

THE NEED FOR INNOVATIVE SURVIVAL MODELLING APPROACHES IN HEALTH TECHNOLOGY ASSESSMENTS OF EARLY-STAGE ONCOLOGY INDICATIONS

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OBJECTIVES

Overall survival (OS) modelling for health economic assessments in oncology has historically focused primarily on the choice of a parametric function that best fits the Kaplan-Meier trial data in order to derive the most plausible extrapolations ('standard approach'). Increasingly, OS outcomes are (very) immature at study read-out, due to enrolled patients being diagnosed and treated earlier and/or trials being evaluated more rapidly on the basis of surrogate endpoints. This poses new challenges to health technology assessment (HTA) requiring robust estimates of (long-term) survival, as conventional parametric extrapolations are subject to a lot of uncertainty in such cases. In this study, we set out to identify the best OS modelling methods in the context of HTA of early-stage oncology indications.

METHODS

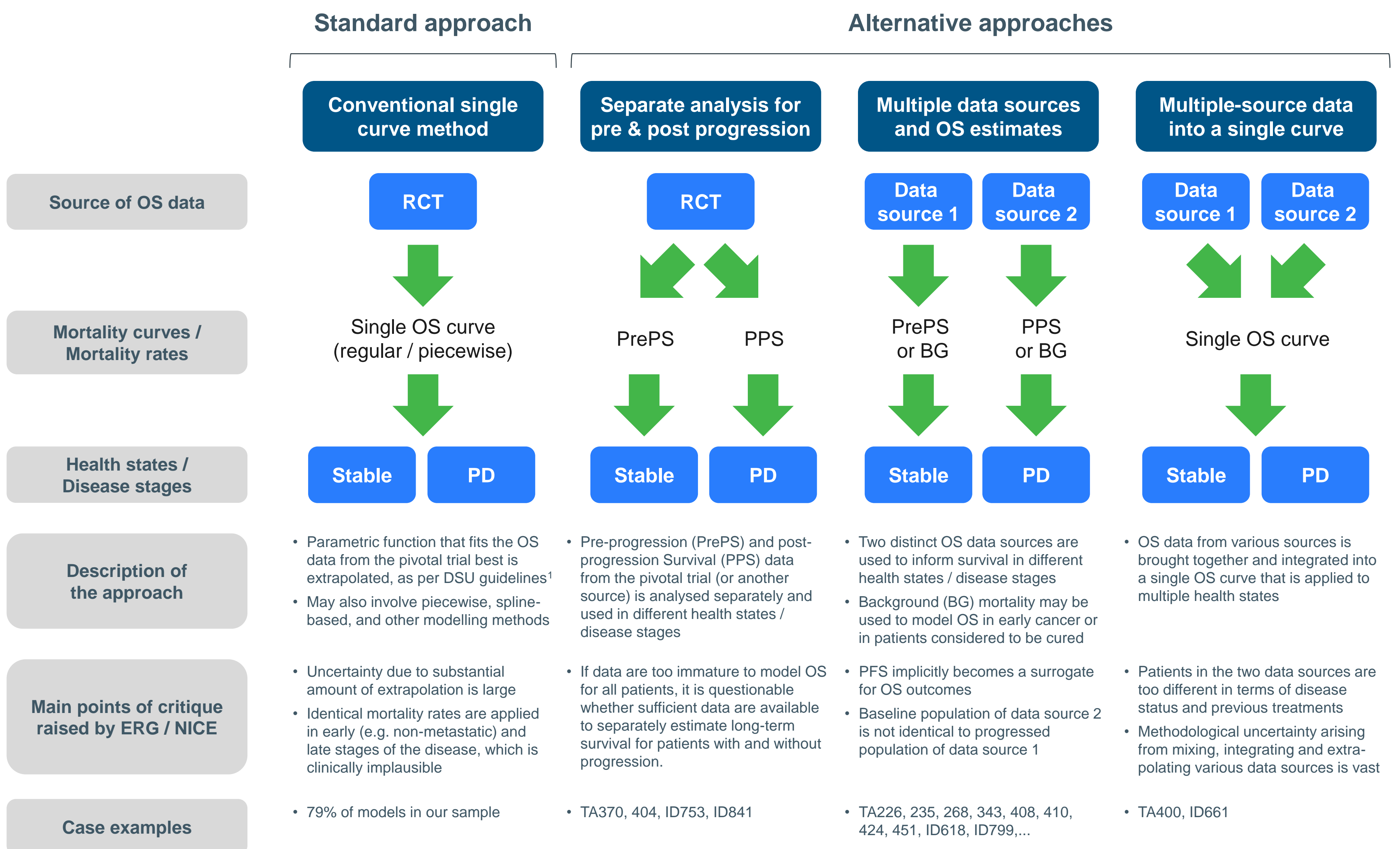
All oncology single technology appraisal (STA) project documents from the 2011 - 2017 period published on the website of the National Institute for Health and Care Excellence (NICE) were included for screening. Modelling methodologies described in the manufacturers' submissions and critique raised by the evidence review group (ERG) and/or NICE Committee were assessed. Based on this review, the OS modelling methods in these NICE STA submissions were categorised as either the 'standard' (single parametric or piecewise curve) or an 'alternative approach'.

RESULTS

Out of the 131 NICE oncology STAs submitted since 2011, 42 concerned blood cancers, 5 early-stage solid tumours and 84 late-stage solid tumour indications. In 104 individual STAs (79%), the conventional OS modelling methodology using a single parametric curve to inform OS in the model was applied, whereas 27 (21%) used other approaches. Alternative survival modelling methods were applied in 38% of blood cancer STAs (16/42), 100% of early-stage solid tumour indications (5/5), and in only 7% of late-stage solid tumour indications (6/84).

A Markov approach was used in 24 out of these 27 non-standard analyses (89%). Two models used Partitioned Survival Analysis (PartSA) and assumed patients with stable disease to be cured after a certain period of time. The remaining model was developed using a hybrid approach, i.e. a decision tree terminating in a Markov model. Although PartSA is the most common method in advanced cancers, considering the manner in which they are built, it is only logical that OS in such models is usually based on a single survival curve. In early oncology indications, Markov models may offer the benefit that different OS assumptions and treatment lines can be incorporated in distinct health states (e.g. before and after disease progression).

The most commonly used and accepted alternative OS modelling approaches were differentiating pre- and post-progression survival based on the pivotal trial data, and using multiple different survival functions per health state from different data sources. All alternative methods, however, were subject to NICE criticism.



CONCLUSIONS

In the absence of mature pivotal trial OS data, manufacturers used various approaches to incorporate additional data or assumptions in their models. However, careful consideration of available options is needed, as highlighted by criticism raised by the ERG/NICE-committee when applicants deviate from conventional survival modelling methods. Therefore, models should be developed early to allow room for validation with clinical/HE experts and preliminary discussions with HTA agencies.

1. Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from <http://www.nicedsu.org.uk>

Abbreviations - BG: Background mortality of age-adjusted general population; ERG: Evidence Review Group; OS: Overall Survival - HTA: Health Technology Assessment; PartSA: Partitioned Survival Analysis; PD: Progressed Disease; PrePS: Pre-Progression Survival; PPS: Post-Progression Survival; RCT: Randomised Controlled Trial; STA: Single-Technology appraisal