HTA14

A review of NICE technology appraisals in oncology including economic evaluations with time-varying network meta-analysis

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Background

- Unlike traditional NMA which typically synthesises the average HR across each trial, a TV NMA allows for the estimation of treatment effects that can vary as a function of time.
- There are multiple factors why the HR can evolve over time, including healthy survivorship effects, differences in use of later lines of therapy and increasing presence of cure in surviving patients; also, newer treatments with different mechanisms of action mean the assumption of a constant HR may not be reasonable. In these instances, TV HRs are more likely to be needed to accurately capture and predict outcomes within economic models.[1-2]
- TV NMAs are becoming increasingly common to estimate relative effect estimates of cancer treatments. In England, there is currently no guidance from NICE or the DSU on how to choose the most appropriate type of TV NMA, how to implement the results in economic models or to extrapolate the results beyond the time horizon of the trials' follow-up.
- Each type of TV NMA and each implementation method can require substantial time and resource to undertake, meaning economic models may not include all feasible or appropriate NMA types and implementation methods as executable options.
- We reviewed the NICE TAs including economic evaluations with TV NMA and list the associated considerations from the submitting company, the EAG and NICE Committees.

Objective

- To identify and review TV NMA methodologies used in NICE TAs, and how these are justified by submitting companies and evaluated by the EAGs and NICE Committees.

Methods

- A targeted literature review was undertaken in June 2025 using the NICE website.
- Completed cancer-related TAs incorporating TV outcomes in NMAs were included. The search was restricted to TAs published from August 2017 (publication date of the first appraisal using a FP NMA).
- NICE guidance documents and committee papers were reviewed to determine the type of TV NMA used and the justification provided. The review also assessed how TV NMA results were implemented in economic analyses, and the extrapolation beyond trial follow-up.
- Two independent reviewers performed the screening and data extraction in parallel.

Results

Literature review

- A total of 175 NICE TAs were identified; of those, 24 met the final inclusion criteria (Figure 1, Table 1). One appraisal focussed on early-stage disease (TA1017). The rest focussed on late-stage settings, including unresectable, locally advanced or metastatic cancers.
- PSMs were employed by 20 of the submitting companies. One of those companies also considered a state transition model (TA709). Another four appraisals considered state transition models (TA687, TA964, TA1017, TA1065). In one of those, the committee requested an updated model using a PSM (TA687).

Table 1. List of included NICE TAs

TA number	TA428	TA463	TA498	TA512	TA520	TA584	TA595	TA650	TA645	TA661	TA666	TA687/TA593	TA705	TA709	TA724	TA725/TA579	TA858	TA865	TA964	TA997	TA1017	TA1046	TA1063	TA1065
Publication year	2017	2017	2018	2018	2018	2019	2019	2020	2020	2020	2020	2021	2021	2021	2021	2021	2023	2023	2024	2024	2024	2025	2025	2025
Company	MSD	Ipsen	Eisai	Eusapharma	Roche	Roche	Pfizer	MSD	Merck KgaA	MSD	Roche	Novartis	Roche	MSD	BMS	Eli Lilly	MSD and Eisai	BMS	Ipsen	MSD	MSD	Astellas	AstraZeneca	BMS
EAG	Aberdeen	BMJ-TAG	BMJ-TAG	BMJ-TAG	LRiG	SHTAC	Warwick Evidence	SHTAC	LRiG	LRiG	ScHARR	BMJ-TAG	Aberdeen	BMJ-TAG	York CRD	BMJ-TAG	LRiG	KSR	Exeter	KSR	LRiG	LRiG	KSR	PenTag
Tumour type	NSCLC	RCC	RCC	RCC	NSCLC	NSCLC	NSCLC	RCC	RCC	H&N SCC	HCC	BC	NSCLC	Colorectal	NSCLC	BC	RCC	Oesophageal	RCC	G&GOJ	NSCLC	G&GOJ	BC	Colorectal
Intervention	PEM	CABO	LEN + EVE	TIVO	ATEZO	ATEZO + BCP	DACO	PEM + AXI	AVE + AXI	PEM +/- CHEMO	ATEZO + BEV	RIBO + FUL	ATEZO	PEM	NIVO + IPI	ABE + FUL	LEN + PEM	NIVO + CHEMO	CABO + NIVO	PEM + CHEMO	Peri-operative PEM	ZOL + CHEMO	CAP + FUL	NIVO + IPI
Submitted base case NMA	TC	Parametric	TC	TC	FP	FP	FP	TC	Parametric	FP	TC	TC	FP	FP	FP	FP	FP & TC	Parametric	FP	TC	FP	Spline	Piecewise	FP

Which type of TV NMA was preferred and was this justified?

