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Network Meta-Analysis of (Individual Patient) Time to Event Data alongside (Aggregate) Count Data

CHE Research Paper 95

Network meta-analysis of (individual patient) time to event data alongside (aggregate) count data

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Abstract

Objectives: Network meta-analysis (NMA) methods extend the standard pair-wise framework to allow simultaneous comparison of multiple interventions in a single statistical model. Despite published work on NMA mainly focussing on the synthesis of aggregate data (AD), methods have been developed that allow the use of individual patient-level data (IPD) specifically when outcomes are dichotomous or continuous. This paper focuses on the synthesis of IPD and AD time to event data, motivated by a real data example looking at the effectiveness of high compression treatments on the healing of venous leg ulcers.

Methods: This paper introduces a novel NMA modelling approach that allows IPD (time to event with censoring) and AD (event count for a given follow-up time) to be synthesised jointly by assuming an underlying, common, distribution of time to healing. Alternative model assumptions were tested within the motivating example. Model fit and adequacy measures were used to compare and select models.

Results: Due to the availability of IPD in our example we were able to use a Weibull distribution to describe time to healing; otherwise, we would have been limited to specifying a uniparametric distribution. Absolute effectiveness estimates were more sensitive than relative effectiveness estimates to a range of alternative specifications for the model.

Conclusions: The synthesis of time to event data considering IPD provides modelling flexibility, and can be particularly important when absolute effectiveness estimates, and not just relative effect estimates, are of interest.

1. Background

In clinical practice, and at a wider societal level, treatment decisions in medicine need to consider all relevant alternative health care technologies. Such decisions are ideally informed by evidence on the relative effectiveness of treatments generated by randomised controlled trials (RCTs) (which may be further used to inform estimates of cost-effectiveness). Using evidence from individual RCTs may limit informed decision making since studies usually only provide comparative evidence on two treatments, potentially missing other relevant technologies which are also treatment options. This limitation can be overcome if all RCTs evaluating interventions relevant to the treatment decision are considered collectively, for example, with the use of network meta-analysis (NMA). NMA is a well-established statistical technique that extends standard the pairwise meta-analysis framework to allow simultaneous comparison of multiple interventions in a single statistical model. (1, 2) This approach then produces relative effect estimates (and associated descriptions of uncertainty) for all treatments connected by the network of evidence – even where head-to-head trials for comparisons do not exist (indirect data).

NMA using individual patient data

Published work on NMA mainly focuses on the synthesis of aggregate data (AD) (sometimes called summary data, e.g. group means and standard errors available from study reports) (3, 4); however, methods have been developed that allow use of individual patient-level data (IPD) in NMA (5-7). The appeal of including IPD in a NMA is that it is likely to reduce statistical heterogeneity across the network (and in this way help resolve possible inconsistencies); and it may also allow for subgroup effects to be estimated that could guide more personalised treatment decisions (5). The use of IPD, alone or in combination with AD, has been shown to improve inference in NMAs where the outcome of interest is dichotomous (or binary) by aiding convergence, and by providing unbiased treatment–covariate interactions [that would otherwise be affected by ecological bias (8)]. For continuous outcomes, IPD is likely to also lead to more precise estimates of treatment effects, even in the absence of treatment–covariate interactions (9).

NMA using time to event related outcome data

Where individual studies present hazard ratios, these AD can be pooled directly using standard methods (analogous to pooling count data where relative effectiveness measures are the odds ratios or relative risks) (10). However, other AD outputs such as median/mean time to event (11) and cumulative counts of patients having the outcome event in a period of time (12) have also been meta-analysed in a network – by specifying an underlying time to event distribution hazard ratios can be generated from these outputs (13). Whereas IPD having been used in pairwise analysis (12), there has been limited development of methods in the NMA framework.

Developing a NMA combining AD and IPD data to synthesise time to event related outcomes

This paper describes a modelling framework that combines AD and IPD in the synthesis of time to event related outcomes. This work was motivated by a NMA for which we had data from multiple RCTs comparing treatments for the healing venous leg ulcers. A proportion of the RCT data was available in IPD format (time to event and time to censoring), with the remaining data available as AD, i.e. count data. To maximally draw from the available data we aimed to statistically synthesise jointly the available AD and IPD, in this way generating better estimates and providing fuller characterisations of uncertainty to best inform decisions on the use of the treatments of interest.

2. Motivating example: high compression treatments for venous leg ulcers

The case study relates to compression systems aiming to deliver high compression (classed as ≥40 mmHg compression at the ankle) to promote venous leg ulcer healing. Available standardised systems are: two layer hosiery (HH), the four layer bandage (4LB), the short stretch bandage (SSB), the zinc paste bandage (ZINC), and the two layer bandage system (2LB). A detailed description is provided in Box A1 in Appendix with further details of these systems presented elsewhere (14).

