Can't see the wood for the trees: Using common likelihoods to share information regarding selection of functional form in survival analysis

Neil Hawkins (✉ neil.hawkins@glasgow.ac.uk)

Institute of Health and Wellbeing, University of Glasgow <https://orcid.org/0000-0003-3199-221X>

Chris Parker

Celgene Ltd

David A. Scott

Diabetes Research Centre, University of Leicester

Technical advance

Keywords: survival analysis, extrapolation, parametric models

Posted Date: August 13th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-55390/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Can't see the wood for the trees: Using common likelihoods to share information regarding
selection of functional form in survival analysis

Neil Hawkins PhD,¹ Chris Parker MSc,² David A. Scott MSc³

¹ Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow, UK

neil.hawkins@glasgow.ac.uk [ORCID: 0000-0003-3199-221X]

² Celgene Ltd, 1 Longwalk Road, Stockley Park, Uxbridge, UK

cparker@celgene.com

³ Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester,

UK ds647@leicester.ac.uk [ORCID: 0000-0001-6475-8046]

Corresponding author: Neil Hawkins

Abstract

Background: The estimation of mean survival is a key consideration when estimating the cost-effectiveness of interventions. Estimation typically requires extrapolation using parametric survival analysis and may be sensitive to choice of functional form. We demonstrate a simple method that allows goodness-of-fit information to be assessed jointly across studies, where such information is believed likely to be exchangeable, to help inform the selection of functional form for parametric survival analysis.

Methods: Individual patient data for survival was estimated from digitised Kaplan-Meier curves for four trials in advanced soft tissue sarcoma. A range of parametric survival models were fitted. Two approaches were explored for identifying the preferred parametric model: (i) selecting functional forms independently for each study; and (ii) selecting a common functional form across studies. Akaike's Information Criterion (AIC) or Bayesian Information Criterion (BIC) were used to select optimal functional form. For approach (ii) joint BIC or AIC statistics were calculated for each model by combining the components of the AIC or BIC, respectively, across studies. A bootstrap analysis was conducted to estimate the uncertainty in selection of functional form.

Results: Estimates of mean survival varied markedly according to choice of functional form. Independent selection led to different functional forms being selected for each study with considerable uncertainty regarding the optimum functional form according to AIC or BIC. In this case study, selecting an optimum functional form based on joint AIC or BIC across studies reduced uncertainty in model selection and variance in mean survival compared to selection of functional form independently.

Conclusion: Extrapolation of estimates of survival may be sensitive to choice of functional form. If it is believed, a priori, reasonable to share information regarding the choice of

functional form for survival analysis across studies, estimating joint goodness-of-fit information across studies could reduce uncertainty and lead to more reliable estimates of mean survival and cost-effectiveness.

Keywords: survival analysis, extrapolation, parametric models

Background

Health economic models are an important tool helping decision-makers to identify the most cost-effective health care technologies. These models often use estimates of time-to-event for outcomes such as survival to estimate costs and health outcomes. Typically, a lifetime horizon is appropriate for cost-effective modelling to inform healthcare decision making. In order to estimate lifetime costs and outcomes for all relevant technologies, extrapolation – based on parametric survival analysis – beyond the time horizon of observed events in clinical trials is often necessary.

It is commonplace to use parametric survival models to estimate mean survival in health technology assessment (HTA). However, estimates of cost-effectiveness may be sensitive to the choice of parametric model. A published review of extrapolation modelling in National Institute for Health and Care Excellence (NICE) technology appraisals identified inconsistencies in the approaches employed for estimating mean survival [1]. This included processes for identification of an appropriate parametric survival function.

Recommendations for identification of the most appropriate parametric survival function have been published [1-3]. These recommendations focus on identifying a “preferred”

parametric survival function from a set of candidates for an individual study and reference the use of external information on expected survival to validate and inform model selection [4,5].

When fitting survival models we often assume that information on the choice of parametric survival function is exchangeable *across treatments* within a study. In this paper, we extend this notion and assume that parametric survival function is exchangeable *across studies* within a disease area by sharing information regarding the chosen survival function.

