

Principal Investigator

[REDACTED]

General Information

[REDACTED]

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: NIHR Doctoral Research Fellowship

How did you learn about the YODA Project?: Internet Search

Conflict of Interest

[REDACTED]

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s):

1. [NCT00638690 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Exploring the impact of different analysis and extrapolation methods for time-to-event data on estimates of lifetime cost-effectiveness.

Narrative Summary:

Estimates of cost-effectiveness are very important in helping to decide which treatments should be funded. These estimates often require predictions of future health outcomes. Different methods lead to different predictions, which in turn lead to different estimates of cost-effectiveness. This work shall compare and contrast the different methods for predicting future outcomes. Results shall be used to help develop good practice guidance on which prediction methods to use, and when. Improved predictions help to ensure that the most cost-effective treatments are funded, which in turn shall help to improve outcomes for people receiving treatment. For more details see

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Scientific Abstract:

Background: Within health technology assessment (HTA), estimates of long-term health outcomes are an important input when estimating cost-effectiveness. A HTA of abiraterone acetate estimated lifetime outcomes for overall survival and progression-free survival. Exponential, Weibull, lognormal and log-logistic models were considered but didn't provide a good fit to the data. Instead Kaplan-Meier data were used, with extrapolations from an exponential model fit at a switch-point near the end of follow-up. Estimates of cost-effectiveness were sensitive to the choice of switch-point.

Objective: Explore if more flexible parametric models provide a better fit to the data, avoiding the arbitrary choice of switch-point.

Study Design: Secondary statistical analysis and HTA.

Participants: COU?AA?301 trial participants who had received one prior chemotherapy.

Main Outcome Measures: Lifetime overall survival and progression-free survival.

Statistical Analysis: The two outcomes shall be analysed with parametric models including, but not limited to, generalised gamma, generalised F, Royston-Parmar, and generalised additive models. Goodness of fit of each model shall be assessed using both information criteria and via visual comparison of modelled and observed survival. Beyond time, no further covariates shall be considered. Separate models shall be fit to each treatment arm. The model-based cost-effectiveness analysis shall replicate that described in the National Institute for Health and Care Excellence technology appraisal guidance TA259 (albeit with new time-to-event inputs)

Brief Project Background and Statement of Project Significance:

Limited healthcare budgets mean that not all clinically effective interventions can be funded. Health technology assessments (HTAs) use estimates of cost-effectiveness to help decide which interventions should be funded. If an intervention has lifetime effects (for example it extends survival), then lifetime estimates of costs and benefits are required. Typically the available evidence only covers a limited timeframe. In these situations there is a requirement to extrapolate outcomes beyond the evidence base to provide estimates of lifetime effectiveness and cost-effectiveness.

A previous review of UK HTAs that were completed by December 2009 concluded that inconsistent, and sometimes arbitrary, approaches were taken to extrapolation, with flexible modelling methods rarely considered and the chosen approach never fully justified (Latimer, 2013). One approach used in the extrapolation of outcomes for prostate cancer interventions is to use the observed Kaplan-Meier estimates up to a certain 'switch-point'. A parametric model is fit to data after this switch-point and used for extrapolation. However, this approach has been criticised as cost-effectiveness estimates can be sensitive to the choice of cut-point, which is arbitrary, and hence susceptible to gaming (Kearns et al 2013 Figure 2, NICE 2016).

Further research is required into the benefits of using more flexible parametric distributions for the analysis and extrapolation of outcomes in HTA (Royston and Lambert 2011, Latimer 2013). Guidance on the use of such models would help to both decrease inconsistencies in the extrapolation methods used, and improve the accuracy of extrapolations. This in turn will lead to improved estimates of cost-effectiveness, which will help to optimise the outcomes for healthcare systems that are required to make funding decisions under budgetary constraints. As a

result, people receiving treatment from these healthcare systems shall experience improved outcomes. Public confidence in the methods used in HTA (and hence subsequent funding decisions) would also be improved.