Effectiveness evidence from RCTs was obtained from the most recent update of the relevant Cochrane review available to us (15), and from a recent multicentre RCT which compared 4LB with HH. All available RCT evidence was assessed for inclusion in the current NMA: a detailed process that has been reported elsewhere (14). The final NMA contained data from 16 RCTs on the relative effectiveness of high compression systems for the treatment of venous leg ulcers. Data for two of the 16 included RCTs (VenUS I and VenUS IV, hereby denominated studies 1 and 2) had full IPD data available (841 participants) which included time to healing or censoring for each participant, together with other individual-level characteristics such as treatment centre, ulcer duration and size and also patient mobility. For the remaining RCTs (1105 participants), aggregate data on the number of healed ulcers were extracted from the source review alongside information regarding treatment type, number of participants allocated to each treatment group, mean duration of follow-up (if this was not stated, trial duration was used), mean ulcer duration and size.

The 16 included RCTs described nine unique high compression treatments: the five standard treatments (4LB, SSB, ZINC, HH and the 2LB) and four *ad hoc* systems (14). The *ad hoc* group consisted of treatments deemed irrelevant to current clinical practice, and are not reported further (results can be provided upon request). These studies were, however, included in the NMA as their data may still be relevant, for example, in describing determinants of healing.

Table 1 describes the data available and Figure 1 presents the network between treatments formed by the evidence (14, 16-30). The most populated comparison was the 4LB vs. SSB comparison, informed by seven RCTs: six available as AD (16-20, 29) and one IPD (30). The link between the 2LB and 4LB was informed by two RCTs and each of the remaining six comparisons in the NMA were informed by AD extracted from one RCT for each comparison (Table 1).

Table 1: Analytic dataset

ID	Study	Treatment	Follow up (weeks)	Number patients	Mean duration (months)	Mean size (cm^2)	Number healed	Evidence format available
16	Duby *et al* 1993 [16]	4LB	12	25	20.5	11.9	11	AD
		SSB	12	25	26.7	13.1	10	
17	Scriven *et al* 1998 [17]	4LB	52	32	13	13.3	17.6	AD
		SSB	52	32	21	8.3	18.24	
18	Partsch *et al* 2001 [18]	4LB	16	53	1.25	1.5	33	AD
		SSB	16	59	1	1.9	43	
19	Ukat *et al* 2003 [19]	4LB	12	44	--	17.7	13	AD
		SSB	12	45	--	12.2	10	
20	Franks *et al* 2004 [20]	4LB	24	74	2	5	59	AD
		SSB	24	82	2	3.5	62	
21	Junger *et al* 2004b [21]	SSB	12	60	5.57	5.95	19	AD
		HH	12	61	4.14	5.62	29	
22	Kralj *et al* 1996 [22]	4LB	24	20	7.9	18.6	7	AD
		Ad hoc: Ba	24	20	6.9	17.2	8	
23	Polignano *et al* 2004b [23]	4LB	24	39	--	10.1	29	AD
		ZINC	24	29	--	9.3	19	
24	Wilkinson *et al* 1997 [24]	4LB	12	17	--	11.2	8	AD
		Ad hoc: BHeH	12	18	--	8.6	8	
25	Colgan *et al* 1995 [25]	4LB	12	10	9.3	27.5	6	AD
		Ad hoc: BzeaH	12	10	66.5	48.5	7	
26	Blecken *et al* 2005 [26]	4LB	12	12	--	50.08	4	AD
		Ad hoc: HV	12	12	--	48.98	4	
27	Moffatt *et al* 2008 [27]	4LB	4	42	48.8	5.7	3	AD
		2LB	4	39	46.6	11.8	6	
28	Szewczyk *et al* 2010 [28]	4LB	12	15	--	6	9	AD
		2LB	12	16	--	5.3	10	
29	Wong *et al* 2012 [29]	4LB	24	107	--	--	72	AD
		SSB	24	107	--	--	77	
30	Iglesias *et al* 2004 [30]	4LB	52	195	3	3.81	107	IPD
		SSB	52	192	3	3.82	86	
14	Ashby *et al* 2013 [14]	4LB	52	224	12.29	9.30	157	IPD
		HH	52	230	10.82	9.41	163	

AD – aggregate-level data; IPD – individual patient data; 4LB, SSB, HH, Zinc paste,2LB and the *ad hoc* systems Ba, BHeH, BzeaH, HV as described in Box A1 in Appendix

