cipriani, Purgato and Barbui, 2009). The randomisation mechanism minimises confounding bias and provides a basis for estimating the strength of any causal relationship. However, the external validity of RCTs can be low due to strict inclusion and exclusion criteria that may produce a sample population that is unrepresentative of the broader patient population.

Non-randomised evidence (NRE) is a broad term that can include interventional studies such as single-arm trials, synthetic control arms, and other non-randomised controlled trials, as well as real-world evidence (RWE) that includes evidence from sources such as chart reviews and registries. Non-randomised studies are lower on the traditional hierarchy of evidence due to the higher potential for bias, including confounding, selection bias, performance and detection bias as a result of the absence of randomisation and/or blinding (Cochrane Handbook for Systematic Reviews of Interventions, 2022). Given these limitations, NRE should not replace randomised evidence. However, a series of case studies highlight circumstances in which an RCT may not be feasible, practical or, in some cases, ethical. This is where NRE can play an important/valuable role in facilitating HTA decision-making and patient access in areas of high need.

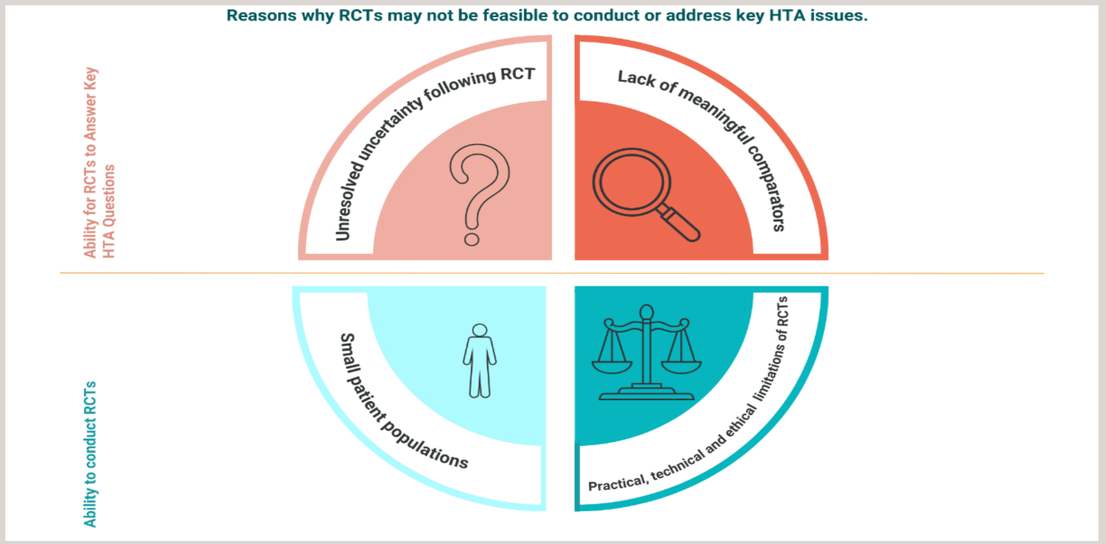
Case Study Themes and Selection

Situations where RCTs may not be Feasible or Practical

Four situations in which RCT evidence may not be feasible or practical for informing regulatory and HTA decisions were identified for case study identification. These situations are illustrated in Figure 1. Products were then selected based on the coverage of these topics within the review of the case. In the end, four products were selected to illustrate the use of NRE.

Objectives

This study examines the application of NRE in regulatory and HTA decision-making through a series of case studies, and to demonstrate how NRE can complement RCTs to facilitate timely access to innovative treatments



