ABSTRACT

The process of approving and assessing new drugs is often quite complicated, mainly due to the fact that multiple criteria need to be considered. A standard way to proceed is with benefit risk analysis, often under the Bayesian paradigm to account for uncertainty and combine data with expert judgement, which is operationalised via multi-criteria decision analysis (MCDA) scores. The procedure is based on a suitable model to accommodate key features of the data, which are typically of mixed type and potentially depended, with factor models providing a standard choice. The contribution of this paper is threefold: first, we extend the family of existing structured factor models. Second, we provide a framework for choosing between them, which combines fit and out-of-sample predictive performance. Third, we present a sequential estimation framework that can offer multiple benefits: (i) it allows us to efficiently re-estimate MCDA scores of different drugs each time new data become available, thus getting an idea on potential fluctuations in differences between them, (ii) it can provide information on potential early stopping in cases of evident conclusions, thus reducing unnecessary further exposure to undesirable treatments; (iii) it can potentially allow to assign treatment groups dynamically based on research objectives. A drawback of sequential estimation is the increased computational time, but this can be mitigated by efficient sequential Monte Carlo schemes which we tailor in this paper to the context of Bayesian benefit risk analysis. The devel-
oped methodology is illustrated on real data on Type II diabetes patients who were administered Metformin (MET), Rosiglitazone (RSG) and a combination of the two (AVM).

1 Introduction

Regulatory authorities called on to authorise new drugs often face a difficult challenge on how to choose an action in the presence of multiple competing objectives. Rising demand for individualised treatments, the increasing number of stakeholders, and a higher level of complexity in the kind of questions asked today, all make the challenge even harder. Multiple high profile drugs have been withdrawn over the past 20 years (Guo, Pandey, Doyle, Bian, Lis, and Raisch, 2010), some permanently, while others have been remarketed under revised labelling and guidance (Wallach, Wang, Zhang, Cheng, Nardini, Lin, Bracken, Desai, Krumholz, and Ross, 2020). Given the complexity and the gravity of this challenge, it is important to provide stakeholders with structured quantitative approaches for benefit-risk assessment of medicines. Such approaches, like the one developed in this paper, typically rest on using observational data to estimate suitable models and the parameters thereof, while at the same time balancing competing objectives.

One high profile drug with a controversial past is Rosiglitazone. Rosiglitazone is a drug for the treatment for Type II diabetes that was marketed under the commercial name Avandia. It gained market authorisation in the United States in 1999 and in the European Union in 2000. New data subsequently emerged about possible cardiovascular risks associated with Rosiglitazone, confirmed by a meta-analysis in 2007 (Nissen and Wolski, 2007), which resulted in a European suspension of the marketing authorisation in 2010. This suspension included its use as a fixed dose combination with Metformin or Glimepiride for Type II diabetes, which had been approved in 2003 for Metformin and 2006 for Glimepiride. The drug remained available in the United States, but only under a restricted-access programme put in place in 2010. In 2011 the US regulators reverted the recommendation and suspended the drug. In 2013 the drug regained approval, following a study that found Rosiglitazone to be as safe as other diabetes drugs. Today the drug is withdrawn from most countries in the world, but remains available in the United States. For a complete review of the regulatory history of Rosiglitazone see (Wallach et al., 2020).

