Cross-Agency Appraisal of Real-World Evidence in Oncology and Rare Disease Drug-Indication HTA Appraisals Across Select APAC Markets and England: A Comparative HTA Appraisal Review (2021-2026)

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RWD22

Introduction

Real-world evidence (RWE) increasingly supplements clinical trial evidence in oncology and rare disease health technology assessments (HTA), including through external controls, longer-term outcomes and evidence in under-represented populations[1]. Its use may introduce additional uncertainty related to data quality, selection bias, residual confounding and population comparability, affecting HTA decision-making[1]. While RWE frameworks have advanced internationally, how APAC HTA agencies appraise and act upon these uncertainties remains less well characterised, particularly for the same drug–indication pairs across jurisdictions[2].

Objectives

Across drug–indication sets appraised by ≥2 agencies in select APAC markets and England, this study aimed to:

- **Characterise** RWE sources and uses;
- **Compare** agency appraisal of RWE and associated uncertainties; and
- **Assess** the role of RWE in reimbursement decision-making.

Methods

1 | Screening and eligibility

Publicly available oncology and rare disease HTA appraisals (2021-2026) from NICE, PBAC/MSAC, ACE, and CDE (Taiwan)–were screened[3].

Inclusion criteria

RWE informed ≥ 1 prespecified clinical use:

- ✓ External control arms for relative treatment effects
- ✓ Long-term outcome validation of immature trial data
- ✓ Extrapolation to under-represented populations

Exclusion criteria

RWE used to inform:

- × Epidemiology / disease characterization
- × Standard of care / treatment positioning
- × Resource utilisation and costs
- × Treatment usage, dosing and adherence
- × Patient-reported outcomes (PROs)

Drug-indication sets required appraisal by ≥2 HTA agencies.

2 | Data extraction

A structured template captured RWD source and geographic origin; RWE use; agency appraisal and RWE-related uncertainties; reimbursement recommendation; and role of RWE in decision-making.

3 | Data analysis

Directed content analysis compared RWE use, agency appraisal of RWE and its role in decision-making across agencies using predefined extraction domains.

Results

11 drug–indication sets (26 submissions; 24 oncology, 2 rare disease) identified

19 recommendations were positive, 6 negative and 1 temporary/conditional.

Table 1: **RWD and applications by HTA agency**

Drug	NICE	PBAC/MSAC	ACE	CDE (Taiwan)
Asciminib *3L+ Ph+ CML- CP*	▲ **HMRN** | ECA, LTV ● Retrospective studies x2 | ECA, LTV		● Retrospective studies x2 | ECA	▲ **HMRN** | ECA, LTV ● Retrospective studies x2 | ECA
Cemiplimab *Metastatic / locally advanced CSCC*	▲ **UK SACT** | EXT ● Retrospective studies x7 | EXT, LTV	● Retrospective studies x9 | ECA		
Dostarlimab *Advanced / recurrent dMMR EC*	▲ **NCRAS** | ECA	● UK retrospective study | ECA		
Elranatamab *4L+ RRMM*	● US prospective study | LTV	● Flatiron, COTA | ECA		▲ Taiwan retrospective study | EXT ● Flatiron, COTA | ECA ● LocoMMotion, MoMMent | ECA
Epcoritamab *3L+ DLBCL*	● SCHOLAR-1 | ECA		● SCHOLAR-1 | ECA	
Talquetamab *4L+ RRMM*	▲ **UK SACT** | ECA, LTV ● France retrospective study| LTV ● REALiTEC,/REALiTAL retrospective study | ECA, LTV		● LocoMMotion, MoMMent | ECA	
Tisa-cel *3L+ DLBCL*			● CORAL, SCHOLAR-1 | ECA	● CORAL, SCHOLAR-1 | ECA
Tisa-cel *R/R B-cell ALL (≤ 25 years old)*	● Germany retrospective study | ECA, EXT		● Germany retrospective study | ECA	● **CORAL, SCHOLAR-1, CIBMTR, PRWCC** | ECA, EXT
Axi-cel *R/R LBCL**	▲ **UK SACT** | LTV, EXT ● SCHOLAR-1 | ECA	● Retrospective studies | LTV	● SCHOLAR-1 | ECA	
Onasemnogene abeparvovec *SMA type 1 (< 2 years)*			● **Unspecified registry** and observational studies | LTV, EXT	● Unspecified RWD | LTV, EXT
Glofitamab *3L+ DLBCL*	● SK retrospective study | ECA		● SK retrospective study |ECA	