Essentially, we identify the best fitting model across the group of studies assuming that the parametric survival function should be the same for all studies. We do this by estimating a common goodness of fit statistics across the studies.

This paper uses a case study in soft tissue sarcoma (STS), for which trials commonly utilise time-to-event endpoints such as overall survival, to illustrate the application of this approach as an extension to currently recommended methods for estimating mean survival. Whilst our example uses clinical trial data, our methods may equally be applied to observational studies or patient registries.

Methods

Study data

Soft tissue sarcomas comprise a heterogeneous group of rare tumours accounting for 1% of all cancers in adults [6]. Approximately 30-40% of patients diagnosed with STS develop advanced or metastatic disease for which overall survival is poor (median 14-17 months) [7].

Systemic chemotherapy with palliative intent is the only treatment option for the majority of patients with advanced and/or metastatic disease, and as such, overall survival (OS) is a commonly reported endpoint in trials in this population. Treatment with anthracycline-based

chemotherapy, primarily doxorubicin, either as monotherapy or in combination with ifosfamide, is recommended in first-line. Treatment options after failure of doxorubicin and ifosfamide are limited and there are no standard recognised therapies. Treatments used in clinical practice include; gemcitabine, docetaxel, dacarbazine, and trabectedin [6,8].

Our illustration used a set of four clinical trials in advanced soft tissue sarcoma identified from a published systematic review [9]. Six treatments were investigated across four studies [10-13]; two studies were comparative randomised controlled trials (RCTs), and two were non-comparative single arm studies. Each treatment was trialled once. For each study we calculate mean survival for cost-effectiveness analysis by estimating the whole survival curve.

Mean survival estimation

All studies reported Kaplan-Meier (KM) plots for OS. The published KM curves were digitised using TechDig software [14] to estimate the survival probability at a range of time points. KM curves were cut off at a common timepoint (12 months) to simulate the effects of having limited study follow-up (Figure 1). A published algorithm was then used to estimate the individual patient data (IPD), generating a time-to-event and a censoring variable for each patient [15].

[Figure title] Figure 1: Kaplan-Meier plots for individual studies

[Insert Figure 1 here]

[Figure legend] Overall survival in months

Selection of parametric survival function

Eight parametric survival functions were considered: exponential, gamma, generalised F , generalised gamma, Gompertz, lognormal, log-logistic, and Weibull. These represent the commonly used distributions in cost-effectiveness modelling and are the set recommended by NICE [16] with the addition of the generalised F [17], providing additional flexibility with four parameters. For the comparative studies, a joint survival model was fitted to both arms using a treatment dummy covariable.

Two approaches were explored for identifying the parametric survival function for a given study; (i) selecting independent parametric survival functions for each study (henceforth referred to as independent selection) and (ii) selecting a common parametric survival function for all studies (henceforth referred to as common selection).

Independent selection

The parametric survival functions which minimised Akaike's Information Criterion (AIC) or Bayesian Information Criterion (BIC) for each study were chosen as the 'preferred' model.

The AIC for a given study (j) and survival model (m) is defined as:

$$AIC_{j,m} = -2 \ln(L_{j,m}) + 2k_{j,m}$$

where $\ln(L)$ is the log-likelihood, k is the number of model parameters, and n is the sample size.

The BIC for a given study (j) and survival model (m) was defined as:

$$BIC_{j,m} = -2 \ln(L_{j,m}) + k_{j,m} \ln(n_j)$$

BIC penalises additional parameters more heavily than the AIC for samples relevant to survival analysis ($n \geq 8$).

131 For independent selection, a parametric survival function was selected for each study by (i)
 132 minimising AIC

$$m_j = \min_m \{AIC_{j,m}\}$$

133 and (ii) by minimising BIC,

$$m_j = \min_m \{BIC_{j,m}\}$$

134 This approach treats all studies as independent with no information being shared across
 135 studies. The survival parameters for each study-specific parametric model (m_j) were then
 136 estimated, which provided an estimate of mean survival ($\hat{s}$) for each treatment (t),

$$\hat{s}_t = S(m_j) = 1 - F(m_j)$$

137 where $S(m_j)$ is the survivor function and $F(m_j)$ is the cumulative distribution function.