Benefit risk analysis (BRA) is an umbrella term that encompasses any structured approach for weighing the benefits (typically the efficacy) against the risks (typically dangerous or unwanted side effects) of drug treatments. The goal is to assist stakeholders decide if a drug works, and whether the potential side effects are acceptable. Since the decision depends on personal preferences and risk tolerances, the proposed frameworks include various ways of embedding formal or informal utility functions. Mt-Isa et al. (2014) conducted a review of the benefit risk literature categorising
the approaches into quantitative frameworks, metrics for benefit-risk assessment, estimation techniques and utility survey techniques, and qualitative frameworks. Out of these four groups, the first two are formal quantitative approaches based on statistical theory, whereas the latter two are more informal. Common single metrics are the benefit risk ratio (BRR) (Carlisle et al., 2016) and net clinical benefit (NCB) (Shakespeare et al., 2001) whereas more recently researchers have suggested extension metrics such as RV-NNT and MCE (Holden, 2003). Single metrics like these, while providing useful summaries, in practice cannot holistically evaluate a drug as they focus instead on specific aspects of the decision making process. A practical limitation is that they require the benefit and risks to be already expressed in common scales. A theoretical limitation is that complex decision making often cannot be easily summarised by single numbers, especially if the uncertainty is not taken into account. Ratio-based metrics, in particular, have received criticism for being unstable or misleading, often hiding the uncertainty embedded into the final decision that rests on the actual value (Lynd and O’Brien, 2004; Shaffer and Watterberg, 2006; Sutton et al., 2005).

Multi-criteria decision analysis (MCDA) is one of the most comprehensive quantitative frameworks for benefit risk assessment and it is widely used today (Keeney et al., 1993; Mussen et al., 2009; Dodgson et al., 2009). It is a quantitative framework that allows users to weight outcomes by their utilities and can support any integrated single metric score. It has been developed over the last 50 years (Jong and Stone, 1976) and has subsequently been used for assessing the benefit-risk balance of drugs (Glasziou and Irwig, 1995), or other interventions (Ponce, Bartell, Wong, LaFlamme, Carrington, Lee, Patrick, Faustman, and Bolger, 2000). In particular, it has been recommended by Mussen et al. (2007) and Garrison Jr et al. (2007) as a necessary tool in the regulatory setting (Mühlbacher, Juhnke, Beyer, and Garner, 2016). MCDA also lends itself to sensitivity analysis around crucial variables, a methodology commonly referred to as SMAA (Tervonen and Figueira, 2008; Tervonen et al., 2011; Lahdelma et al., 1998) for which there is also a software package (Tervonen, 2014).

There has been some recent work on Bayesian modelling for MCDA analysis. Waddingham, Mt-Isa, Nixon, and Ashby (2016) conducted an analysis of multiple data sets, formed by both aggregated and patient level data, to incorporate uncertainty in the MCDA score. They propose a Bayesian probabilistic model to propagate the uncertainty caused by sampling variability to the final outcome of an MCDA study. The methodology is demonstrated using a model applied to nine binomial variables and one count variable. The model assumes that all variables are independent, and does not include assessing the model fit. Li, Luo, Yuan, and Mt-Isa (2019) proposed a two-factor latent trait model to account for correlation amongst outcome variables, accommodating a combination of continuous and binary outcomes of interest. Furthermore, their approach introduced the use of latent factors that represent the benefit and risks.
This recent line of research successfully demonstrates the benefits of Bayesian modelling for drug evaluations. Waddingham et al. (2016) used Bayesian modelling to incorporate parameter estimation uncertainty into the final MCDA score, and demonstrated the importance of taking that uncertainty into account for drug evaluation. Costa et al. (2017); Li et al. (2019) showed how to account for the correlation between continuous types of data, typically the treatment efficacy outcomes, and discrete types of data, typically adverse events. Naturally, in order to account for any correlation, such models are fitted on individual level data, rather than summary data. These modelling advances are important steps towards comprehensive drug evaluations. Since the final decision depends on parameter estimates from a model, it is crucial to be able to at least check if the proposed model is supported by the data before basing any decisions on the results of inference. Moreover, assessing the predictive performance is essential in order to choose amongst competing models.

