A review of external evidence used to support survival extrapolation in assessments of cancer drugs by the National Institute for Health and Care Excellence (NICE)

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Background

When making a health technology assessment (HTA) submission for a new cancer treatment, companies often need to rely heavily on data collected as part of the clinical trial programme in order to provide estimates of its likely clinical- and cost-effectiveness versus the current standard of care. For cancer treatments in particular, survival extrapolation often plays an important role in committee deliberations, with models typically fitted to trial data to provide estimates of survival over a lifetime horizon.

There are several well-recognised limitations of clinical trial data, including limited duration of follow-up, generalisability of the trial population compared with a 'real-world' population, and other trial design features (such as crossover and subsequent therapies) which may affect how useful the trial data can be for HTA decision making. To address some of these limitations, external evidence can be used to supplement data available from the pivotal clinical trial programme when performing survival extrapolation. Despite the broad range of external evidence sources that can be considered, there is no published guidance regarding how this should be done, and so it is unclear as to how (and to what extent) external evidence is being used across technology appraisals, as well as how consistent this is.

Objectives

This review aimed to investigate how external evidence has been used in recent appraisals of cancer drugs conducted by the National Institute for Health and Care Excellence (NICE) to aid extrapolation of survival outcomes. Supporting documentation for NICE appraisals are publicly available, including the company's submission, a review by the independent external assessment group (EAG), and the committee's key considerations.

Methods

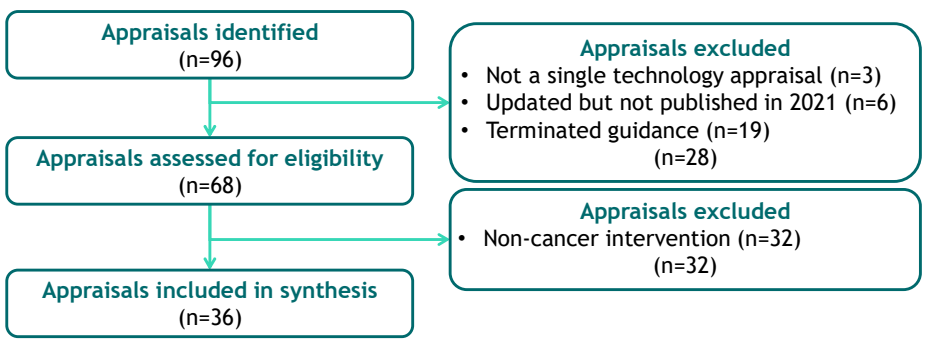
The NICE website (https://www.nice.org.uk/guidance/published) was searched on 11 February 2022 to identify non-terminated single technology appraisals of cancer drugs published in 2021. Guidance from 2021 was selected to provide a recent overview of external evidence use in HTA decision making, for completed appraisals.

Committee papers were searched for relevant information covering the survival modelling approach taken by the company for the intervention and its comparator(s); independent EAG critique; and related commentary from the committee. Consideration was also given to the timing of when external evidence was introduced into the HTA decision making process (for example, provided in the original submission versus introduced at technical engagement stage). Related information, including the choice of model structure and whether the appraisal was a Cancer Drugs Fund (CDF) review was also extracted for context.

Results

From a total of 96 appraisals published in 2021, 36 appraisals were considered relevant for review (please see references list for full set of TA numbers). **Figure 1** illustrates the identification of appraisals, and reasons for exclusion.

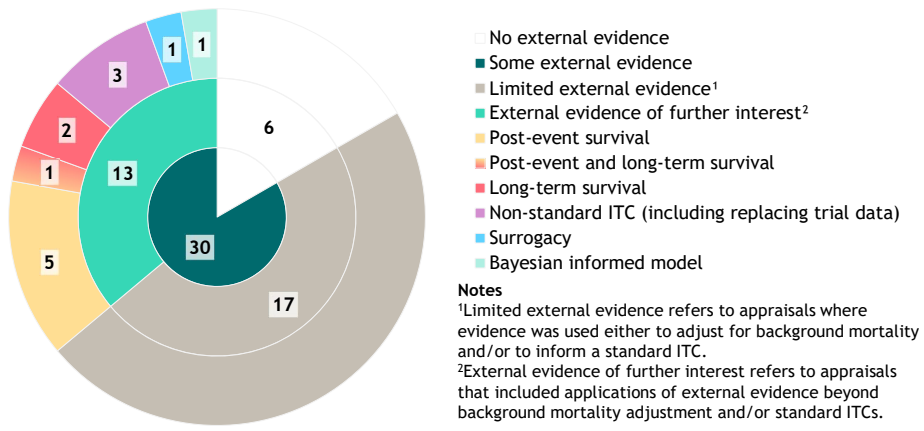
Figure 1: Identification of appraisals included in synthesis



A breakdown of the included appraisals by how external evidence was used is presented in **Figure 2**. The three concentric circles illustrate how many appraisals used some form of external evidence versus none at all (inner circle), if this was limited only to either background mortality adjustment and/or a 'standard' indirect treatment comparison (ITC) such as a network meta-analysis) versus some other use of external evidence (middle circle), and then the use of the external evidence in those deemed to be of further interest (i.e., not simply to adjust for background mortality or apply a standard ITC; outside circle).