Legend: Positive recommendation | Negative recommendation | Conditional / temporary recommendation
▲ Local source ● Foreign source | **red text: registry data** | *Italicised text:* Disease indication |
ECA: External control arms for relative treatment effects | LTV: long-term outcome validation of immature trial data |
EXT: Extrapolation to under-represented populations
*3L+ population for NICE and ACE, 2L for PBAC / MSAC | reimbursement conditions for elranatamab: lifetime cap of 39 infusions; indication restricted to ≥4 prior lines (vs. ≥3 lines internationally)

Across reviewed submissions, RWE was used most frequently as external control arm (n=21), followed by longer-term outcome validation (n=9) and extrapolation to under-represented populations (n=7). National registries (e.g. SACT, NCRAS) were used by NICE and referenced through NICE's conclusions by CDE (Taiwan). CDE (Taiwan) used one local retrospective study for elranatamab. ACE used data from international cohorts with no mention of local RWE data. SCHOLAR-1 was the most used data source, appearing in five submissions across 3 agencies with different reimbursement outcomes. Epcoritamab used SCHOLAR-1 for both NICE and ACE, but NICE gave positive recommendation due to acceptable cost-effectiveness while ACE concluded the uncertain clinical benefit and unfavourable cost-effectiveness precluded subsidy.

RWE also influenced decision-making in 10 of 26 submissions (Table 2).

Table 2: **RWD and their influence on HTA recommendations**

HTA submission	RWD source(s)	How RWD influenced HTA recommendations
Axi-cel (NICE)	UK SACT	• SACT validated ZUMA-1 outcomes in NHS practice and resolved uncertainty around IVIg use, supporting transition from conditional CDF funding to routine commissioning.
Cemiplimab (PBAC)	Retrospective cohorts	• PBAC incorporated Hober et al. into the economic model as more representative of real-world effectiveness, altering cost-effectiveness estimates and supporting a positive recommendation; other cohorts informed BSC and chemotherapy comparators.
Cemiplimab (NICE)	UK SACT, retrospective studies	• SACT characterised the NHS population (75% aged ≥70), supporting BSC as the relevant comparator alongside expert evidence. Sun et al. informed BSC survival (median OS 5 months), contributing to the end-of-life assessment and economic evaluation supporting routine reimbursement.
Talquetamab (NICE)	UK SACT, French retrospective cohort, REALiTEC and REALiTAL	• RWE corroborated trial and comparator outcomes in clinical practice, increasing NICE's confidence in the evidence supporting reimbursement.
Glofitamab (ACE)	South Korea retrospective study	• Residual prognostic imbalance, small effective sample size and cross-study differences limited the validity of the RWD comparison, contributing to uncertain comparative effectiveness and the negative recommendation.
Talquetamab (ACE)	LocoMMotion, MoMMent	• Limited generalizability of RWD to local treatment practice • Single-arm trial design limited interpretation of ORR and OS endpoints, high cytokine-release syndrome and serious TEAEs observed in MonumenTAL-1 suggest that talquetamab may have an inferior safety profile • Patient-reported health state utilities used in the model were subject to high risk of bias due to the open-label, non-comparative design of the trial, and lacked face validity across cohorts.
Epcoritamab (ACE)	SCHOLAR-1	• Lower survival rates in the SCHOLAR-1 subset, residual imbalances in prognostic factors between arms after adjustment, residual bias caused by unobserved effect modifiers and prognostic factors contributed to uncertain clinical effectiveness.
Epcoritamab (NICE)	SCHOLAR-1	• SCHOLAR-1 provided the external R-based CIT comparator for treatment-effect estimation and long-term survival modelling, directly informing the cost-effectiveness analysis supporting reimbursement
Onasemno-gene abeparvovec (ACE)	Unspecified foreign registry, observational studies	• Observational studies and foreign registry data provided evidence of treatment benefit but without a comparator arm, the magnitude of benefit was uncertain. ACE concluded the evidence was insufficient to demonstrate superiority over risdiplam — the subsidised comparator — particularly regarding long-term durability. • The absence of Singapore-specific SMA registry data meant no local benchmark existed to validate the international evidence
Elranatamab (PBAC)	Flatiron Health, COTA	• Inconsistent IPTW-adjusted treatment effects (ORR, OS, PFS) across RWE sources and residual confounding raised concerns about the validity of comparative effectiveness estimates.