In this paper, we aim to enhance the available methodology in a few new directions. First, we explore and expand the factor analysis models currently being used in benefit risk analysis to accommodate the mixed type and potentially dependent data. This is done by incorporating Bayesian structural equation modelling (Muthén and Asparouhov, 2012; Vamvourellis et al., 2021), tailored to the data features of this paper. Moreover, we consider pooled versions of these models, in other words models where the parameters are the same across treatment groups. This results in an increased number of models, thus reinforcing the importance of model choice and assessment. The second contribution of this paper targets those tasks and suggests to aim for a model that, on the one hand, is rich enough to attain adequate goodness of fit, but at the same time has good predictive performance and avoids overfitting. Thirdly, we present a sequential clinical study design paradigm that offers multiple benefits: (i) it allows us to recursively update the estimates of MCDA scores each time new patients receive the treatment. This allows us to monitor differences in the MCDA scores between drugs as data accumulate and get an idea on potential fluctuations thereof; (ii) it permits stopping the exposure as soon as the research requirements are satisfied, reducing unnecessary further exposure to undesirable treatments; (iii) it allows us to assign treatment groups dynamically based on research objectives; for example, if the effects of one treatment are estimated with high confidence within a few data points while for another they remain uncertain, we can shift subjects away from the first group and into the second as needed. From a computational point of view, sequential re-estimation results in increased computational time, but this can be substantially mitigated by efficient Sequential Monte Carlo (SMC) schemes, which we tailor in this paper to accommodate the features of the models it considers. To our knowledge this is the first application of SMC algorithms to benefit risk analysis. It is also worth noting that, even in batch data, sequential algorithms offer some advantages over Markov chain Monte Carlo
(MCMC) schemes in some cases. For example, they can offer an estimate of the model evidence to compute Bayes factors, as well as provide an alternative, computationally more robust, scheme than MCMC methods, especially when the target posterior distribution is multimodal.

The paper is structured as follows. In Section 2, we lay out the comprehensive modelling framework for benefit risk analysis of different drug treatments, including modelling the data generation process and the MCDA approach. We review various model alternatives based on latent variable modelling, including exploratory factor analysis as well as structural equation models, in order to hone into specific aspects of the data generation process that is of interest. Section 3 introduces the framework for assessing different models and choosing the most suitable for the data at hand. In Section 4, we introduce the sequential inference paradigm. In Section 5, we demonstrate the benefits of the proposed methodology by applying it to a real-world clinical case study for type II diabetes treatments such as Rosiglitazone, Metformin, and Glimepiride. We conclude with a discussion of limitations and future work.

2 Factor Models for Multi-criteria Decision Analysis

2.1 Multi-criteria Decision Analysis Score and Data

We define MCDA amongst $R$ treatments, based on data collected on $P$ criteria for a set of $N$ subjects in the following way. The criteria of a clinical trial typically consist of the benefits of the treatment and the adverse events that are experienced by the subjects, denoted by $y_{ijr}$ for $i = 1 \ldots N$, $j = 1 \ldots p$, and $r = 1 \ldots R$. Commonly, the benefits are efficacy measurements represented by continuous variables, whereas adverse events refer to measurable experiences of negative side effects, commonly expressed as the frequency of occurrences for each event considered. The MCDA approach adopted in this paper requires that the expected value of each outcome with respect to the population of $N$ individuals, denoted by $E(y_{ijr})$, be accompanied by a function $U_{jr} := u_j \{E(y_{ijr})\} \rightarrow [0, 1]$, that maps from a pre-specified range in the observations space onto an integrated benefit-risk scale from 0 to 1. These functions, typically common across subjects and treatment groups, map the range of outcomes to a subjective continuous measure of utility or value, with 0 representing the worst case scenario, and 1 representing the best case scenario. In this paper, we work with simple linear mappings; however, other types of mappings can be used as well in our approach. The MCDA score also requires multiplying each $U_{jr}$ with a weight $w_j$ that reflects the relative importance or preference of a full swing from worst to best of the $j$-th criterion relative to the rest. Such weights are elicited by expert clinicians tasked with evaluating a drug treatment, or by individual patients who want to compare the possible treatments available to them according to their personal benefit risk preferences. To keep notation clean and simple we assume these