Specific Aims of the Project:

The specific aim of this project is to assess the impact of using different parametric statistical models for the analysis of time-to-event data on estimates of the cost-effectiveness of abiraterone acetate versus placebo (both with prednisone) for or castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen.

What is the purpose of the analysis being proposed? Please select all that apply.

Research that confirms or validates previously conducted research on treatment effectiveness

Research Methods**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

The data source is the COU?AA?301 trial of abiraterone acetate in castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy (De Bono et al, 2011). The inclusion and exclusion criteria shall match those used in the NICE technology appraisal guidance TA259. In particular, analysis is restricted to people who had received one prior chemotherapy only.

Main Outcome Measure and how it will be categorized/defined for your study:

The main outcome measure is the incremental cost-effectiveness ratio (ICER) measured by the incremental cost per quality-adjusted life years (QALYs) gained. This shall be estimated by the health-economic model. Inputs shall match those used in the NICE technology appraisal guidance TA259, with updated estimates of overall survival and progression-free survival.

With regards to the secondary re-analysis of clinical effectiveness, the main outcome measures are the modelled hazard curves (or equivalently, the modelled survival curves) by treatment arm, along with measures of uncertainty.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor variable is time. Standard time-to-event models implicitly model survival as a function of time, whilst more flexible models include time as an explicit covariate (Royston and Lambert, 2011). Of note, treatment group shall not be included as a predictor variable, as the assumption of proportional hazards has been shown to be violated for the COU?AA?301 trial (De Bono et al, 2011). Instead treatment group shall be used to stratify analyses.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Treatment group shall be used to stratify analyses (see answer to previous question).

Statistical Analysis Plan:

For both time-to-event outcomes (overall survival and progression-free survival) the statistical analysis will estimate lifetime survival. A variety of different model structures shall be considered, to assess the robustness of results to the choice of model structure. This will include, but is not limited to: generalised gamma, generalised F, Royston-Parmar models, and generalised additive models (Jackson 2016, Liu, Pawitan and Clements 2016). The relative goodness of fit of each model shall be assessed using both information criteria and via visual inspection (comparing modelled survival and hazard curves with Kaplan-Meier or actuarial estimates). The effect measures of interest are the modelled hazard curves (or equivalently, the modelled survival curves) by treatment arm, along with measures of uncertainty. To enable extrapolation, only parametric models shall be considered. Analyses shall be frequentist, and it shall be assumed that all censoring is uninformative: TA259 did not indicate that this assumption was unrealistic (NICE, 2016). Analyses shall be performed using R.

A decision analytic model (DAM) shall be built to estimate the cost-effectiveness of abiraterone acetate versus placebo (both with prednisone). The statistical estimates of overall survival, progression-free survival, and health-

related quality of life, along with the uncertainty in these estimates, shall be used as inputs to the DAM. Additional inputs shall mirror those used in TA259 (NICE, 2016). The DAM shall be built in R, and shall follow the NICE reference case (NICE, 2013). It shall be validated by using the base-case TA259 inputs and comparing outputs with those presented in TA259. The primary outcome of interest shall be the probabilistic incremental cost-effectiveness ratio (incremental costs divided by incremental health effects), along with the uncertainty in this estimate.

Project Timeline:

Upon receiving approvals (if granted), it is anticipated that performing the statistical analyses and building the health economic model will take up to four months. Subsequent writing-up the results for publication is anticipated to take up to two months. This application is in support of a PhD, which is expected to complete in December 2019.

Dissemination Plan:

Following approval, the research plan shall be registered at clinicaltrials.gov (for a similar pre-registration, see [REDACTED]). A manuscript shall be submitted for publication within six months of the research completing. Target journals include Medical Decision Making, Statistical Methods in Medical Research, and Statistics in Medicine. Any resulting publication will be open access.

Bibliography:

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- Jackson, C. H. (2016). flexsurv: a platform for parametric survival modelling in R. *Journal of Statistical Software*, 70(8), 1-33.
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