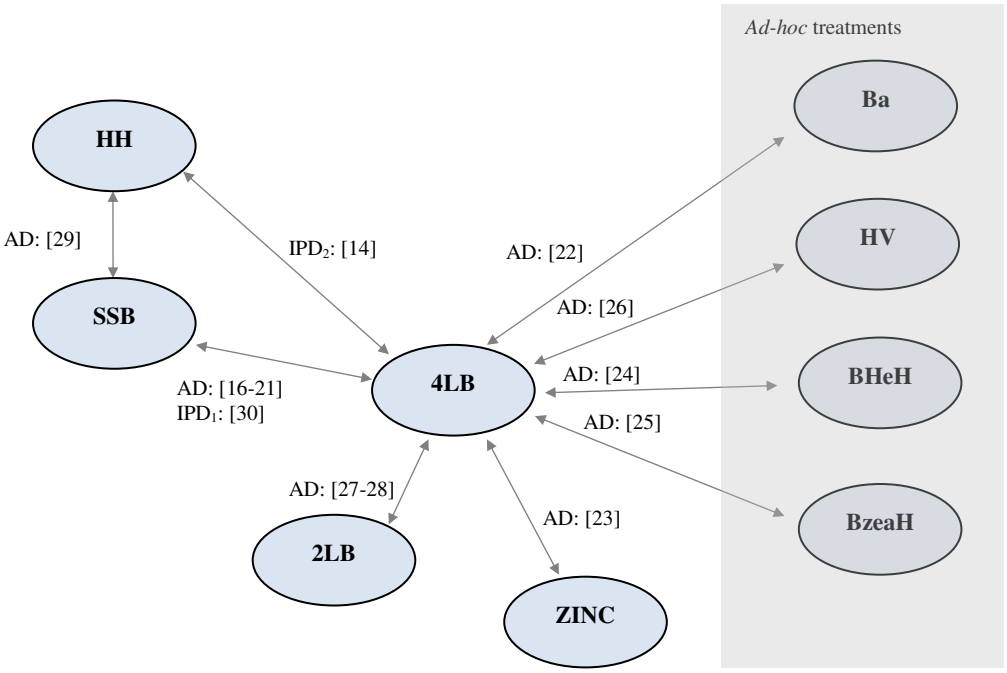

Figure 1: Network of RCTs

In the network, a unique treatment category is indicated by a circle. Arrows between circles indicate that these treatments had been compared in a trial (trials are identified using '[]', numbered as in column 'ID' in Table 1. (4LB, SSB, HH, Ba, Zinc paste, BHeH, BzeaH, HV and 2LB as described in Box A1 in Appendix)

3. Methods

We first describe in detail the modelling framework for our main analysis, *model A*. We then detail the process of evaluating alternative assumptions to this model, thus highlighting and challenging specific assumptions of the modelling framework proposed. All synthesis was conducted in a Bayesian framework.

3.1. Statistical model for the data

We describe *model A* in two interrelated parts [analogous to Sutton *et al* (31) and Saramago *et al* (5)]: *part I* describes the modelling of the IPD and *part II* the modelling of the AD.

Model A, part I- modelling the IPD studies, controlling for baseline covariates

$$t_{ijk} \sim Weibull(s, h_{ijk}) I(t^c_{ijk})$$
$$\boldsymbol{log(h_{ijk}|Z_{ij})} = \begin{cases} \boldsymbol{\mu_b^{IPD} + \gamma_j^c + \beta_0^m \cdot Z_{ij}} & \boldsymbol{b = A, B, C, \ldots} \text{ if } \boldsymbol{k = b} \\ \boldsymbol{\mu_b^{IPD} + d_{Ak} + d_{Ab} + \gamma_j^c + \beta_0^m \cdot Z_{ij}} & \text{if } k \text{ alphabetically after } b \end{cases} \quad \text{(A1)}$$
$$\boldsymbol{Z_{ij} \sim N(a^m, b^m)} \qquad \boldsymbol{\gamma_j^c \sim N(0, \tau)} \qquad \boldsymbol{\gamma \sim N(0, \tau)}$$

Time to ulcer healing (t_{ijk}) of the i^{th} participant in the j^{th} study and in the k^{th} treatment arm was assumed to be Weibull distributed (32) with *shape*[1] parameter, *s*, and *scale* parameter, h_{ijk}. For some participants, time to event was not observed, and these observations were censored at the time the participant last had trial data recorded, t^c_{ijk}. The baseline hazard function, linear on the log-scale, was modelled as a function of the log-hazard of an event for the baseline treatment *b*, μ_b^{IPD}, of treatment effects, d_{bk}, and of a set of baseline regression terms, $\beta_0^m \cdot Z_{ij}$, where β_0^m are the covariate effects of a set Z_{ij} of *m (=4)* regressors available in the IPD data sets (14): the log of the baseline ulcer area and duration (in months) (both centred around its mean value); and two dummy variables ('walks with difficulty' and 'immobile') referring to participant mobility (reference category is 'walks freely'). The effects of these covariates on the hazard of healing were assumed to be equal in both IPD studies (i.e. the coefficient of each covariate was constant). Due to the existence of missing covariate information for some individuals, a distributional assumption was imposed on the covariate values, indicating that Z_{ij} are Normally distributed with mean a^m and precision b^m, common across all IPD studies. This procedure assumes that the missing mechanism was 'at random'[2], which enables the use of multiple imputation techniques through MCMC[3]. Additionally, to account for centre variability within each IPD study, γ_j^c was defined for each centre, *c*, in the j^{th} study, these were combined using a common frailty effect, γ, described by a normal distribution with mean zero and precision τ.

The treatment effects, d_{bk}, were log-hazard ratios for treatment *k* relative to the study-specific baseline treatment *b*, partitioned here as $d_{bk} + d_{Ab}$. Prior distributions were specified for

[1] The shape parameter of the Weibull distribution, *s*, can be interpreted directly as follows: i) if $0 < s < 1$, hazard rate decreases over time; ii) if $s = 1$, hazard rate is constant over time (hazard exponentially distributed); and if $s > 1$, it indicates that the hazard increases with time (Collet 2003).

[2] The missing-at-random assumption (sometimes called the ignorability assumption) considers that the probability that an observation is missing may depend on the observed values but not the missing values, as sufficient data has already been collected.