5
weights are common across all subjects in this work. However, it is easy to accommodate individual-specific weights \( \{w_{ij}\}_{i,j} \) as long as \( \sum_j w_{ij} = 1 \) for all \( i \). Without loss of generality we proceed with common weights and define the population-based MCDA score for the \( r \)-th treatment as

\[
M_r := \sum_j w_j U_{jr} = \sum_j w_j \cdot u_{jr} \{E(y_{ijr})\}.
\]

(1)

In the presence of a probability model for the data based on some unknown parameters \( \Theta \), the expectation in the population-based MCDA score \( M_r \), as defined above in Equation (1), is typically a function of the model parameters. Hence we can write \( M_r(\Theta) \) as typically the weights and the \( U_{jr} \) functions defined above are considered as known. The parameter vector \( \Theta \) is usually estimated based on some available data \( Y \). Under a frequentist inference approach one may estimate \( \hat{\Theta} \) from \( Y \) to get \( M_r(\hat{\Theta}) \) and then work out some hypothesis test, considering also the variance of the differences between \( M_r(\Theta) \) between different drugs or treatments \( r \). Under the Bayesian paradigm, and given some suitable prior \( \pi(\Theta) \), the aim is to get access to the posteriors \( \pi(M_r(\Theta)|Y) \). One can then calculate quantities such as the posterior probability that a drug \( r \) has a greater MCDA score than another one. In either case, there are at least two sources of variability depending on (i) which model is chosen, and (ii) what data have been available at the time of the decision. In the remainder of this section and the next one we develop methodology for Bayesian benefit risk analysis that allows exploring both of these sources.

### 2.2 Factor Analysis for Mixed Type Data

As the MCDA score of (1) for each treatment depends on the unknown values of the population means, its calculation requires estimating them from data based on an appropriate model. The data consist of \( p \) observed variables denoted by \( y = (y_1, \ldots, y_p) \) that can be of mixed type and potentially dependent. We consider several models in this paper, aiming for one that fits the data well but at the same time is parsimonious and good in terms of predictive performance. The models are defined in the following subsections. In almost all cases a separate model is defined for each drug or treatment \( r \), thus we suppress the relevant notation, e.g. from \( y_{ijr} \) to \( y_{ij} \), for simplicity unless stated otherwise.

#### 2.2.1 Latent variable framework

One approach that can accommodate continuous or categorical variables is a factor analysis model. According to this approach, to model a set of observations for \( p \) items \( y = (y_1, \ldots, y_p) \) we introduce \( k \) continuous latent factors, denoted by \( z = (z_1, \ldots, z_k) \). The associations between the observed items can be explained through the latent factors
and their loading structure \( \Lambda \) as follows

\[
y^*_i = \alpha + \Lambda z_i + \epsilon_i, \quad i = 1, \ldots, n
\]  

(2)

where \( y^* = (y^*_1, \ldots, y^*_p) \) are auxiliary variables that help us express a general framework. When the \( j \)-th item \( y_j \) is a continuous variable, we assume that the underlying variable is directly observed \( y_j = y^*_j \). In the context of clinical trials, the amount of glucose detected in the bloodstream could be such an item measured on the continuous scale.

When the \( j \)-th item is a categorical variable we can model it as a manifestation of the underlying latent variable \( y^*_j \) as follows. For a binary item we model it as

\[
y_j = I(y^*_j > 0)
\]

where \( I(\cdot) \) is the indicator function. For an ordinal item with \( m_j \) categories,

\[
y_j = a \text{ if } \tau_{a-1} < y^*_j \leq \tau_a, \quad a = 1, \ldots, m_j \text{ where } \tau_0 = \infty, \tau_1 < \tau_2 < \ldots < \tau_{m_j-1}, \tau_{m_j} = +\infty.
\]

Examples of such categorical variables in the context of clinical trials are typically related to adverse events. For instance, experiencing allergic reactions could be a binary item, whereas the experiencing of pain on a scale of 1 to 5 would be an ordinal variable.