- FP NMAs were most preferred by both companies and EAGs (Figure 2).
- Method diversity is slightly larger on the company side, but EAGs continue to suggest FP is the standard.
- No clear trend over time (publication year) in the type of NMA submitted by companies or preferred by EAGs.
- Excluding the MTA and pathways appraisal, agreement between the company and EAG occurred in 13 of 22 appraisals (TA428, TA520, TA584, TA595, TA661, TA705, TA709, TA724, TA725/TA579, TA1065, TA645, TA865, TA1046). Disagreement generally occurred when companies used non-FP TV NMAs or time constant models when PH was violated.
- Alternative TV NMA types were usually justified at clarification; exclusion of other types was rarely questioned when FP was chosen as base case. More than one TV NMA type was provided by four companies (Figure 3) (TA463, TA512, TA1046, TA1063).

How were the TV NMA results implemented in the economic models and was the reference treatment justified?

- When applying TV HRs, comparators (eleven appraisals: TA428, TA595, TA687, TA709, TA725, TA858, TA865, TA964, TA1046, TA1063, TA1065) and interventions (nine appraisals: TA520, TA584, TA650, TA661, TA666, TA705, TA724, TA997, TA1017) were interpreted as reference treatments (Figure 4). In five appraisals (TA661, TA709, TA724, TA725, TA1017) companies commented on their choice. Alternative reference treatments were not explored in scenario analyses, and EAGs clearly commented on the reference choice in two appraisals (TA687, TA964).
- Most companies implemented TV NMA results by generating new survival curves using TV HRs applied to a reference treatment, rather than directly using FP NMA coefficients. This approach was never justified, nor was the alternative method considered. EAGs did not explicitly comment on implementation methods in any appraisal.

Figure 3. NMAs implemented by the company*

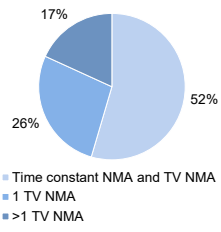


Figure 4. Reference treatment

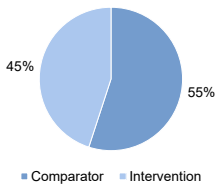
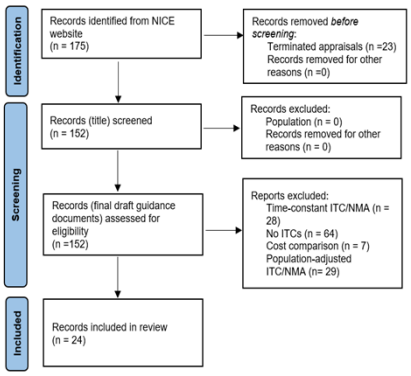


Figure 1. PRISMA flow diagram



How were the TV NMA results extrapolated beyond the time horizon of the trials' follow up?

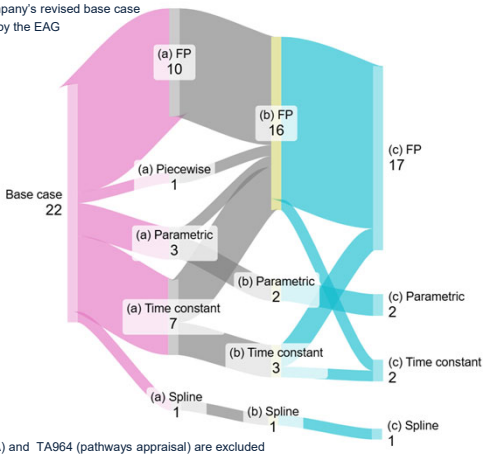
- In no TA were trial data truncated for NMA. It was unclear if EAGs considered the different lengths of follow-up or sample sizes in the tails of the data in their assessments.
- Reporting on additional constraints was limited across appraisals. Most did not mention applying extra constraints in the base case. Seven appraisals clearly reported using treatment effect waning assumptions from specific timepoints, as requested by the Committee (TA520, TA584, TA595, TA1017, TA1046, TA1063, TA1065). Two appraisals explicitly stated that TV NMA informed extrapolations for the entire time horizon (TA498, TA724).

