Use of Real-World Data in Decision Making for Oncology: A Review of Recent Health Technology Appraisals in the United Kingdom

Koufopoulou M[1], Wissinger E[2], Oladapo T[1], Stewart F[3], Depalma S[3], Devani D[2], Rangi ND[1], Fusco N[2]
[1]AmerisourceBergen, London, UK; [2]AmerisourceBergen, Carollton, TX, USA; [3]AmerisourceBergen, Hannover, Germany

Background

- Randomized controlled trials (RCTs) are the gold-standard data source for National Institute for Health and Care Excellence (NICE) appraisals in oncology.
- By means of highly controlled designs, well-conducted RCTs can offer high internal validity, providing a rigorous tool to examine treatment effects in a given patient population.
- However, conducting RCTs may not always be possible (for instance, when randomization is deemed unethical).[1] And even when RCTs are available, strict inclusion and exclusion criteria often limit the generalizability of RCT results to patients seen in clinical practice, making the extrapolation of treatment efficacy to treatment effectiveness more challenging.[2,3]
- Some other challenges of incorporating RCT results in NICE appraisals may also include other issues such as comparators that do not reflect the standard of care, limited follow-up times, or use of unvalidated surrogate endpoints.[1]
- Real-world evidence (RWE), or evidence generated outside of clinical trials—when of sufficient quality and low risk of bias and confounding—can supplement the results from clinical trials, providing insights with high external validity on, for instance, effectiveness and/or safety of the drug in real-world practice or the natural history of disease.[4]
- Most real-world data (RWD) sources are observational, including, among others, electronic health records, claims data, patient registries, or cohort studies with primary data collection to address specific research questions.
- The NICE strategy for 2021 to 2026 has 4 underpinning key pillars, one of which is "the use of RWE to resolve gaps in knowledge and drive forward access to innovations for patients."[5]
- To address this goal, NICE has developed the RWE framework, which sets sights on "identifying when RWD can be used to reduce uncertainties and improve guidance" and on "describing best practices for planning, conducting, and reporting RWE studies to improve the quality and transparency of evidence."[1]
- The release of this guidance shows NICE's support for the utilization of RWE to facilitate regulatory decisions in several therapeutic areas, including oncology.

Objectives

- This research aimed to evaluate the role of RWE in NICE submissions for oncology in England and Wales:
  - To determine the extent to which RWE was utilized to demonstrate the clinical effectiveness of a technology.
  - To explore the impact of RWE on NICE recommendations and critiques provided by the Committee.

Methods

- Searches were conducted using NICE's interface for "Published guidance, NICE advice and quality standards" to identify relevant published appraisal documents, with a focus on assessments in oncology.
- The search was restricted to appraisals published between October 1, 2019, and October 31, 2022.
- Appraisals in oncology reporting the use of RWE to demonstrate treatment effects were identified and key findings were extracted.

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Results

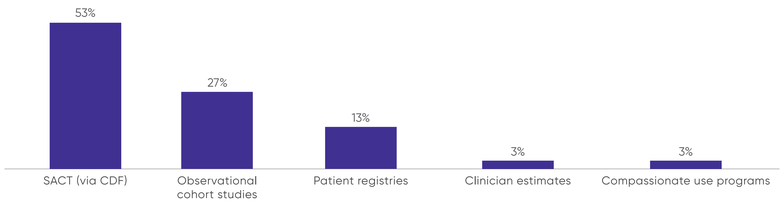
RWE use in oncology:

- Among the 102 NICE appraisals in oncology, RWE use was reported in around a third (n=30) of the appraisals to support clinical trial evidence for drug effectiveness.
- Indications for the use of RWE were in solid tumours (70%, n=21/30) and haematological cancers (30%, n=9/30).
  - Solid tumours included breast cancer, head and neck cancer, hepatocellular carcinoma, lung cancer, gynaecological cancer, renal cell carcinoma, skin cancers, soft tissue sarcoma, squamous cell carcinoma, systemic mastocytosis, and urothelial carcinoma.
  - Haematological cancers comprised chronic lymphocytic leukemias, chronic myeloid leukaemia, follicular lymphoma, multiple myeloma, mycosis fungoides and Sézary syndrome, T-cell lymphoma, and Waldenström's macroglobulinemia.
- The NICE Committee noted that RWE is commonly used, as it is generalizable to UK clinical practice compared to trials. Secondly, RWE acts as comparator data where head-to-head trials with comparator treatments are lacking. Thirdly, RWE is also used to validate economic modelling.
- In the majority of the appraisals (57%, n=17/30), RWE was utilized in indirect treatment comparisons for assessing comparative treatment effects. These include matching-adjusted indirect comparisons, simulated treatment comparisons, or naïve/unadjusted indirect treatment comparisons. In the other 43% (n=13/30) of the appraisals, RWE was used to overcome the limitations in survival data by comparing the relative effectiveness of treatments with previously published studies or utilizing external/historical/pseudo/simulated control arms.
- RWE also supported modelling by allowing extrapolation of survival data and model validation for projected survival data and by providing inputs for various scenario analyses.

Types of RWE data sources:

- As shown in **Figure 1**, the most common source of RWD was the Systemic Anti-Cancer Therapy (SACT) data available through the Cancer Drugs Fund (CDF) (53%, n=16).
- Other known sources included previously published observational cohort studies (27%, n=8), patient registries and audits (13%, n=4; such as the Haematological Malignancy Research Network database, Hospital Episode Statistics database, and National Cancer Analysis System registry), clinician estimates (3%, n=1), and compassionate use programs (3%, n=1).

Figure 1. Real-world data sources used in oncology appraisals



Key: CDF – Cancer Drugs Fund; SACT – Systemic Anti-Cancer Therapy.

Recommendation for use:

- The NICE guidance recommends a treatment for National Health Service (NHS) or CDF use based on its cost-effectiveness, certainty of clinical benefit, or end-of-life criteria.
- As presented in **Table 1**, approximately 90% (n=27/30) of the treatments were recommended for NHS use, while 1 was recommended for CDF use. The remaining 2 treatments were not recommended for use either on the NHS or via CDF due to high incremental cost-effectiveness ratios.

References: 1. National Institute for Health and Care Excellence (NICE). NICE real-world evidence framework. Accessed April 2023. https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837 **2.** Rothwell PM. Factors that can affect the external validity of randomised controlled trials. *PLoS Clin Trials*. 2006 May;1(1):e9. doi: 10.1371/journal.pctr.0010009 **3.** Karim S, Xu Y, Kong S, Abdel-Rahman O, Quan ML, Cheung WY. Generalisability of common oncology clinical trial eligibility criteria in the real world. *Clin Oncol (R Coll Radiol)*. 2019 Sep;31(9):e160–e166. doi: 10.1016/j.clon.2019.05.003. **4.** Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *J Natl Cancer Inst*. 2017 Nov 1;109(11). doi: 10.1093/jnci/djx187. **5.** National Institute for Health and Care Excellence (NICE). NICE strategy 2021 to 2026. Accessed April 2023. https://static.nice.org.uk/NICE%20strategy%202021%20to%202026%20-%20Dynamic,%20Collaborative,%20Excellent.pdf