We can then interpret Equation (2) in sufficient generality that it encompasses more than one type of data, as is often the case in clinical trials. The parameters of Equation (2) are understood as follows: \( \alpha \) is a \( p \times 1 \) vector of intercepts and expresses the population mean for each item, \( \Lambda \) is the \( p \times k \) matrix of factor loadings and \( n \) is the sample size. The factors \( z_i \) are usually assumed to be normally distributed, \( z_i \sim N_k(0, \Phi) \), although other distributions are also possible. The \( \epsilon_i \)s are error terms assumed to be independent from each other and from the \( z_i \)s.

Specific choices for the distribution of the error term \( \epsilon_i \)s lead to the following well-known models:

\[
\epsilon \sim \begin{cases} 
N(0_p, \Psi), & \text{if } y_i \text{ is continuous} \\
N(0_p, \Psi), & \text{if } y_i \text{ is binary and the probit model is adopted} \\
I_p, & \text{if } y_i \text{ is binary and the logit model is adopted,} \\
\prod_{j=1}^p \text{Logistic}(0, \pi^2/3), & \text{if } y_i \text{ is binary and the logit model is adopted,}
\end{cases}
\]

where \( 0_p \) is a \( p \)-dimensional vector of zeros and \( I_p \) denotes the identity matrix of dimension \( p \). In the case of having only continuous data with normally distributed \( z_i \)s and \( \epsilon_i \)s as above, we can marginalise out the latent factors to obtain

\[
y^*_i \sim N(\alpha, \Lambda \Phi \Lambda^T + \Psi), \quad i = 1, \ldots, n.
\]  

(3)

Nevertheless, the above operation is generally not possible if the dataset contains some categorical variables.

For binary data it is also possible to reformulate the model as shown below:

\[
\begin{aligned}
y_i \sim \prod_{j=1}^p \text{Bernoulli}(\pi_{ij}(\eta_{ij})) \\
\pi_{ij}(\eta_{ij}) = \sigma(\eta_{ij}) & \text{ or } \pi_{ij}(\eta_{ij}) = \Phi(\eta_{ij}), \quad \eta_{ij} = [\eta_i]_j \\
\eta_i & := \alpha + \Lambda z_i,
\end{aligned}
\]  

(4)
where \( \sigma(\cdot) \) denotes the sigmoid function and leads to the logit model, whereas \( \Phi(\cdot) \) denotes the cumulative density function of the standard Normal distribution and leads to the probit model. Ordinal data can also be handled in a similar manner.

When we know in advance which factors contribute to what items, the model is considered to be structured, also known as confirmatory factor analysis (CFA). Such knowledge is typically expressed by constraining certain elements of the loading matrix \( \Lambda \) to zero. For example, a confirmatory model used in this paper sets several elements of \( \Lambda \) to zero in such a way that the first factor loads only onto the outcomes that measure benefits, and the second factor loads only onto the outcomes that measure risks. When the loading structure is unknown the loading matrix is \( \Lambda \) unconstrained and the model is referred to as exploratory factor analysis (EFA). EFA has more free parameters, hence it is often necessary to place restrictions to ensure identifiability, such as restricting \( \Lambda \) to be upper triangular or setting \( \Phi = I_k \).

Both approaches may have different numbers of factors with a limiting case being the saturated model, under which

\[
y_i^* \sim N(\alpha, \Sigma),
\]

where \( \Sigma \) is a full covariance matrix, except for the constraint of having ones in its diagonal entries corresponding to binary variables for identifiability reasons.