Product	Indication/Epidemiology	Issues with RCTs	Type of non-randomised data collected	How did non-randomised evidence facilitate decision-making?	Methodology	External validity	Decision
Cemiplimab	- metastatic or locally advanced cutaneous squamous cell carcinoma (aCSCC) - incidence ranging from 8.9 to 37.6 per 100,000 in Europe, (European Medicines Agency, 2019)	- Unresolved uncertainty - Lack of meaningful comparators - Small patient population	- US chart review - UK systemic anticancer therapy dataset	**Chart review informed control arm and SACT informed patient baseline characteristics.** **RWE indicated that life expectancy with the disease and survival extension associated with cemiplimab met End of Life criteria**	Indirect treatment comparisons (STC and MAIC) and naive comparison (fitting survival extrapolations directly to observed data) were conducted but considered to have uncertainty.	There was uncertainty about whether the trial results were generalisable to the UK (as per SACT) and in survival extrapolations, but committee considered cemiplimab likely to extend survival.	**Cemiplimab was considered to meet End of Life criteria and was therefore recommended**
Blinatumomab	- Minimal residual disease positivie B-cell acute lymphoblastic leukaemia (MRD+ BCP-ALL) - Prevalence is estimated to be 23 and 27 per 100,000 persons (EMA 2018)	- Lack of meaningful comparators - Small sample size	Retrospective cohort study receiving standard chemotherapy	**Retrospective study informed control arm.** **While the single arm trial demonstrated that blinatumomab extended life, clinical evidence and model confirmed that life expectancy was not less than 24 months, therefore End of Life criteria were not met.**	Primary analysis set from single-arm trial and retrospective study were compared using propensity score model. OS was extrapolated for both arms and informed by Phase 3 RCT of blinatumomab in another ALL indication.	The indirect comparison method was considered appropriate, but results were considered subject to uncertainty and not generalisable to full licensed population (2nd complete remission population not included). Revised economic model submitted in response to committee's request was considered generalisable to UK practice.	**Blinatumomab was considered cost-effective for patients with ALL in 1st complete remission and recommended for this population.** **The committee considered there was not enough evidence to assess for patients in second complete remission.**
Autologous gene therapy	- adenosine deaminase deficiency–severe combined immunodeficiency (ADA-SCID) - Incidence between 1 in 200,000 and 1 in 1,000,000 live births (Hershfield 2006)	- Lack of meaningful comparators - Small patient population - Ethical issues	Retrospective cohort study receiving HSCT	**Comparison facilitated by historical control arm**	A formal indirect comparison was not possible due to the lack of a common comparator, small patient numbers and lack of data, therefore the company provided a narrative synthesis.	UK patients were expected to be younger in clinical practice than the trial population, therefore clinical benefit was expected to be greater in practice.	**Autologous gene therapy for ADA-SCID was recommended through the HST route and considered to be a clinically effective treatment that improves survival relative to HSCT and reconstitutes the immune system**
Onasemnogene abeparvovec	- paediatric Type 1 spinal muscular atrophy (SMA) - incidence of less than 0.4 per 10,000	- Lack of meaningful comparators - Small patient population - Ethical issues	Natural history study of patients receiving Best Supportive Care in US	**Natural history study was used to estimate outcomes for Best Supportive Care**	A formal indirect comparison was not possible due to small sample sizes and lack of head-to-head trials; therefore, adjustments were not made for differences in patient characteristics.	The natural history study was based on US practice, with a higher proportion of patients receiving tracheostomy than in the UK. However, it was considered the best available source given the prospective design and relative mature outcome data	**Onasemnogene abeparvovec was recommended through the HST route and was considered to improve survival compared to Best Supportive Care.**