[3] When imputing missing information, MCMC generates independent draws of the missing data from its predictive distribution. Multiple imputation through MCMC techniques is attractive for exploratory or multi-purpose analyses involving a large number of estimands.

μ_b^{IPD} $\left(\sim N(0, 10^6)\right)$, for each of the *m* regression coefficients β_0 $\left(\sim N(0, 10^6)\right)$, for a^m $\left(\sim N(0, 10^6)\right)$ and b^m $\left(\sim N(0, 10^6)\right)$, for the shared between centre variability τ $\left(\sim Gamma(0.01,0.01)\right)$ and for s $\left(\sim Gamma(0.01,0.01)\right)$. Vague prior distributions were given to $d_{bk} \sim N(0, 10^6)$. Note that $d_{AA} = 0$, where A was treatment 4LB, arbitrarily chosen as reference treatment.

Model A, part II - modelling the AD studies

$$\begin{aligned} r_{jk} &\sim Bin(p_{jk}, n_{jk}) \\ p_{jk} &= 1 - exp\left(-h_{jk}^{AD} \cdot \left(t_{jk}^{AD}\right)^s\right) \\ log\left(ha_{jk}|X_{ij}\right) &= \begin{cases} \mu_{jb}^{AD} & b = A, B, C, \ldots \text{if } k = b \\ \mu_{jb}^{AD} + d_{Ak} + d_{Ab} & \text{if } k \text{ alphabetically after } b \end{cases} \end{aligned} \quad \text{(A2)}$$

Within the AD studies, the observed number of participants with a healed study ulcer, r_{jk}, from the total number of individuals in the j^{th} trial and in the k^{th} treatment arm (intention to treat), n_{jk}, was assumed to be Binomially distributed. The underlying probabilities of an event for each arm and in each trial were represented by p_{jk}. In turn, p_{jk} was expressed as a function of the hazard, h_{jk}^{AD}, of follow-up time, t_{jk}^{AD}, and the shape parameter *s*. The hazard function, linear on the log-scale, was modelled by the baseline log-hazard of an event for treatment *b* in study *j*, μ_{jb}^{AD}, and by the log-hazard ratio for treatment *k* and baseline treatment *b*, d_{bk} $(= d_{Ak} + d_{Ab})$. Note that there are parameters common to both model parts (equations A1 and A2), namely the log-hazard ratios and the shape parameter of the time to healing distribution. Prior distributions were specified for μ_{jb}^{AD} $\left(\sim N(0, 10^6)\right)$.

3.2. Alternative modelling assumptions

A set of assumptions made within *model A* were challenged; these are detailed below.

Exploring between-study variation

Model A assumed that each included RCT aimed to measure a common treatment effect (fixed-effect); however, it is likely that there was between-study variation. *Model B* included a random effect to characterise between-study heterogeneity, by considering $\delta_{jbk} \sim N(d_{bk}, \sigma^2) \sim N(d_{Ak} + d_{Ab}, \sigma^2)$ rather than just d_{bk} – this is common to both *parts I* (eq. A1) and *II* (eq. A2).

Time to healing distributions

Model A used the Weibull distribution to describe time to healing. Our choice of survival distribution was limited as distributions such as the Log-Logistic or the Log-Normal do not allow the probability of healing over time to be expressed in a closed form, and hence impede the approach proposed here for the joint synthesis of IPD and AD. Other distributions, such as the Gompertz, were not readily defined within the software used in this work (WinBugs/OpenBugs), specifically under censoring. Nonetheless, the goodness of fit could still be assessed in each IPD data source individually. To do so, we applied parametric regression survival-time models (32) to both IPD data sources (16, 24) independently (covariates and frailty effect considered, as in *model A*).

Distributional shape parameter

Model A assumes that the Weibull shape parameter of the hazard of healing was common to both IPD data sources. It is possible though that this parameter differed between studies, in which case hazard ratios could be affected. Thus, we implemented two alternative NMA models to ascertain

the impact of this assumption on the relative effectiveness estimates: *model C1* used the shape parameter from the first IPD study to describe the AD studies and *model C2* used the shape parameter from the second IPD study (14) to describe these same studies. Because *models C1* and *C2* represent simple modifications of *model A* we do not present these algebraically.

Treatment-covariate associations

Model A uses baseline covariates to adjust for clinical heterogeneity in the IPD. To further explore the impact of covariates on the relative treatment effects (i.e. whether they were effect modifiers), and potentially help explain between-study heterogeneity, we also included interaction terms between alternative treatments and baseline ulcer area and duration— as described by Cooper *et al* 2009 (33) and Saramago *et al* 2012 (5). *Model D* assumed a regression (slope) coefficient for the interaction terms, this effect is common across treatments and thus common to *parts I* (eq. D1) and *II* (eq. D2). This assumption was data driven, as this was the only option we were able to implement with the data available (i.e. compared to assuming 'exchangeability' or 'independence') (33). Note that interaction estimates obtained are influenced by the full evidence base for which study mean covariate(s) values are available, including trials considering *ad hoc* treatments. Given *model D* is substantially different to *model A* we describe it algebraically here.

