Analysing clinical trial data to provide inputs to decision models

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PURPOSE

To analyse data from the OPTIMA trial to estimate input parameters for a decision model assessing cost-effectiveness in patients with advanced HIV for whom standard therapies had failed. The input parameters required to estimate such models often differ from the summary statistics on treatment efficacy available from trials. However, the resulting information is valuable to a range of potential analyses.

DECISION PROBLEM

The OPTIMA trial was designed to provide guidance on best medical management for patients with advanced HIV disease with multi-drug resistance. The trial evaluated the use of intensive antiretroviral treatment (ART) consisting of >5 antiretroviral drugs and structured treatment interruptions over a median of four years follow-up.

The information collected during the OPTIMA trial could be used to inform best medical management in a number of different ways by answering a series of questions:

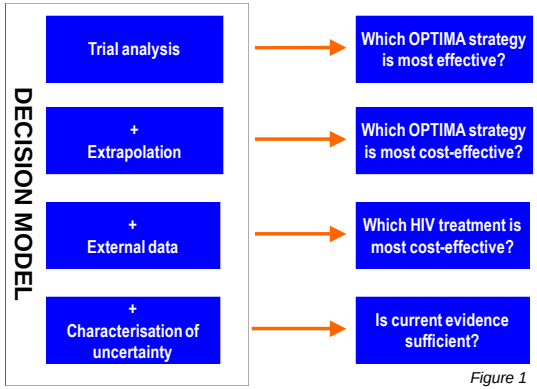


Figure 1

(i) Which OPTIMA strategy is most effective? Time-to-event methods were used to estimate hazard ratios for death, AIDS-defining events and serious adverse events (SAEs) during follow-up. Such hazard ratios can directly inform questions of efficacy, however in the absence of dominance (one treatment is superior on all outcomes) additional analysis is required.

(ii) Which OPTIMA strategy is most cost-effective? Health economic data collected during the trial would allow a comparison of average costs and quality-adjusted survival during the follow-up period. However, such summary statistics cannot directly inform questions about cost-effectiveness where a set of treatments impact on mortality or are heterogeneous in their accrual of costs and benefits with time. Thus it is necessary to employ methods for extrapolation.

(iii) Which HIV treatment is most cost-effective? The OPTIMA trial compared four treatment strategies, but other treatment options are available, including newer antiretroviral drugs. To compare the full range of potential treatments it is necessary to incorporate external evidence.

(iv) Is current evidence sufficient? The use of weak data to inform best practice could lead to opportunity losses for patients, and so characterisation and assessment of the decision uncertainty is required, which requires a thorough representation of the current evidence.

Analysis of clinical trial data can inform a range of questions by employing a decision model to:

- *extrapolate data beyond the follow-up period;*
- *incorporate additional data from a range of sources in a systematic manner;*
- *quantify the level and cost of decision uncertainty.*

However, the desired features of analyses to inform decision models can differ from those aimed at addressing questions of efficacy.

SURVIVAL ANALYSIS FOR DECISION MODELS

• Explicit characterisation of baseline hazard

Survival analysis for efficacy included Kaplan-Meier plots, log-rank tests and Cox regression. These methods cannot be used for extrapolation without:

- *characterising the baseline hazard;*
- *incorporating assumptions on how the risk of events changes beyond the observed period.*

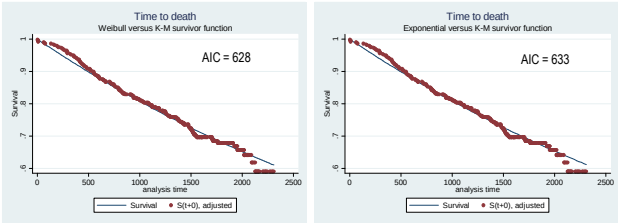
E.g. apply the hazard ratio from a Cox model to external evidence for baseline disease progression with the assumption of a lifetime treatment effect.

A fully parametric model estimates both the baseline hazard and treatment effect. To fit:

- *Specify the shape of survivor function from the range of potential distributions*
- *Use goodness of fit tests and visual inspection of the similarity between the fitted and observed survival to inform the choice of distribution.*

Visual inspection of OPTIMA data suggested a constant hazard over time, indicating an Exponential distribution. Goodness of fit signified by low Akaike Information Criterion (AIC) confirmed Exponential and Weibull distributions as appropriate in the models explaining overall survival as a function of baseline covariates.