138 To avoid overestimation of mean survival in the absence of discounting, the survival curve
 139 for each treatment was integrated over 15 years based on maximum expected survival in this
 140 population.

141

142 **Common selection**

143 For the common selection approach, a common AIC or BIC is estimated across studies
 144 applying the same survival model m to all studies. This was calculated by summing the log
 145 likelihood, the number of parameters, and the number of subjects across studies

$$AIC_m = \sum_{j=1}^J -2 \ln(L_{j,m}) + \sum_{j=1}^J 2k_{j,m}$$

$$BIC_m = \sum_{j=1}^J -2 \ln(L_{j,m}) + \sum_{j=1}^J k_{j,m} \cdot \ln \left(\sum_{j=1}^J n_j \right)$$

146 where J is the total number of studies and m is the model being tested. This is analogous to
 147 estimating the AIC or BIC for a study by summing the components from the individual study
 148 arms.

149 The preferred functional form for the survival model is identified by minimising the
 150 ‘common’ AIC or BIC.

$$M_{AIC} = \min_m \{AIC_m\}$$

$$M_{BIC} = \min_m \{BIC_m\}$$

151 The survival parameters for the preferred parametric model were estimated individually for
 152 each study which provided an estimate of mean survival for each treatment,

$$\hat{S}_t = S(M) = 1 - F(M)$$

153 **Bootstrap**

154 The variance in the estimated mean and uncertainty in the choice of parametric survival
 155 function were estimated for each study under both methods of selection using a bootstrap
 156 analysis [18]. The bootstrap analysis was conducted by taking one thousand samples with
 157 replacement from the IPD for each study. Within each bootstrap sample (i), the preferred
 158 parametric survival function was chosen using both methods of selection:

- 159 • Independent selection,

$$160 \quad m_{j,i} = \min_m \{AIC_{j,m,i}\} \text{ or}$$

$$m_{j,i} = \min_m \{BIC_{j,m,i}\}$$

161

$$\hat{s}_{t,i} = S(m_{j,i})$$

- Common selection,

$$M_i = \min_m \{AIC_{m,i}\} \text{ or}$$

$$M_i = \min_m \{BIC_{m,i}\}$$

$$\widehat{S}_{t,i} = S(M_i)$$

The uncertainty in mean survival was obtained from the variance of estimated means across samples. Uncertainty in parametric survival function selection was estimated based on the proportion of bootstrapped samples for which each parametric survival function was preferred under each method of selection.

Kaplan-Meier approach

We also compared the individual and common selection methods to a “Kaplan-Meier” approach. The Kaplan Meier sample average estimate was used to estimate survival until the timepoint at which 80% of observed events had occurred. Subsequently, a fully parametric model with an exponential survival function was used. The exponential models were fitted using data from the cut-point onwards. They included a covariable representing treatment for the parallel trials. A similar approach, referred to as the Kaplan-Meier–exponential method, has been described in the related literature [16].

Results

The parametric survival function associated with the lowest AIC (Table 1) or BIC (Table 2) varied across studies. For AIC using independent selection, the lognormal, log-logistic, log-logistic, and gamma survival functions were selected for studies 1 to 4, respectively. Using common selection across studies, the log-logistic survival function had the lowest AIC. For BIC using independent selection, the exponential, exponential, log-logistic, and gamma survival functions were selected for studies 1 to 4, respectively. Using a common selection across studies, the exponential survival function had the lowest BIC.