Product	Cemiplimab	Blinatumomab	Autologous gene therapy	Onasemnogene abeparvovec
EMA Approval	**June 2019**	**January 2019**	**May 2016**	**May 2020**
NICE (UK)	**Approved - Cancer Drugs Fund**	**Approved -Reimbursement with limitation**	**Approved**	**Approved - Highly Specialised Technologies (HST); Reimbursement with limitation**
	In addition to the clinical evidence of single area studies, the company presented non-randomised data from two UK chart reviews conducted outside of the UK but there was still considered a lot of uncertainity in the application. A chart review study in the UK was submitted after two years which had many notable issues with design and data. However, NICE accepted that the data as meeting the end-of-life criteria (NICE, 2022a).	NICE granted approval in 2019, based primarily on the single-arm pivotal study (BLAST) and retrospective study (NICE, 2019a; Boissel et al., 2023). The assessment committee considered the indirect comparison appropriate but noted that results may not be generalisable to the full licensed population and were considered subject to uncertainty, in part due to the use of a novel molecular response as an endpoint.	Evidence review group (ERG) accepted evidence that focused on the integrated Strimvelis population of 18 patients drawn from 4 different single-arm studies and a historical UK-comparator drawn from the same external retrospective analysis used to inform the regulatory assessment (Hassan et al., 2012). ERG acknowledged that the population presented in the clinical evidence was appropriate for decision-making given the rarity of ADA-SCID and low patients numbers	ERG accepted the company's approach to pooling the datasets without adjustments and cited the risk that adjusting for confounders would have reduced sample size but not improved precision or accuracy in the results (NICE, 2021). Clinical experts opinion was used to support maintainence of motor endpopints over the long term, based on the single-arm trials.
GBA (DE)	**No Added Benefit**	**Non-Quantifiable**	**Not reviewed**	**No Added Benefit**
	IQWiG did not consider the magnitude of the survival benefit sufficient to overcome uncertainties in the open-label single-arm trial. Additionally, IQWiG noted that the RWD study lacked patient-relevant outcomes, such as symptoms, health-related quality of life and adverse events (IQWiG, 2024).	They did not consider the additional evidence submitted by the manufacturer from the pilot single arm trial (BLAST) nor the retrospective study to be suitable for decision-making(IQWiG, 2019).	No comments.	IQWiG reported the single-arm trial was subject to uncertainty, and therefore the magnitude of the incremental effects needed to be "substantial" to conclude that Zolgensma provided added benefit to Spinraza (IQWiG, 2021). Real-world evidence on Zolgensma is being collected to inform the G-BA's re-assessment in 2027.
HAS (FR)	**ASMR V**	**Not Approved**	**Not reviewed**	**ASMR III; ASMR V**
	HAS (France) recommended Libtayo in 2020, but due to an absence of comparative data from the Phase 2, open-label, single-arm, the clinical benefit of Libtayo was considered to provide low clinical benefit and no clinical added value.	They did not approve Blincyto for MRD+ BCP-ALL, , citing it as an "unsolicited reimbursement in this indication" and noting that Amgen did not request the inclusion of the new indication (HAS, 2020a).	No comments.	HAS noted a number of uncertainties in the clinical assessment, including limited follow-up data, methodological limitations of unadjusted indirect comparisons and the safety profile (HAS, 2024). HAS noted that a re-evaluation would take place within three years to assess the data from the RESTORE registry.
AIFA (IT)	**Recommended - Reimbursed**	**Recommended - Reimbursed**	**Recommended - Reimbursed**	**Partial - Reimbursed**
	AIFA (Italy) judged that the NRE from the Phase 2, open-label, single-arm was considered to be inconclusive, low quality, and insufficient to inform an evaluation of added therapeutic value.	Recommended based on the pivotal single-arm trial (BLAST) although treatment was not seen as innovative in this indication due to the 'low quality' of evidence (AIFA, 2019). AIFA considered that the evidence demonstrated high rates of MRD negativity observed after a single treatment cycle despite limitations intrinsic to indirect comparisons.	AIFA approved Strimvelis pricing and reimbursement in Italy in less than 2 months through an accelerated procedure (Aiuti 2017). The product is reimbursed through an outcome-based payment by results, with rebates in cases where patients fail to sustain the curative benefit.	The assessment of clinical effectiveness was based on STR1VE-US data and compared in the economic evaluation to NeuroNext data and nusinersen, which was informed by the SHINE study, a long-term follow-up of the ENDEAR RCT (AIFA, 2021). The a single-arm trial design made it difficult to evaluate whether safety events are associated with treatment or due to the underlying disease.

Themes from Case Review

- **In rare and ultra-rare diseases, RCTs are often unfeasible.** RCTs in such populations would either be statistically underpowered or need to recruit patients from so many different centres that the trial would not be representative of any individual jurisdiction. This challenge is likely to grow in an era of personalised medicine and ever more breakthroughs in the treatment of genetic disorders. NRE allows researchers to assign all available patients to the intervention arm and construct a control arm from historical sources.
- **There are ethical concerns around randomising patients to supportive care for life-threatening conditions.** In such circumstances, it may be unethical to assign patients to a supportive care control arm and deny them access to a potentially life-extending breakthrough treatment.
- **Innovative curative-intent therapies would essentially require lifetime RCTs to confirm duration of benefit**. Curative-intent breakthroughs, such as gene therapies for childhood genetic disorders, would require unfeasibly long 'lifetime' RCTs to confirm the duration of benefit (e.g. gene therapy for ADA-SCID). Administrative data and other forms of NRE are a more practical approach to confirming the duration of benefit.
- **Even the best-designed RCTs may fail to resolve all aspects of clinical uncertainty.** Differing standards of care between jurisdictions can result in uncertainty regarding the efficacy and value of a treatment in a specific subgroup of patients. NRE can be used to construct external control arms for country-specific standards of care and address the relative value of different treatments.

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