External data sources used in the 36 identified appraisals included national population-level statistics (i.e., life tables), registry data, observational studies, and data from other clinical trials (typically in a 'similar' population). In addition, some appraisals made use of clinical opinion or assumptions based on published literature to influence survival extrapolations.

Figure 2: Breakdown of appraisals by use of external evidence



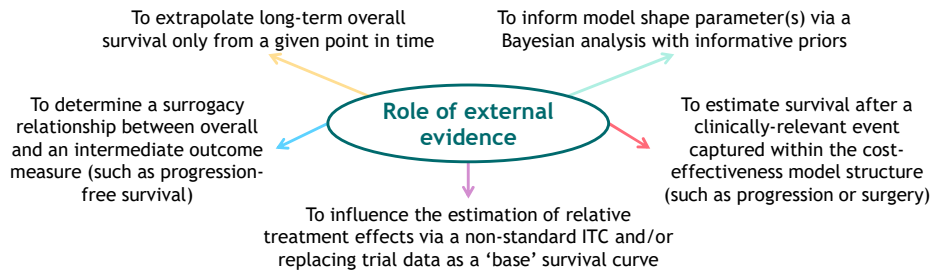
Notes
[1]Limited external evidence refers to appraisals where evidence was used either to adjust for background mortality and/or to inform a standard ITC.
[2]External evidence of further interest refers to appraisals that included applications of external evidence beyond background mortality adjustment and/or standard ITCs.

Thirty appraisals included at least one source of external evidence as part of the estimation of survival for either the intervention or a comparator. Of these, 17 appraisals included limited external evidence, either in the context of a standard ITC or to adjust extrapolations to account for background mortality.

Across all 36 appraisals, the majority (at least n=23) factored background mortality estimates into extrapolations. However, owing to limited reporting, it was not always clear whether or not extrapolations were adjusted to account for background mortality. Another commonly cited reason for including external evidence was based on the need to derive an ITC for the intervention versus at least one comparator which was not reflected by the pivotal clinical trial.

An overview of how external evidence was used in the 13 appraisals of further interest is provided in **Figure 3**.

Figure 3: Role of external evidence in the 13 appraisals of further interest



Technical descriptions of how external evidence was incorporated were often limited, ranging from seemingly simple background mortality adjustment, to more complicated use of informative priors via a Bayesian analysis. It is acknowledged however that more specific technical detail may have been contained within submission appendices that are not routinely published on the NICE website. The EAG and committee did not reject any proposed method in its entirety, but most approaches were subject to criticism.

Softer use of external evidence (e.g., determining the most suitable model based on clinical expert feedback) was reported in at least 15 appraisals, but full details were often missing or were not specific to survival extrapolation.

Conclusions

This review found that several different types of external evidence have been used to inform the estimation of survival in recent NICE appraisals of cancer drugs. We identified 13 appraisals which factored external evidence from either a clinical trial or a non-trial source into the survival model fitting process specifically. However, of the remaining appraisals, external evidence was used only to either retrospectively adjust extrapolations for face validity reasons or to derive an estimate of survival for a given treatment for which direct comparisons of survival were unavailable.

Further research is required to understand how, when, and why external evidence should, or should not, be used. However, even in the absence of such research, the findings from this review demonstrate how external evidence is commonly factored into contemporary HTA decision making, but often with limited technical descriptions. Without clear descriptions of approaches taken, transparency in HTA processes is limited, and the ability for future HTAs to apply accepted methodology is hindered. External evidence is expected to play an increasingly important role in future HTAs, and so reporting standards must be improved in order to facilitate the use of relevant-yet-complex statistical methods for survival extrapolation.

References

NICE appraisals included in synthesis: 668, 669, 670, 673, 677, 680, 683, 684, 687, 689, 691, 692, 693, 695, 704, 705, 707, 709, 712, 713, 716, 720, 721, 722, 724, 725, 728, 736, 737, 739, 740, 741, 742, 746, 754, 756. Appraisal documentation can be accessed via the NICE website: https://www.nice.org.uk/guidance/taXXX (replace XXX with the relevant appraisal ID).

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