Table 1: AIC statistics

Parametric survival function	Study 1	Study 2	Study 3	Study 4	Common
Exponential	456.6	431.5	368.7	1422.9	2679.6
Gamma	458.6	432.3	358.8	<u>1404.8</u>	2654.5
Generalised F	460.3	434.7	361.5	1408.4	2664.9
Generalised gamma	458.1	433.2	360.7	1405.8	2657.7
Gompertz	458.3	433.4	361.2	1412.6	2665.6
Log-logistic	457.9	<u>431</u>	<u>358.6</u>	1404.9	<u>2652.4</u>
Log-normal	<u>456.2</u>	431.8	362.2	1405.6	2655.8
Weibull	458.5	432.7	358.7	1405.9	2655.8

Bold underlined values are for preferred parametric survival function

Table 2: BIC statistics

Parametric survival function	Study 1	Study 2	Study 3	Study 4	Common
Exponential	<u>459.5</u>	<u>436.8</u>	371.4	1430.7	<u>2789.1</u>
Gamma	464.4	440.4	364.3	<u>1416.5</u>	2837
Generalised F	471.9	448.1	372.5	1428	2993.4
Generalised gamma	466.8	443.9	368.9	1421.4	2913.2
Gompertz	464.1	441.5	366.7	1424.3	2848.1
Log-logistic	463.7	439.1	<u>364.1</u>	1416.6	2834.9
Log-normal	462	439.9	367.7	1417.3	2838.3
Weibull	464.4	440.7	364.2	1417.7	2838.3

Bold underlined values are for preferred parametric survival function

Table 3 presents the mean survival predictions for each treatment based on the candidate parametric survival functions as well as the Kaplan-Meier approach for a single sample. The

choice of parametric survival function influenced the mean survival predictions; the within-study variation in mean survival between parametric survival functions ranged from 7.7 months (study 4, treatment 2) to 13.9 months (study 3, treatment 1).

Table 3: Mean survival predictions for each parametric survival function from a single sample (months)

Parametric survival function	Study 1	Study 2	Study 3		Study 4	
	Treat 1	Treat 1	Treat 2	Treat 1	Treat 1	Treat 2
Exponential	22.81	12.48	20.8	19.75	18.49	16.4
Gamma	23.02	11.75	18.84	14.35	15.27	13.77
Generalised F	40.52	23.31	32.13	25.57	19.33	17.19
Generalised gamma	39.16	14.52	24.43	13.55	17.69	15.57
Gompertz	33.57	12	19.29	11.7	12.76	11.85
Log-logistic	33.79	17.39	26.43	18.33	21.01	18.89
Log-normal	<u>36.32</u>	17.63	29.27	20.48	22.16	19.05
Weibull	23.45	11.63	18.58	13.26	14.46	13.17
Kaplan-Meier/Exp	26.68	23.05	28.91	21.72	21	19.16

Underlined data show preferred parametric survival function under independent selection

using AIC, bold data show preferred parametric survival function under independent selection using BIC, and highlighted data show preferred parametric survival function under joint selection using AIC (log-logistic) and BIC (exponential).

There was considerable uncertainty regarding the choice of parametric survival function. The bootstrap estimation for the probability that the preferred parametric survival function was selected varied from 20% to 45% across studies for the AIC (Table 4) and between 12% and 69% for the BIC (Table 5). For example, whilst fitting each of the models to the trial data showed the log-logistic was the best model choice for study 3 using AIC, the bootstrapped estimates revealed the Gompertz, log-normal and Weibull also had relatively high probabilities of being the best model choice (Table 4). To illustrate the uncertainty, Figure 2 shows 16 bootstrapped samples of Study 3 and the best fitting model under the AIC in each case.

Using common selection across studies, the estimated probability that the log-logistic model was chosen with the AIC was estimated as 29% and the estimated probability that the exponential model was chosen was estimated as 100% with the BIC. More specifically, sharing goodness-of-fit information across studies reduced the estimated uncertainty in model selection.