Legend: Positive recommendation | Negative recommendation

Common observations across agencies in their appraisal of RWE

All four agencies share core methodological concerns about RWE, i.e. selection bias, confounding, heterogeneity, MAIC attenuation, and comparator validity, but differ in emphasis. Residual uncertainty is managed through mechanisms including managed access, risk-sharing, prospective evidence generation, and reassessment, applied with varying formality across systems.

NICE scrutinises external-control construction, population comparability and robustness of adjusted estimates, with residual uncertainty informing reimbursement decisions.

Distinctively, NICE manages evidence uncertainty through the CDF, using managed access to prospectively generate RWD for scheduled re-evaluation.

PBAC/MSAC scrutinise evidence maturity, particularly for technologies supported by single-arm or immature trial data, with additional follow-up/mature data requirement.

RWE-derived treatment effects used in economic models are scrutinised for transitivity and applicability to Australian clinical practice.

ACE cites limited applicability of RWE treatments and patient populations to local practice across multiple submissions, alongside small sample sizes and residual confounding following matching.

RWE uncertainty compromises comparative clinical effectiveness, which, alongside unfavourable cost-effectiveness, limits reimbursement.

CDE explicitly considers other HTA agencies' assessments of RWE and indirect evidence (e.g., CDA-AMC, PBAC, NICE) and incorporates these precedents into its appraisal.

Across submissions, CDE has assessed the transferability of RWD-derived patient populations, treatment patterns/settings, and healthcare resource use and costs to Taiwan.

Conclusions

RWE decision relevance appeared to depend on broader clinical and economic uncertainty. Future research should examine additional reimbursement determinants including unmet need, clinical efficacy and safety, costs and economic evidence across more APAC jurisdictions, disease areas and longer timeframes, supplemented by primary research where appraisal documentation is limited.

Abbreviations: 2L, second-line; 3L+, third-line or later; 4L+, fourth-line or later; ACE, Agency for Care Effectiveness; APAC, Asia-Pacific; BSC, best supportive care; CAR-T, chimeric antigen receptor T-cell; CDA-AMC, Canada's Drug Agency; CDE, Center for Drug Evaluation; CDF, Cancer Drugs Fund; CIBMTR, Center for International Blood and Marrow Transplant Research; CIT, chemoimmunotherapy; CP-CML, chronic-phase chronic myeloid leukaemia; COTA, Cancer Outcomes Tracking and Analysis; cSCC, cutaneous squamous cell carcinoma; DLBCL, diffuse large B-cell lymphoma; dMMR, mismatch repair deficient; EC, endometrial cancer; ECA, external control arm; EXT, extrapolation to under-represented populations; HMRN, Haematological Malignancy Research Network; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IPTW, inverse probability of treatment weighting; IVIg, intravenous immunoglobulin; LTV, long-term outcome validation of immature trial data; MAIC, matching-adjusted indirect comparison; MSAC, Medical Services Advisory Committee; NCRAS, National Cancer Registration and Analysis Service; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ORR, objective response rate; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; PRO, patient-reported outcome; PRWCC, Pediatric Real World CAR Consortium; R/R, relapsed/refractory; RRMM, relapsed/refractory multiple myeloma; RWD, real-world data; RWE, real-world evidence; SACT, Systemic Anti-Cancer Therapy; SK, South Korea; SMA, spinal muscular atrophy; TEAE, treatment-emergent adverse event; UK, United Kingdom; US, United States.

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Poster presented at ISPOR Asia Pacific, 6-8 September 2026, Bangkok, Thailand