Model D, part I- modelling the IPD studies

$$t_{ijk} \sim Weibull(s, h_{ijk}) I(t^c_{ijk})$$

$$\boldsymbol{log(h_{ijk}|Z_{ij})} = \begin{cases} \boldsymbol{\mu_b^{IPD} + \gamma_j^c + \beta_0^m \cdot Z_{ij}} & \boldsymbol{b = A, B, C, \ldots \text{ if } k = b} \\ \boldsymbol{\mu_b^{IPD} + d_{Ak} + d_{Ab} + \gamma_j^c + \beta_0^m \cdot Z_{ij} + \beta^n \cdot X_{ij}} & \text{if } k \text{ alphabetically after } b \end{cases} \quad \text{(D1)}$$

$$\boldsymbol{Z_{ij} \sim N(a^m, b^m)} \qquad \boldsymbol{\gamma_j^c \sim N(0, \tau)} \qquad \boldsymbol{\gamma \sim N(0, \tau)}$$

Time to ulcer healing is modelled in the same way as in *model A*. A set of covariate-treatment interaction regression terms, $\beta^n \cdot X_{ij}$, are here defined, where β^n are the association effects, assumed common across studies and the same regardless of treatment (excluding control) , corresponding to a set X_{ij} of n (=2) covariates including the log of the baseline ulceration area and baseline ulcer duration (in months). For the remainder of the parameters of interest, prior distributions were assigned as in *model A*.

Model D, part II - modelling the AD studies

$$r_{jk} \sim Bin(p_{jk}, n_{jk})$$

$$p_{jk} = 1 - exp\left(-h_{jk}^{AD} \cdot \left(t_{jk}^{AD}\right)^s\right)$$

$$log(ha_{jk}|X_{ij}) = \begin{cases} \mu_{jb}^{AD} & b = A, B, C, \ldots \text{ if } k = b \\ \mu_{jb}^{AD} + d_{Ak} + d_{Ab} + \beta^n \cdot X_j & \text{if } k \text{ alphabetically after } b \end{cases} \quad \text{(D2)}$$

$$X_j \sim N(e^m, f^m)$$

The underlying probabilities of an event for each arm in each trial, p_{jk} , were regressed against *n (=2)* a set X_{ij} of study-level covariates [the log of the baseline ulceration area and baseline ulcer duration (in months)]. Uninformative prior distributions were assigned to the regression coefficients, β^n $\left(\sim N(0, 10^6)\right)$, to e^m $\left(\sim N(0, 10^6)\right)$ and f^m $\left(\sim N(0, 10^6)\right)$. All other components of the model are as described for *model A*.

3.3. Model selection and implementation

The NMA analyses were undertaken in the WinBUGs software (34). In all models the MCMC sampler was run for 10 000 iterations and these were discarded as 'burn-in'. Models were run for a further 5000 iterations, on which inferences were based. Chain convergence was checked. The WinBUGS code is included for reference in the Appendix. Within the NMA, goodness of fit was assessed using the deviance information criterion (DIC) (35). Results were presented using hazard ratio estimates (and associated credibility intervals, CrIs) and also using the probability of each compression system being the 'best' treatment in terms of being the most clinically effective (36).

The statistical software STATA (37) was used to fit alternative time to event distributions to the IPD datasets individually. Goodness of fit was assessed with the Akaike Information Criteria (AIC) statistic (38).

4. Results

Table 2 shows parameter estimates obtained for *model A* (first column) and alternative models testing its assumptions (*models B* to *D*, second to fifth columns). The results for *model A* highlight that the modelling framework proposed is feasible. The results of testing the assumptions are described next, in turn.

Exploring between-study variation

Despite estimates of HRs from the random effect model (*model B*) being associated with wider CrIs than those from *model A* (as expected), point estimates were found to be fairly similar except for the comparison between HH *vs.* 4LB: HH is estimated to be more effective in *model B* (HR 1.63, 95% CrI 0.76-3.53) compared to *model A* (HR: 1.05, 95% CrI 0.85 to 1.29), although the CrI of the former includes the later. The treatment with the greatest estimated probability of healing was HH in *model B* (59%), rather than 2LB (72%) as in *model A*. Differences may be explained by any existing variation between studies of SSB *vs.* 4LB indirectly impacting on the evidence loop 4LB *vs.* SSB *vs.* HH. Baseline covariate effect estimates remained similar. However, note that the gain in quality fitting of the random-effects model compared to the fixed-effects is null (DIC: 5396.21 and 5396.22, respectively). Previous published work assessing evidence on the SSB *vs.* 4LB comparison (39) similarly found no evidence of between-study heterogeneity.

Time to healing distributions

The Weibull was the time to healing distribution used in *model A*. Whilst we were limited in the use of other distributions, goodness of fit was explored by applying alternative time to event distributions to the IPD studies individually. Table 3 shows results of such analysis (AIC statistic). The best fitting distributions for both studies were the Log-Logistic and Log-Normal. Of the remaining, the Weibull and Gompertz distributions provided better fit than the Exponential; this was expected given the flexibility of these distributions in assuming increasing, decreasing or constant hazards over time. The Weibull was best in IPD study 2 and the Gompertz best in IPD study 1.