Table 4: Bootstrap estimated probabilities of uncertainty in model choice (AIC)

Parametric survival function	Study 1	Study 2	Study 3	Study 4	Common
Exponential	26%	22%	0%	0%	0%
Gamma	0%	1%	7%	<u>34%</u>	8%
Generalised F	1%	12%	6%	0%	4%
Generalised gamma	24%	6%	0%	0%	22%
Gompertz	2%	1%	13%	0%	0%
Log-logistic	0%	<u>20%</u>	<u>30%</u>	17%	<u>29%</u>
Log-normal	<u>45%</u>	37%	22%	39%	31%
Weibull	1%	1%	23%	9%	6%

Bold underlined data are for preferred parametric survival function

Table 5: Bootstrap estimated probabilities of uncertainty in model choice (BIC)

Parametric survival function	Study 1	Study 2	Study 3	Study 4	Common
Exponential	<u>69%</u>	<u>58%</u>	5%	0%	<u>100%</u>
Gamma	0%	0%	23%	<u>36%</u>	0%
Generalised F	24%	30%	22%	0%	0%
Generalised gamma	0%	6%	31%	0%	0%
Gompertz	0%	0%	6%	0%	0%
Log-logistic	0%	0%	<u>12%</u>	17%	0%
Log-normal	5%	3%	0%	39%	0%
Weibull	1%	2%	0%	8%	0%

Bold underlined data are for preferred parametric survival function

[Figure 2 title] Figure 2: Sixteen bootstrapped samples from Study 3 and best fitting model under each sample

[Insert Figure 2 here]

The standard error associated with the mean survival estimates was reduced when using bootstrapped common selection compared to both independent selection and the Kaplan-Meier method (Table 6). Sharing goodness-of-fit information across studies to identify a preferred common model can therefore reduce uncertainty in survival estimates. Table 6 shows the averages across the 1000 bootstrapped samples thus will not correspond to Table 3 which comprises on a single sample.

Table 6: Survival predictions averaged over bootstrapped samples (months)

Study	Treatment	Kaplan-Meier/ exponential	AIC Independent selection	AIC Common selection	BIC Independent selection	BIC Common selection
		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
1	1	32.07 (7.59)	35.76 (12.13)	34.97 (10.04)	28.19 (9.56)	23.1 (2.95)
2	1	22.91 (4.88)	18.18 (6.63)	17.49 (5.48)	14.95 (5.03)	12.93 (2.29)
2	2	29.3 (5.97)	27.34 (7.57)	26.39 (6.71)	23.69 (6.18)	21.31 (4.31)
3	1	25.24 (8.52)	16.64 (4.56)	16.38 (3.04)	16.14 (3.75)	20.02 (2.59)
4	1	20.23 (2.61)	16.73 (3.55)	16.56 (2.66)	16.72 (3.44)	16.64 (2.05)
4	2	21.7 (2.49)	18.75 (4.08)	18.51 (3.08)	18.75 (4.01)	18.49 (1.68)

Discussion

These results demonstrate that, in our case study, mean survival estimates are sensitive to which parametric survival function is selected. The choice of parametric survival function based on AIC or BIC was found to be uncertain leading to uncertainty in estimates of mean survival and hence any cost-effectiveness estimates based on these estimates. Our findings

are in agreement with the current debate around the process in choosing an appropriate parametric survival function and thereby informing economic evaluation [1-3].

In our case study, this simple method of sharing goodness-of-fit information across studies reduced the uncertainty in both parametric survival function selection and the corresponding estimates of mean survival compared to independent selection. The utility of this approach for other analysis will depend on whether it is believed, a priori, reasonable to share information regarding the choice of functional form for survival analysis across studies. If it is, estimating joint goodness-of-fit information across studies could reduce uncertainty and lead to more reliable estimates of mean survival and cost-effectiveness. More complex models for sharing information regarding functional form exist that allow for uncertainty in the choice of functional form [19] and should also be considered.

We utilised the Guyot algorithm [15] to estimate IPD from KM curves, a new technique when Latimer [1,3] and Bagust and Beale [2] entered the debate over methods for extrapolation of trial data. With the widespread use of this algorithm enabling estimation of a IPD from published studies, this debate is more important than ever.

