USING CURE MODELS IN ECONOMIC ANALYSES: A REVIEW AND CONCEPTUAL GUIDELINE ON MODELLING THE CURE STATE

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BACKGROUND

Cure Model Overview

- For regulatory and health technology appraisal (HTA) groups to evaluate the full value of a new technology, extrapolating beyond the observed clinical trial evidence is often necessary. For this to occur, many years of follow-up are required to track every patient in a cohort until their attrition, despite HTA submissions usually taking place well before these data are available.
- Therefore, a key challenge in health economic modelling is how best to predict (extrapolate) long-term outcomes when no such long-term data exist.
- In certain indications and with certain health technologies, patients after a certain timepoint may not develop the event of interest however long they are followed (excluding natural events unrelated to the disease). Those who are not going to develop the event of interest are often referred to as "cured subjects," or "long-term survivors."
- In such cases where a curative technology is expected to affect not only the absolute level of survival observed in a treated cohort but also the long-term survival curve behavior, a "cure model" (sometimes called a "cure rate model") may be the most appropriate extrapolation technique to use.

Challenges

- If a cure model approach is deemed to be appropriate (i.e., if the health technology is expected to have a long-term/permanent curative effect on outcomes in that disease indication, and if there is sufficient data that suggests patients are cured after a certain timepoint), specific modelling assumptions must be made to accurately reflect patient outcomes once such a cure state is reached.
- Since data informing these assumptions are often lacking and since these cure assumptions are typically applied over a long time horizon, cure modelling approaches are often subjective and can have a significant impact on the model results and conclusions. [1]
- Currently, few guidelines for best practices in cure modelling are available and so the approaches and assumptions used can vary considerably.
- Here, we aimed to review the approaches and assumptions used in previously submitted cure models in order to develop a conceptual guideline for best practices for informing the costs and outcomes patients incur in the cure state.

OBJECTIVES

This work aims to summarise the key considerations and provide a conceptual guideline for modelling a cure health state.

METHODS

- A targeted review and extraction of recent National Institute for Health and Clinical Excellence (NICE) immuno-oncological and chimeric antigen receptor (CAR) T-cell therapy submissions was performed to assess industry uptake and NICE acceptance of cost-effectiveness models incorporating long-term survivorship ("cure" states). The key assumptions used to model the cure state were then extracted and compared to assess any similarities, differences or areas where noteworthy subjectivity was present.
- Based on the key assumption areas noted in the extraction results, a conceptual guideline for cure health state assumptions was developed.

RESULTS

Table 1: NICE CAR-T Review Summary

Appraisal #	Therapy assessed	Disease indication	Model time horizon	Cure model used?	Follow-up time available from their trial data	"Cure" time cut-off used and reasoning	Cure state survival rate used	Primary comparator and its extrapolation assumptions	Utility in cure state used	Medical resource costs in cure state
NICE: ID1166[2]	Tisagenlecleucel-T	Relapsed or refractory diffuse large B-cell lymphoma	Lifetime (46 years)	Yes	Median follow-up: 28.6 months	A 2-year time point was selected based on clinician feedback and evidence from Maurer et al (2014). It was noted that there was a large plateau extending beyond 2 years for their PFS curve.	Extrapolated using a lognormal mixture cure model. Cured patients are assumed to be subject to background (non-lymphoma) mortality only. Non-cured patients are subject to the background mortality and to additional mortality from lymphoma.	Comparators: [R-]Gem-Ox, [R-]GDP or pixantrone monotherapy. Extrapolated using Exponential model. Cure model was not explored, as there was no survival plateau in the KM curves and the treatment is considered palliative.	Equal utility values as in the progression-free state.	Cured patients incurred the same monthly follow-up costs as those in the progression-free state. PFS medical resource costs were assumed to decreased over time, as monitoring becomes less intensive.
NICE: ID1115[3]	Axicabtagene ciloleucel	Diffuse large B-cell lymphoma after 2 or more systemic therapies	Lifetime (44 years)	Yes	Median follow-up: 15.4 months	A 2-year time point was selected based on evidence from Maurer et al (2014).	Extrapolated using a logistic regression model to estimate the "cure fractions" (proportion of patients in long-term remission). Patients with long-term remission were assumed to have the age- and gender-matched background mortality. Non-cured patients are subject to the background mortality and to additional mortality from lymphoma.	Best supportive care (BSC) as a blended comparator including several therapy options. Cure model was extrapolated by exploring the various parametric functions and following the same methodology to that of the intervention group. However, the base case model used the standard Gompertz extrapolation for BSC.	Equal utility values as the age and gender matched general population.	Cured patients are assumed to no longer incur the costs of medical resource use.
NICE: ID1167[4]	Tisagenlecleucel-T	Relapsed or refractory B-cell lymphoblastic leukaemia in people aged up to 25 years	Lifetime (88 years)	Yes	Redacted from document. Plateau was evident from approximately 19, 24 and 32 months in the 3 pooled trials.	A 5-year time point was selected based on feedback from UK clinical experts, and on the NICE mock appraisal of regenerative therapies performed by the York group.	Extrapolated using a logistic regression model to estimate the "cure fractions" (proportion of patients in long-term remission). Patients with long-term remission were assumed to have the age- and gender-matched background mortality. Then three standard parametric models, Weibull, gamma and lognormal, were fitted and compared to estimate survival on the proportion of patients *not* experiencing long-term remission.	Salvage chemotherapy with options for patients to receive subsequent allo-SCT after initial treatment. Cure model was extrapolated by exploring the various parametric functions and following the same methodology to that of the intervention group. As with the intervention group, these patients were assumed to be cured after 5 years.	Equal utility values as in the event-free state.	Cured patients incurred the same monthly follow-up costs as those in the 5+ year event-free state.