Distributional Weibull shape parameter of healing hazard

The Weibull shape parameters estimated within *models C1* and *C2* indicate that in IPD study 1 (30) the hazard of healing was expected to decreases over time (s_1 = 0.93, 95% CrI 0.86-1.01), while in IPD study 2 (14) it is expected to increase (s_2 = 1.27, 95% CrI 1.17-1.38). Note that there is no overlap in the CrIs. However, results show that relative effectiveness estimates are robust to the range of assumptions tested: the estimated HRs did not differ between *models C1* and *C2*, and did not substantially differ from *model A*.

Treatment-covariate associations

Model D tested the inclusion of interaction terms. Results (column 5 of Table 2) found that the covariates included did not appear to be treatment effect modifiers in this case study. However, estimating these two additional regression terms increased uncertainty in relative treatment effects estimates, specifically for ZINC and 2LB.

Table 2: Parameter estimates from the alternative MTC synthesis models.

		Model A			*Model B*			*Model C1*			*Model C2*			*Model D*		
Hazard ratios		HR median (95% CrI)		P	HR median (95% CrI)		P	HR median (95% CrI)		P	HR median (95% CrI)		P	HR median (95% CrI)		P
Treatment effects	***4LB***	---	---	5.5	---	---	1.4	---	---	6.2	---	---	5.7	---	---	4.3
	SSB	0.88	(0.76, 1.03)	0.4	0.96	(0.77, 1.22)	0.6	0.89	(0.77, 1.04)	0.6	0.89	(0.77, 1.04)	0.6	0.84	(0.70, 0.99)	0.2
	HH	1.05	(0.85, 1.29)	16.1	1.63	(0.76, 3.53)	59.2	1.03	(0.83, 1.27)	14.9	1.03	(0.84, 1.27)	15.0	1.03	(0.84, 1.28)	11.1
	ZINC	0.77	(0.41, 1.42)	6.2	0.78	(0.37, 1.62)	2.8	0.78	(0.41, 1.44)	6.5	0.78	(0.41, 1.43)	6.7	0.75	(0.03, 29.49)	17.5
	2LB	1.40	(0.65, 3.05)	71.9	1.39	(0.62, 3.30)	36.0	1.38	(0.66, 3.05)	71.8	1.38	(0.63, 3.04)	72.0	1.59	(0.61, 5.34)	67.0
Baseline characteristics	***Log area***	0.71	(0.66, 0.76)	---	0.71	(0.66, 0.76)	---	0.70	(0.65, 0.75)	---	0.70	(0.65, 0.75)	---	0.71	(0.65, 0.76)	---
	Log duration	0.92	(0.90, 0.94)	---	0.92	(0.90, 0.94)	---	0.92	(0.91, 0.94)	---	0.93	(0.91, 0.94)	---	0.92	(0.90, 0.94)	---
	Difficulty in walking	0.71	(0.60, 0.85)	---	0.73	(0.60, 0.86)	---	0.72	(0.60, 0.85)	---	0.72	(0.60, 0.85)	---	0.71	(0.60, 0.80)	---
	Immobile	0.67	(0.23, 1.52)	---	0.66	(0.23, 1.51)	---	0.72	(0.24, 1.65)	---	0.72	(0.25, 1.67)	---	0.68	(0.24, 1.59)	---
Interactions	***Log area***	---	---	---	---	---	---	---	---	---	---	---	---	1.00	(0.97, 1.10)	---
	Log duration	---	---	---	---	---	---	---	---	---	---	---	---	1.00	(0.99, 1.00)	---
	Btw-centre SD	0.04	(0.01, 0.13)	---	0.05	(0.01, 0.13)	---	0.05	(0.01, 0.15)	---	0.05	(0.01, 0.15)	---			---
	Btw-study SD	---	---	---	0.13	(0.01, 0.51)	---	---	---	---	---	---	---	---	---	---
	λ(s)	1.07	(1.01, 1.13)	---	1.07	(1.01, 1.14)	λ_1**	0.93	(0.86, 1.01)	λ_1	0.93	(0.86, 1.01)	---	1.07	(1.01, 1.14)	---
							λ_2	1.27	(1.17, 1.38)	λ_2**	1.27	(1.17, 1.38)				
	DIC	5396.2			5396.2			5371.2			5371.5			5377.4		

Model A – Fixed-effects NMA, Weibull model of IPD+AD; *model B* – Random-effects NMA, Weibull model of IPD+AD; *model C1* - Fixed-effects NMA, Weibull model of IPD+AD, shape parameter derived from IPD study 1 only; *model C2* - Fixed-effects NMA, Weibull model of IPD+AD, shape parameter derived from IPD study 2 only; *model D* - Fixed-effects NMA, Weibull model of IPD+AD, considering 2 treatment-effect modifiers

** Shape parameter used in the synthesis model section for summary data.

4LB = four layer bandage; SSB = Short stretch bandage; HH = two layer hosiery; 2LB = two layer bandage;

HR = hazard ratios; CrI = credibility interval; SD = standard deviation; P = probability of being the best treatment choice in terms of healing (%); DIC – deviance information criteria

Table 3: Goodness of fit (AIC statistics) of alternative time to ulcer healing models for IPD studies 1 and 2.