Typically, a lifetime horizon is appropriate for economic modelling to inform healthcare decision making. The observed study data therefore need to be “extrapolated”. Whilst external information such as administration data, registries, or expert opinion has been used for validation of extrapolation, recent approaches have proposed its use to inform extrapolation [4,5]. Guyot et al [4] proposed using external information, such as registries, to inform model extrapolation through the use of polynomial functions and population matching techniques. This raises questions about the availability and choice of such data, obtaining access, heterogeneity compared to the study population, missing data, and analysis complexity.

On the principle of parsimony, we aimed to identify simpler parametric models in preference to more complex models which utilise additional parameters to fit to the observed data. We nevertheless used both AIC and BIC methods for identifying the preferred parametric survival function. The BIC discounts the goodness-of-fit of more complex models more heavily compared to AIC.

Uncertainty in the data used in this analysis supports the use of simpler more generalisable models, which are more likely to be identified by BIC. However, there may be other measures and wider criteria which could be considered. This contrasts with Jackson et al [20] who cite the predictive ability of the AIC makes it more appropriate in a health economic modelling context.

The parametric functions included in the set of candidates specified cover proportional hazards and accelerated failure time metrics. Recommendations for identifying a preferred parametric model state the need to assess the plausibility of the proportional hazards assumption, which when violated should lead to proportional hazards models being removed from the set of candidates [1]. Such an approach could be implemented alongside the approaches presented here.

Limitations

Bagust and Beale [2] describe aspects of RCTs which prevent a good model fit being obtained. These include the mode of action of treatments, confounding by post-protocol therapies and heterogeneity. These could all differ across studies, and our approach does directly not account for this. However, we feel sharing of goodness-of-fit information across studies is a useful adjunct to the existing recommendations for model selection [1,2].

Use of AIC or BIC for identifying the preferred parametric survival function only ranks the set of candidate models based on within-trial fit, hence does not consider long term extrapolation. Ensuring long term extrapolations are clinically plausible is a key consideration when modelling survival data, and as such, we would recommend applying the same assessment to the survival predictions obtained with independent and common selection by removing models providing implausible extrapolations from the set of candidates.

A potentially limiting underlying assumption is that the preferred model is among the set of candidate models [2,21]. Inevitably, none of the models may be suitable for the dataset under consideration, however the set considered in this analysis includes all of the parametric survival models available in commonly used statistical packages and that are recommended by the NICE Decision Support Unit [1]. In addition, we have included the four-parameter generalised F , an umbrella distribution containing the exponential, Weibull, lognormal, log-logistic, and gamma distributions [22,23], hence the set of candidate models is comprehensive in its ability to model a variety of hazard functions.

Conclusions

The process for conducting parametric survival analysis for cost-effectiveness analysis has been widely discussed, and recommendations for identifying the most appropriate parametric models have been presented in the literature. These recommendations focus on identifying a “preferred” parametric survival function from the set of candidates, and treat individual studies included in the analysis independently.

However, we have demonstrated that sharing of goodness-of-fit information across studies, if this is believed to reasonable *a priori*, can potentially enhance this model selection process by reducing uncertainty in structural assumptions.

Given the considerable uncertainty in selecting a parametric survival function and the influence of this process on mean survival estimates, these methods could be used to reduce uncertainty in the selection of parametric survival function and lead to more reliable estimates of mean survival and cost-effectiveness.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations: Bayesian Information Criterion (BIC); Akaike's Information Criterion (AIC); health technology assessment (HTA); Kaplan-Meier (KM); National Institute for Health and Care Excellence (NICE); overall survival (OS); randomised controlled trials (RCTs); soft tissue sarcoma (STS)

Declarations:

Ethics approval and consent to participate: Not applicable

Consent for publication: All authors consent to publication

Availability of data and materials: The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: None

Funding: DAS acknowledges the support of NIHR Collaboration for Leadership in Applied Health Research and Care East Midlands (CLAHRC EM), UK. The funding agreement ensured the author's independence in designing the study, interpreting the data, writing, and publishing the report. CP and NH did not receive any funding.