Reviewer (ERG) comment summary:

- A short time for data collection relative to the extrapolation period comes with significant uncertainties. For the models with 2-year horizons, the ERG suggests that a longer cure point cut-off (5-year) *may* be more appropriate (but is not required).
- Even if a survival plateau is observed at the end data collection, if the plateaus are based on a very small sample size there is additional uncertainty that the plateau indicates a cure.
- Models assuming that cured patients revert to the same survival, utility and medical resource use cost of the general population does not currently appear to be robustly supported by evidence.
- Overall, the ERG concluded that using cure models for these therapies is a sufficiently plausible approach for decision making purposes but there are significant uncertainties with insufficient data.

Cure State Considerations

- Based on the above review, four essential areas of consideration were identified for cure state modelling:

1. Cure state initiation timepoint:

One of the main areas of uncertainty in cure modelling is determining when a patient can be considered no longer at risk of experiencing a disease-related event. Typically, the cure state is initiated at a point where the clinical data shows an extended plateau in the event rate. This approach was generally accepted by the NICE ERG, however having a sufficiently long follow-up time for data collection is essential to defend the cut-off timepoint selection.

2. Event rate assumptions:

Whether a patient who is "cured" experiences events (particularly events related to survival and progression) equal to the general (healthy) population, or if they still incur disease-related outcomes even after their disease has been effectively cured is another area of uncertainty in designing a robust cure health state. This assumption should be based on sound clinical input as well as quantitative evidence (again, preferably with a sufficiently long period of data collection).

3. Medical resource use assumptions:

Relating to the above point, the medical resources required once a patient is cured should be established. In the review of past models, patients in the cure state were assumed to have effectively zero medical resource use in some models, while in other models cured patients were assumed to still require some recurring (but diminishing) medical resources use. This assumption should also be informed by clinical expertise and real-world evidence where available.

4. Utility assumptions:

Lastly, how a patient's health-related quality of life (HRQoL) stands once they are cured must be determined. Even after being cured patients may still experience a HRQoL detriment for an extended period of time. If that is the case, the utility values used in a model's cure state should reflect this. Cure state utility assumptions varied in the model review, where some models assigned cured patients the same utility as in the progression/event-free health state, while other models assigned a general (healthy) population utility value. This assumption area, like the others mentioned, ideally should be based on robust long-term data and clinical input. Additionally, utility values should be age and gender-matched to accurately reflect the population of interest.

CONCLUSIONS

- **Cure models are associated with a set of complex assumptions that must be carefully considered when developing a valid analysis.**
- **By methodically approaching these assumptions, the expected outcomes and costs of curative therapies can be modelled to more accurately reflect real-world treatment expectations with reduced uncertainty.**
- **Robust and detailed guidance on best practices would be valuable in reducing bias, ensuring clinical validity, and capturing the important outcomes when developing cure models**

REFERENCES

1. *Grant, T. S., Burns, D., Kiff, C., & Lee, D. (2020). A Case Study Examining the Usefulness of Cure Modelling for the Prediction of Survival Based on Data Maturity. PharmacoEconomics, 38(4), 385-395.*
2. *NICE Single Technology Appraisal. (2018). Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166].*
3. *NICE Single Technology Appraisal. (2018). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115].*
4. *NICE Single Technology Appraisal. (2018). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167].*