Time to event model	Akaike Information Criteria (AIC)	
	IPD study 1 (22)	**IPD study 2 (14)**
Weibull PH	1102.1	1021.0
Gompertz PH	1072.5	1065.5
Exponential PH	1102.7	1068.4
Log-Logistic AFT	1026.1	971.8
Log-Normal AFT	1032.2	961.5

5. Discussion

This paper introduces a novel NMA modelling approach that allows IPD (time to event with censoring) and AD (event count for a given follow-up time) to be synthesised jointly, by assuming an underlying, common, distribution of time to healing. Available IPD is used directly to inform this distribution (likelihood). Studies reporting the number of participants healed (AD) are used to inform a probability parameter, and a Binomial likelihood was defined for this subset of the evidence-set. The probability of healing is then related (algebraically) to the common distribution of time to healing, by taking the duration of follow-up in each AD study into account. This modelling framework extends the approaches of Soares *et al* (13) and Woods *et al* (40) and is also a natural extension of previously published methodologies of synthesising IPD and AD jointly (5, 31). This work was motivated by a real data example looking at the effectiveness of high compression treatments on the healing of venous leg ulcers.

We found that the key strength of the use of IPD in this context (additional to the known advantages described in the introduction) was the flexibility in modelling these data allowed. For example, had all evidence been available as AD, the modelling process would have been limited to the specification of uniparametric distributions for time to healing [i.e. the Exponential, with constant healing hazard over time, as employed in Soares *et al* (13) and Woods *et al* (40)]. In our motivating example, the Exponential distribution was shown to be less adequate than other distributions in describing the time to event data in the studies for which IPD was available. The availability of IPD allowed using a more complex distribution for time to event outcomes to be implemented, in this case the Weibull. This may be of particular importance when absolute effectiveness estimates, and not just relative effect estimates, are of interest – and especially where results may need to be extrapolated beyond the follow-up time horizon.

We note that even with this flexibility offered by the use of IPD we were, in practice, limited to using the Weibull distribution. Given this limitation, the synthesis of time to event data will still often require the use of potentially suboptimal distributional assumptions, in which case estimates obtained may be biased. We suggest further research, perhaps focuses on using numerical analysis techniques within the NMA, to try and resolve this issue.

This work was also relevant to once more highlight the importance of considering IPD when wanting to either include baseline characteristics or control for treatment-effect modifiers. The first relates to potential heterogeneity in the baseline hazard, which cannot be explicitly explored with AD only (this is important when analyses aim to explore determinants of baseline hazard, for example). In doing so, and analogously to what is commonly undertaken in related methodologies such as IPD meta-analysis, in this study we assumed a common effect of baseline covariates on the hazard of healing across IPD studies. The second relates to treatment-covariate interactions, that are generally acknowledged to be best estimated using IPD, as ecological bias can be avoided (8). For the proportion of evidence only available as AD, the model here implemented considered study level mean covariate values. Nonetheless, not all studies provided information for these, and imputation was undertaken (imputation is naturally done through the MCMC, and assumes values are 'missing at random').

In our work we assumed the shape parameter of the Weibull time to event distribution to be common across studies. However, assumption testing proved this not to be valid, in this way highlighting the importance of evaluating any assumptions of similarity imposed across studies. Despite relative effectiveness estimates being mainly unaffected, such potential heterogeneity between studies should be explored and accounted for in analyses. Such assumptions of commonality also mean that information may be shared throughout the network, in which case

evidence on treatments other than those on our decision set (the five treatments of interest for which results were reported). This is the case of *model D* that makes use of all evidence (including *ad hoc* treatments) to estimate treatment-covariate interaction, which may indirectly affect the relative effectiveness estimates of interest.

In summary, by allowing flexibility in specifying survival distributions and in dealing and considering potential existing heterogeneity more fully (41), the use of IPD in a time to event outcome setting is particularly useful in guiding HTA decision making. This work also emphasises the value of including anonymised IPD in evidence synthesis work. There is increasing focus on promoting data sharing (42, 43) and this example highlights how use of IPD allows the development of more informative and flexible models that are better able to summarise existing evidence. However, it is important to acknowledge that accessing and analysing IPD can be time consuming and may cause delay. The process needs to be well planned and implemented. In our case both sources of IPD were easily accessed and that directly facilitated the conduct of these analyses and the associated methodological work presented here.

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Appendix

Box A1: Description of main compression systems evaluated

1. Two layer hosiery, HH (smooth first layer, or understocking, providing light compression over which a second overstocking i.e. UK class II or III depending on the understocking slips on);
2. Four layer bandage, 4LB (an elastic system consisting of an orthopaedic wool layer plus three subsequent bandages);
3. Short stretch bandage, SSB (an inelastic bandage system where one to three rolls of bandage are applied over orthopaedic wool);
4. Zinc paste bandage, ZINC (an inelastic system consisting of a paste bandage often with a support bandage on top);
5. Two layer bandage system, 2LB (bottom layer with cohesive compression bandage - sub-compression wadding layer and cohesive bandage).