Figure 2. Choosing a parametric distribution for the survivor function



• Individual (not composite) endpoints

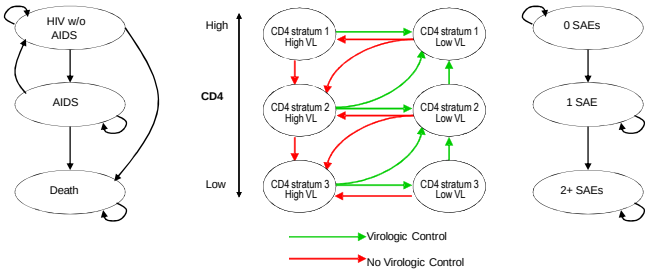
The primary trial outcome was time to first AIDS-defining event or death. For cost-effectiveness analysis each endpoint must be considered separately in order to apply differential weighting in terms of prognosis, health-related quality of life (HRQL) and costs.

• Congruence with model structure

The Markov model describes patients' current disease in terms of HIV, ongoing AIDS events, CD4 level, virologic control and cumulative number of SAEs. Thus it is possible to condition the probability of events, costs and HRQL on these characteristics.

Time spent in each health state is known only for the initial health state. To condition transition probabilities on time in state would require specifying additional health states (tunnel states) to record time in order to overcome the memoryless property of the Markov model.

Figure 3. Health states and transitions represented in the model



RESULTS

The probability of death and AIDS-defining events were estimated as a function of:

- *CD4 count, log viral load, cumulative number of SAEs, ongoing AIDS event and baseline age.*

CD4 and viral load at time of event were assumed equal to preceding laboratory measurement.

Table 1 displays the results from the Exponential survival models, which had the lowest AIC among the models including time-varying covariates.

Table 1. Results from Exponential survival regression

Estimated hazard ratios (95% CI)	**Dependent variable**	
Covariate	**AIDS event** n=328; obs=3447; f=86	**Death** n=328; obs=3816; f=111
Absolute CD4 (per 100 cell change)	0.43** (0.31 - 0.62)	0.53** (0.40 - 0.69)
Log_{10} viral load	1.54 ** (1.19 - 1.99)	1.19 (0.98 - 1.44)
1 SAE	1.02 (0.59 - 1.77)	1.12 (0.60 - 2.08)
2+ SAEs	1.03 (0.60 - 1.74)	3.19* (2.04 - 5.00)
Ongoing AIDS event	n/a	2.28** (1.39 - 3.76)
Baseline age (centred at 48yrs)	1.00 (0.98 - 1.02)	1.03* (1.01 - 1.06)

n = number of patients; obs = number of observations; f = number of failures; *p<0.05; **p<0.01

In sensitivity analysis results were robust omitting any event occurring more than 12 weeks from most recent laboratory measurement.

CD4 count and viral load were important predictors of AIDS-defining events, while for death additional indicators of disease severity (cumulative number of SAEs and the presence of an ongoing AIDS event) and age were also important.

Additional regression analyses of OPTIMA data were able to inform the model estimates of:

- Costs by CD4 stratum, costs of standard ART, costs of AIDS events and SAEs
- HRQL associated with advanced HIV, AIDS events, SAEs and move to salvage therapy
- Progression of viral load and CD4 over time with and without virologic control

The Cholesky decomposition of the covariance matrices were used to calculate correlated random samples of the regression parameters for probabilistic sensitivity analysis.

DISCUSSION

Cost-effectiveness models require an estimate of the baseline disease progression for extrapolation, but the non-parametric and semi-parametric survival analyses conducted to inform questions of efficacy do not provide this. A fully parametric survival analysis allows extrapolation of the baseline rate of events as well as any treatment effects.

Survival analyses can incorporate covariates to describe health states in the model and sub-groups within the overall patient population. Parametric distributions that denote hazards dependent on time in state would imply additional tunnel states to overcome the memoryless property of a Markov model (with the exception of the initial health state). Probabilistic sensitivity analysis utilises the covariance matrix to characterise the uncertainty in the fitted regressions, in order to address questions about the sufficiency of the evidence.

There were no statistically significant differences in efficacy between the strategies compared in the OPTIMA trial. Nevertheless the trial provided a wealth of data to inform a decision model that can be used to answer a range of questions related to best management for patients with advanced HIV and multi-drug resistance. One future application could be to assess the potential cost-effectiveness of newly emerging ARTs in this advanced patient population even if they are not well represented in the early trials of these drugs.