VALUE-BASED DECISION BOUNDARIES ANALYSIS (VB-DBA): A NOVEL METHOD OF INTEGRATING NETWORK META-ANALYSIS AND COST-EFFECTIVENESS MODELLING TO ESTIMATE PRICING THRESHOLDS BASED ON TARGET PRODUCT PROFILES

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BACKGROUND

- Health technology developers use network meta-analyses (NMAs) and cost-effectiveness models (CEMs) to evaluate the commercial viability of new health technologies (HTs) in development by assessing relative efficacy and cost-effectiveness, usually based on a single target efficacy outcome profile, also known as target product profiles (TPPs).[1]
- These early evaluation results enable informed decisions regarding drug development at later stages. However, this approach is significantly limited by its inability to evaluate more than one TPP at one time.
- Thus, the ability to evaluate a range of potential profiles and derive a threshold for the commercial viability of an HT would support more informed decision-making.

OBJECTIVES

This study sought to:

- Develop a novel framework for time-to-event outcomes that assesses various TPP efficacy scenarios for conceptual health technologies in the absence of patient-level data for novel HTs.
- Showcase the framework as a tool to estimate treatment effects that meet certain drug development decision criteria based on the level dominance vs relevant comparators, rather than just considering more than one TPP at a time.[2]
- Present the initial findings of this study based on a hypothetical case-study in renal cell cancer.

METHODS

- Study methods consisted of a three-step process: a systematic review followed by a network meta-analysis feasibility assessment, identifying the anchor study for bootstrapping the TPP-specific log-hazard ratio standard errors and integrating the network meta-analysis results into a cost-effectiveness analysis
- Major quantitative concepts and decision zone definitions are shown in Figures 1 and 2, respectively.
- The NMA model for overall and progression-free survival (OS & PFS) was iteratively run for estimated SE of each log-hazard ratio (LHR) s.t. HR ϵ [t,1] (typically t = 0.1) with distance on an ln scale (α=0.025) for OS and PFS. Survival data was reconstructed from the anchor study using Guyot's algorithm to aid the SE simulation.
- Since standard errors for each TPP ln (HR) is usually not estimable early stages due to lack of data, we propose a statistical simulation approach based on an anchor study, which is chosen based on a weighted checklist score.[2]
- We explore a hypothetical example in which Wonderumab, an immune-oncology therapy by SuperWonder Pharma (SWP), was compared to sunitinib as the standard of care for first-line advanced renal cell carcinoma, this was based on prior work by Su 2020.[7]
- We assume that SWP assumed an initial dominant singular TPP of OS HR = 0.40 and PFS HR = 0.45 against sunitinib with a target price (TP) of $22,000 per month.
- Value-based pricing scenarios (VBP) were estimated for 4^n combinations*; 4 denotes the maximum number of upper boundaries and *n* = number of time-to-event outcomes which were used to estimate commercial potential scores (CPS) ** using assumed weights.

**Focused only on upper boundaries for each decision zone to reduce decision redundancy*
*** Due to space constraints, not all results could be shown here*

METHODS (Cont..)

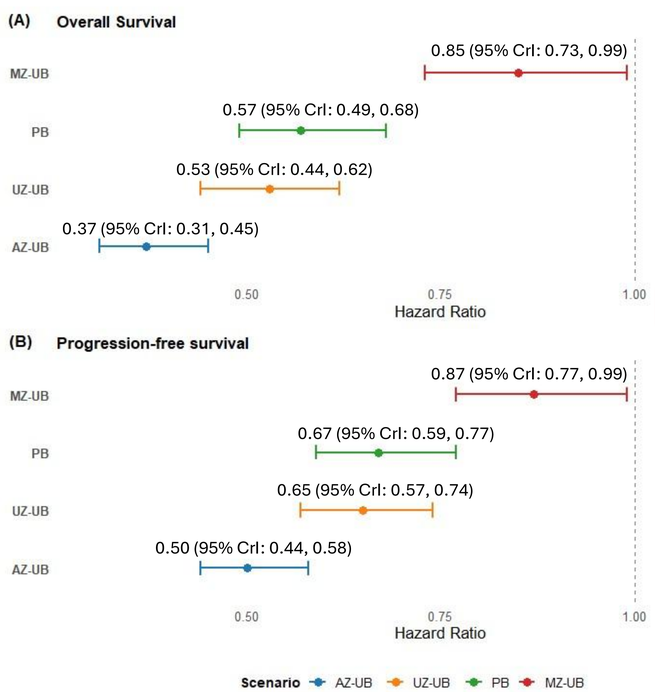
Figure 1. Mathematical Models and Conceptual Foundations