Table 1. Summary of RWD source and NICE recommendation across indications

Indication	Intervention	RWD source	Recommended (NHS/CDF)
Solid tumours			
BC (advanced; HER2-positive)	Tucatinib + trastuzumab	Clinician estimates	Yes (NHS)
BC (advanced; HR-positive, HER2-negative)	Palbociclib + fulvestrant	SACT data	Yes (NHS)
Breast cancer (advanced or metastatic; HR-positive, HER2-negative)	Abemaciclib + fulvestrant	SACT data	Yes (NHS)
Endometrial cancer (advanced or recurrent)	Dostarlimab	Observational study	Yes (CDF)
Gynaecological cancer (relapsed, platinum-sensitive)	Niraparib	SACT data; observational study	Yes (NHS)
HCC	SIRT	Observational study	Yes (NHS)
Melanoma (completely resected stage 3)	Pembrolizumab	SACT data	Yes (NHS)
MCC (metastatic; pre-treated)	Avelumab	Observational study	Yes (NHS)
MCC (metastatic; untreated)	Avelumab	SACT data	Yes (NHS)
NSCLC (advanced; MET gene alterations)	Tepotinib	Observational study	Yes (NHS)
NSCLC (advanced; non-squamous)	Nivolumab	SACT data	Yes (NHS)
NSCLC (metastatic; squamous)	Pembrolizumab + carboplatin and paclitaxel	SACT data	Yes (NHS)
NSCLC (unresectable)	Durvalumab	SACT data	Yes (NHS)
Pleural mesothelioma (unresectable malignant)	Nivolumab + ipilimumab	Registry/audit	Yes (NHS)
RCC (advanced)	Nivolumab + ipilimumab	SACT data	Yes (NHS)
SCC (cutaneous; advanced)	Cemiplimab	SACT data	Yes (NHS)
SCC (head and neck; recurrent or metastatic)	Nivolumab	SACT data	Yes (NHS)
STS (advanced)	Trabectedin	Observational study	Yes (NHS)
Systemic mastocytosis (advanced)	Midostaurin	Registry	Yes (NHS)
Urothelial cancer (advanced; PD-L1-positive)	Atezolizumab	SACT data	Yes (NHS)
Urothelial cancer (invasive; high risk of recurrence)	Nivolumab	Observational study	Yes (NHS)
Haematological cancers			
CLL	Venetoclax	SACT data	Yes (NHS)
CML	Asciminib	Registry	Yes (NHS)
Cutaneous T-cell lymphoma (Mycosis fungoides-type)	Chlormethine gel	Observational study	Yes (NHS)
FL (rituximab treated)	Obinutuzumab + bendamustine	SACT data	Yes (NHS)
FL (previously treated)	Lenalidomide + rituximab	Observational study	Yes (NHS)
FL (refractory)	Idelalisib	Compassionate use program	No (NHS/CDF)
MM (relapsed and refractory)	Daratumumab	SACT data	Yes (NHS)
Mycosis fungoides and Sézary syndrome	Mogamulizumab	Registry	Yes (NHS)
WM	Ibrutinib	SACT data; registry	No (NHS/CDF)

Gynaecological cancer included ovarian, fallopian tube, or primary peritoneal cancer.
Key: BC – breast cancer; CDF – Cancer Drugs Fund; CLL – chronic lymphocytic leukaemia; CML – chronic myeloid leukaemia; FL – follicular lymphoma; HCC – hepatocellular carcinoma; HER2 – human epidermal growth factor receptor 2; HR – hormone receptor; MCC – Merkel cell carcinoma; MM – multiple myeloma; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NSCLC – non-small cell lung cancer; PD-L1 – programmed death-ligand 1; RCC – renal cell carcinoma; RWD – real-world data; SACT – Systemic Anti-Cancer Therapy; SCC – squamous cell carcinoma; SIRT – selective internal radiation therapy; STS – soft tissue sarcoma; WM – Waldenström's macroglobulinemia.

Critiques:

- The Committee noted that while the SACT data were generalizable to clinical practice in the UK, it was limited by immature data, smaller sample size compared to sample size in clinical trials, limited follow-up, and assessment of a limited number of outcomes. Despite these limitations, the Committee concluded that the SACT data may support clinical effectiveness; however, it was not robust for use in economic modelling. Notable examples were found in TA629, TA691, TA713, and TA725, where the survival data from SACT were too immature and were not included in economic modelling, while the extended trial results provided enough clinical evidence for decision making.
- The Committee further noted that while RWD can supplement data from clinical trials, including RWD in indirect treatment comparisons is associated with uncertainties due to key population differences compared to the trial population (ie, differences in potential treatment effect modifiers not adequately accounted for in comparisons). Hence, they may not be a reliable estimate of the relative treatment effectiveness.
- The Committee concluded that the limitations associated with RWD (such as the inherent risk of bias) should be considered in the context of decision making, and that further research would be beneficial to establish the validity of RWD for estimating intervention effect in comparison with RCTs.[1]

Conclusions

- There is a significant utilization of RWE in NICE appraisals either alongside RCTs or as a distinct evidence source. NICE is currently working on developing its RWE Framework, which will provide detailed guidance regarding the conduct of real-world studies. Routine use of RWE may help with filling evidence gaps and accelerate patients' access to innovative technologies.

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Please direct questions to
Maria Koufopoulou at
Maria.Koufopoulou@xcenda.com

AmerisourceBergen
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