Criticisms of the TV NMA methods

- Criticisms included poor model fit, implementation errors, heterogeneity or sparse networks, extrapolation concerns, biased priors, unjustified PH assumptions, clinical plausibility, variation in cost-effectiveness results and unjustified cut-off points.

Figure 2. Sankey diagram of preferred NMA methods over the course of each appraisal*

(a) NMA in the company's original base case
(b) NMA in the company's revised base case
(c) NMA preferred by the EAG



*Note: TA858 (MTA) and TA964 (pathways appraisal) are excluded

Conclusions

Need for guidance and transparency in reporting:

- Clearer documentation in submissions and EAG reports would improve reproducibility and make it easier to follow a given methodological decision through the appraisal and to learn what approaches are considered acceptable.
- Methodologies in submissions may face inconsistent review. This emphasises the need for clearer guidelines to align methodological expectations, especially concerning the application of TV HRs in the economic models (e.g., choice of reference treatment, extrapolations of HRs beyond trial follow-up).

Scenario analyses and justifications:

- Submissions rarely explore alternative approaches in scenario analyses, leaving potential methodological uncertainty unexamined.
- FP models are often used by default, without justification. They can be time-consuming to fit, difficult to interpret, and may yield less reliable long-term projections, warranting careful consideration. Alternatives approaches may include synthesising multiple parameters from parametric survival curves or allowing the hazard rate to vary between a set of discrete time periods.[3-4]

References:

1. Woods B et al. NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017; URL: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list.
2. Gorrod H et al. NICE DSU Technical Support Document 24: Adjusting survival time estimates in the presence of treatment switching: An update to TSD 16. 2024; URL: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list.
3. Ouwens et al. Network meta-analysis of parametric survival curves. Res Synth Methods 2010; 1: 258–271.
4. Freeman et al. Challenges of modelling approaches for network meta-analysis of time-to-event outcomes in the presence of non-proportional hazards to aid decision making: Application to a melanoma network. Stat Methods Med Res. 2022 May;31(5):839-861.

Disclosures: GG, AA and RM are employees of MSD (UK) Limited, London, UK.

Abbreviations: ABE: Abemaciclib; ATEZO: Atezolizumab; AVE: Avelumab; AXI: Axitinib; BC: Breast Cancer; BCP: Bevacizumab, Carboplatin and Paclitaxel; BEV: bevacizumab; BMJ-TAG: BMJ Technology Assessment Group; CAB: Cabozantinib; CAP: Capivasertib; CHEMO: Chemotherapy; CQ: Clarification Questions; DACO: Dacomitinib; DSU: Decision Support Unit; EAG: Evidence Assessment Group; FUL: Fulvestrant; FP: Fractional Polynomial; G&GOJ: Gastric and Gastroesophageal Junction; H&N: Head and Neck; HCC: Hepatocellular Carcinoma; HR: Hazard Ratio; HST: Highly Specialised Technology; IPI: Ipilimumab; KSR: Kleijnen Systematic Reviews; LEN: Lenvatinib; LRiG: Liverpool Reviews and Implementation Group; NICE: National Institute for Health and Care Excellence; NIVO: Nivolumab; NMA: Network Meta-Analysis; NSCLC: Non-Small Cell Lung Cancer; PH: Proportional Hazard; PSM: Partitioned Survival Model; RCC: Renal Cell Carcinoma; SCC: Squamous Cell Carcinoma; ScHARR: School of Health and Related Research; SHTAC: Southampton Health Technology Assessments Centre; TA: Technology Appraisal; TC: Time Constant; TV: Time-Varying; TIVO: Tivozanib; ZOLBE: Zolbetuximab.

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