WiNBUGS code

This code relates to *model A* described above and is here described in a generic form for it to be easy for the user to modify and adapt to specific applications. Five datasets are required to fit the complete model: two containing constants for AD and IPD, two for both studies at IPD level and one for the AD evidence. All data should be loaded before the model is compiled. Because of size and agreements of use, the original data sets are not included in their entirety, but a couple of lines of data are supplied for each study/data combination for illustration purposes.

```
model {
### Part 1: Model for IPD 1 and IPD 2###
for(i in 1:n.subjects1) {
        #Weibull likelihood for IPD 1
        t.obs1[i] ~ dweib(shape,zu1[i])I(t.cen1[i],)
        #Model for IPD 1
        log(zu1[i]) <- mu1 + betac1[centre1[i]] + d[treat1[i]] - d[baseline1[i]] +
        beta_cov * cov1[i]
        cov1[i] ~dnorm(a1,b1)
        }

#Vague priors for IPD 1
mu1~dnorm(0,1.0E-6)
a1~dnorm(0,1.0E-6)
b1~dgamma(0.01, 0.01)
for (i in 1:C1) {
        betac1[i] ~ dnorm(0.0,taua)
        }

for(k in 1:n.subjects2) {
        #Weibull likelihood for IPD 2
        t.obs2[k] ~ dweib(shape,zu2[k])I(t.cen2[k],)
        #Model for IPD 2
        log(zu2[k]) <- mu2 + betac2[centre2[k]] + d[treat2[k]] - d[baseline2[k]] +
        beta_cov * cov2[i]
```

```
        cov2[i] ~dnorm(a2,b2)
        }

#Vague priors for IPD 2
mu2 ~ dnorm(0,1.0E-6)
a2~dnorm(0,1.0E-6)
b2~dgamma(0.01, 0.01)
for (i in 1:C2) {
        betac2[i] ~ dnorm(0.0,taua)
        }

#Vague priors for baseline patient characteristics effects
beta_cov ~ dnorm(0,1.0E-6)

# Part 2: Model for aggregate data #
for(i in 1:n.agg.arm) {
        #Binomial likelihood for AD
        r[i]~dbin(pa[i],n[i])
        #Model for AD
        pa[i] <- 1 - exp( - zu.a[i] * pow(a.time[i], shape))
        log(zu.a[i]) <- mu.a[a.s[i]] + d[a.treat[i]] - d[a.base[i]]
        }

#Vague priors for AD
for(j in 1:n.agg.trials) {
        mu.a[j]~dnorm(0,1.0E-6)
        }

### Model for combining all estimates of treatment effect  #
#Vague prior for shape parameter
shape ~ dgamma(0.01, 0.01)
#Vague priors for shared centre effect
betac.new ~ dnorm(0.0,taua)
taua ~ dgamma(0.01, 0.01)

#Vague prior for basic parameters
d[1]<-0
for (k in 2:treat) {
        d[k] ~ dnorm(0,1.0E-6)
        }

}

### Dataset 1: Constants to define for IPD evidence###
# Number of participants in IPD 1 #
list(n.subjects1 = 386,
# Number of participants in IPD 2 #
n.subjects2 = 454,
# Number of treatments being evaluated
treat = 9,
# Number of centres in IPD 1
```

C1 = 9,
 # Number of centres in IPD 1
C2 = 35)

Dataset 2: Constants to define for AD evidence###
 # Number of AD studies #
list(n.agg.trials = 14,
 # Number of AD study arms #
n.agg.arms = 28)

Dataset 3: IPD 1

treat1[]	baseline1[]	t.obs1[]	t.cens1[]	cov1[]	centre1[]
1	1	3.50	0	1.95	3
1	1	2.33	0	1.94	9
2	1	NA	11.90	2.49	4
...	...	...	...	...	...
...	...	...	...	...	...

END
treat1 = treatment arm (coded 1,2), baseline1 = reference treatment code,
t.obs1 = time to event in months (under censoring), t.cens1 = time of censoring in months,
cov1 = continuous covariate of interest (R+), centre1 = trial centre code (coded 1-9)

Dataset 4: IPD 2

treat2[]	baseline2[]	t.obs2[]	t.cens2[]	cov1[]	centre2[]
1	1	NA	21.28	5.15	1
1	1	1.15	0	0.94	16
3	1	8.41	0	2.31	2
...	...	...	...	...	...
...	...	...	...	...	...

END
treat2 = treatment arm (coded 1,2), baseline2 = reference treatment code,
t.obs2 = time to event in months (under censoring), t.cens2 = time of censoring in months,
cov1 = continuous covariate of interest (R+), centre2 = trial centre code (coded 1-35)

Dataset 5: AD evidence

a.s[]	a.treat []	r[]	n[]	a.base[]	a.time[]
1	1	11	25	1	12
1	2	10	25	1	12
...	...	...	...	...	...
...	...	...	...	...	...

END
a.s = study number, a.treat = treatment arm code (coded from 1 to number of treatments),
r = number of events in trial arm, n = number of patients in trial arm,
a.base = reference treatment code, a.time = follow-up time of trial (in months)

Initial values, either need specifying or generating for the below scalars and vectors
list(d = c(NA,0,0,0,0,0,0,0,0), mu1 = -1, mu2 = -1, mu.a = c(-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1), beta_cov = 0, shape = 1, betac.new = 0, betac1 = c(0,0,0,0,0, 0,0,0,0), betac2 = c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0))