Authors' contributions: NH, CP and DAS all contributed to analysis and drafting of this manuscript

Acknowledgements: NH would like to thank his friends, family, acquaintances

References

- [1] Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Medical Decision Making* 2013; 33(6):743-54
- [2] Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. *Medical Decision Making* 2014; 34(3):343-51
- [3] Latimer NR. Response to "Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach" by Bagust and Beale. *Medical Decision Making* 2014; 34(3):279-82
- [4] Guyot P, Ades AE, Beasley M, Lueza B, Pignon JP, Welton NJ. Extrapolation of Survival Curves from Cancer Trials Using External Information. *Medical Decision Making* 2017;37(4): 353-366
- [5] Jackson C, Stevens J, Ren S, Latimer N, Bojke L, Manca A, Sharples L. Extrapolating survival from randomized trials using external data: a review of methods. *Medical Decision Making* 2017; 37:377–390
- [6] von Mehren M, Randall RL, Benjamin RS, et al. Soft Tissue Sarcoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network* 2016; 14:758-86

351 [7] The ESMO / European Sarcoma Network Working Group. Soft tissue and visceral
352 sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
353 *Annals of Oncology* 2012; 23 (Supplement 7): vii92-99

354 [8] Frezza AM, Stacchiotti S, Gronchi A. Systemic treatment in advanced soft tissue
355 sarcoma: what is standard, what is new. *BMC Medicine* 2017; 15:109

356 [9] Sharma S, Takyar S, Manson SC, Powell S, Penel N. Efficacy and safety of
357 pharmacological interventions in second- or later-line treatment of patients with advanced
358 soft tissue sarcoma: a systematic review. *BMC Cancer* 2013; 13:385

359 [10] Demetri GD, Chawla SP, von MM, et al. Efficacy and safety of trabectedin in
360 patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of
361 prior anthracyclines and ifosfamide: results of a randomized phase II study of two
362 different schedules. *J Clin Oncol* 2009; 27(25):4188-4196

363 [11] Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study
364 comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with
365 previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study.
366 *J Clin Oncol* 2011; 29(18):2528-2533.

367 [12] Nielsen OS, Judson I, van HQ, et al. Effect of high-dose ifosfamide in advanced soft
368 tissue sarcomas. A multicentre phase II study of the EORTC Soft Tissue and Bone
369 Sarcoma Group. *Eur J Cancer* 2000; 36(1):61-67

370 [13] van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue
371 sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial.
372 *Lancet* 2012; 379(9829):1879-1886

373 [14] Techdig. Available at <http://www.thetechdig.net/>

- [15] Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology* 2012; 12:9
- [16] 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>
- [17] Cox C. The generalized F distribution: An umbrella for parametric survival analysis. *Statistics in Medicine* 2008; 27:4301-12
- [18] Bland MJ, Altman DG. Statistics Notes: Bootstrap resampling methods. *BMJ* 2015; 350:h2622
- [19] Murray, Thomas A., Brian P. Hobbs, and Bradley P. Carlin. ‘Combining Nonexchangeable Functional or Survival Data Sources in Oncology Using Generalized Mixture Commensurate Priors’. *The Annals of Applied Statistics* 9, no. 3 (September 2015): 1549–70. <https://doi.org/10.1214/15-AOAS840>
- [20] Jackson CH, Thompson SG, Sharples LD. Accounting for uncertainty in health economic decision models using model averaging. *Journal of the Royal Statistical Society A* 2009; 172:383-404
- [21] Wagenmakers E-J, Farrell S. AIC model selection using Akaike weights. *Psychonomic Bulletin & Review* 2004, 11:192-196
- [22] Jackson CH, Sharples LD, Thompson SG. Survival Models in Health Economic Evaluations: Balancing Fit and Parsimony to Improve Prediction. *International Journal of Biostatistics* 2010; 6(1):34
- [23] Collett D. *Modelling Survival Data in Medical Research. Second Edition*. CRC Press: London, 2003

Figures

Figure 1

Kaplan-Meier plots for individual studies Overall survival in months

Figure 2

Sixteen bootstrapped samples from Study 3 and best fitting model under each sample