Bootstrapping Model	*Based on the Motzer 2022 (anchor), the standard error for each target log-hazard ratio (β) as estimated using the Morris 2019[2] for a total of 1600 datasets based on 1:1 randomization under the proportional-hazard assumption based on the best-fitting Royston-Parmar model as shown below ($1 \leq M \leq 6$)[3]* $$ln(H(t)|x_i) = s(ln[t]|\mathbb{K}, q_0) + \beta x_i$$ $$s(x) = \mathbb{K}_0 + \mathbb{K}_1 z_1 + \mathbb{K}_2 z_2 + \ldots + \mathbb{K}_{M-1} z_{M-1} * M \text{, where } M \text{ is the number of knots}$$
Base Model Used For Iterative NMA	• *Fixed effects model:* $\hat{\delta}_{ik} \sim Normal\left(d_{t_{i,1}t_{i,r'}}, \left(SE\left(\hat{d}_{ik}\right)\right)^2\right)$ *... #Eqn. 3* • *Random effects model:* $\hat{\delta}_{ik} \sim Normal\left(d_{t_{i,1}t_{i,r'}}, \left(SE\left(\hat{d}_{ik}\right)\right)^2 + \tau^2\right)$*, for r ≠ r' in 1,...,$na_i$, for i in 1,...,S;* $\delta_{i,k} \sim Normal(d_{t_{i,1}t_{i,k}}, \tau^2)$ *for S studies and each having na arms[4]*
Commercial Potential Score	*We propose a commercial potential score (CPS) of a novel HT against i= 1,2,….,m comparators for each of combination scenarios j = 1,2,3….,4[n] between n time to event outcomes modelled in the cost-effectiveness analysis with market share weights {w_i}:* $$CPS_j = \sum_{i=1}^{m} w_i * P(VBP_{ji} \geq TP), where\ w_i \geq 0\ and\ \sum_i w_i = 1$$ *, VBP is value-based price and TP is target price*

Figure 2 Decision Zone and Boundary Definitions

Aspiration Zone (AZ)	**Defined as the range of HR values where the novel HT is both statistically significant and numerically superior versus all comparators in the network.**	• AZ lower bound: t • AZ upper bound: a, defined as the first HR value where the above condition is no longer met when varying HR ∈ [t, 1] at increments of 0.025 (α) you can exercise for hours
Upside Zone (UZ)	**Defined as the range of HR values where the novel HT may or may not be statistically significant but remains numerically superior versus all comparators in the network (excluding SoC).**	• UZ lower bound: the next HR value after AZ upper bound • UZ upper bound: b, defined as the first HR value where the above condition is no longer met when varying HR ∈ [t, 1] at increments of 0.025 (α)
Minimum-Go Zone (MZ)	**Defined as the range of HR values where the novel HT is numerically superior and statistically significant compared to the SoC/trial comparator.**	• MZ lower bound: the next HR value after UZ upper bound • MZ upper bound: c, defined as the first HR value where the above condition is no longer met when varying HR ∈ [t, 1] at increments of 0.025 (α)
Pragmatic Zone (PZ)	**Defined as the last HR value (0.1≤HR≤1) in the TPP such that the novel HT achieves statistically significant numerical superiority against 50% of the comparators in the network**	

Figure 3 Estimate of Hazard Ratio for Relevant Boundaries of wonderumab



RESULTS

- The initial SWp target HR seems plausible only for PFS, though plausibility would require confirmation via trail data.
- Wonderumab needs to achieve an HR value of 0.37 (OS) and 0.50 (PFS) against sunitinib to achieve AZ-UB independently and attain total dominance based on relative efficacy.
- For mediocre assets, PB estimates should be set as the new base-case TPP HR target for further evidence generation activities.
- Max CPS (62.5%) was observed with a combination of PFS-AZ-UB = 0.50 and OS-UZ-UB = 0.53.
- This shows that due to non-linearity in cost-effectiveness analysis parameters, the best possible efficacy combinations (OS-AZ and PFS-AZ) may not be needed to achieve the maximum commercial viability, which may be especially relevant when optimistic targets are not biologically plausible.

CONCLUSION

- This is the only integrated framework proposing a method which combines systematic review, NMA, CEM and market shares assuming full displacement.
- The strength of this method lies in the fact that we propose to move away from a singular TPP and show value in deriving estimates throughout the numerically plausible zone that consider current evidence base, aspirational commercial value of a novel HT and inherent limitations of early value assessments.
- Results produced via this method are inherently uncertain due to immature data. However, they remain valuable as a source of key insights early in the HT development lifecycle.

For further questions:

Please feel free to drop an email with the subject DBA at: abhirup@pharmaquant.org

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