### 2.2.2 Bayesian structural equation modelling

The Bayesian formulation of factor models, introduced by Muthén and Asparouhov (2012) and extended by Vamvourellis et al. (2021), provides an alternative model by replacing any exact zero restrictions of parameters in \( \Lambda \) and \( \Psi \), with approximate zero ones. This is done by using informative priors that place a large amount of probability mass around zero; these models are henceforth denoted as approximate zero. The equation framework in (2) is generalised with the addition of a variable-individual specific random effect \( u_{ij} \) as follows

\[
y_i^* = \alpha + \Lambda z_i + u_i + e_i,
\]

where \( u_i \) is a \( p \)-dimensional vector of random effects with a non-diagonal covariance matrix \( \Omega \), and \( e_i \) remains an error term with a diagonal covariance matrix \( \Psi \). The \( u_i \) terms aim to capture associations amongst the variables, beyond those explained by the vector of latent variables \( z_i \), of relatively small magnitude. In the case of continuous data it is possible to marginalise over the latent variables to get the following expression

\[
y_i^* \sim N(\alpha, \Lambda \Phi \Lambda^T + \Omega + \Psi), \quad i = 1, \ldots, n,
\]
where \( \mathbf{u}_i \sim N(0, \Omega) \), \( \mathbf{z}_i \sim N(0, \Phi) \) and \( \mathbf{e}_i \sim N(0, \Psi) \). Compared to the model in (3), the aim is to go from a diagonal matrix \( \Psi \) to an almost diagonal one, \( \Psi + \Omega \), by assigning an informative prior on \( \Omega \) to limit its magnitude compared to \( \Psi \). Overall, the approximate zeros model above may be viewed as an intermediate step between CFA and EFA.

2.2.3 Multiple group models

The models presented so far refer to a single treatment group. When data from more than one group are available, one can proceed with a separate model for each group or a pooled model aiming for more parsimony. For example, in a classical clinical trial there are two arms, control and treatment. More generally a clinical trial can contain \( R \) arms where subjects are allocated to one of the \( R \) groups. We can denote such data by \( \{ y_{i}^{(r)} \}_{i=1}^{n_r} \) where the \( r \)-th group contains \( n_r \) subjects. In this case, rather than modelling each group completely separately, it may be beneficial to pool together certain parameters of the model, such as the covariance structures \( (\Psi, \Omega, \Psi) \). At the same time, the intercept parameters \( \alpha \) and the loadings \( \Lambda \) can be group specific. This way Expression (7) becomes

\[
y_i^{*(r)} \sim N(\alpha_r, \Lambda_r \Phi \Lambda_T^r + \Omega + \Psi), \quad i = 1, \ldots, n,
\]

where now \( r = 1, \ldots, R \) is the index of the clinical arm.

2.3 Priors

We use priors according to standard recommendations in the related literature. More specifically, the non-zero or else principal loadings in the \( \Lambda \) matrix are assigned \( \Lambda_{ij} \sim N(0, \sigma_j^2) \); see, for example, (Conti, Frühwirth-Schnatter, Heckman, and Piatek, 2014; Frühwirth-Schnatter and Lopes, 2018), for the case of continuous data and \( \Lambda_{ij} \sim N(0, 4) \) when \( y_j \) binary, as in (Vitoratou, Ntzoufras, and Moustaki, 2014). For the cross loading under the approximately zero framework, \( \Lambda_{ij} \sim N(0, 0.1^2) \) were used as in Muthén and Asparouhov (2012). Following (Frühwirth-Schnatter and Lopes, 2018), the prior given to the idiosyncratic variances for the continuous variables is

\[
\psi_j^2 \sim \text{InvGamma}^{-1}(c_0, (c_0 - 1)/(S_y^{-1})_{jj})
\]

where \( S_y \) is the sample covariance matrix of the continuous observations \( y \) and \( c_0 \) is a constant that we choose so as to avoid Heywood issues, and bound the samples away from 0. The matrix \( \Phi \) is set to be a correlation matrix, rather than covariance, thus there is a need to restrict the diagonal elements of \( \Lambda \) to one for identification purposes. Normally these elements should be restricted to be positive, to ensure identifiability, but we instead follow a procedure very similar to the parameter expansion scheme of (Ghosh and Dunson, 2009). More specifically, we assign Normal priors to all of
them and apply post-processing on the MCMC output based on their sign. The LKJ prior, introduced in Lewandowski et al. (2009), is assigned to the $\Phi$ correlation matrix. For the $\Omega$ matrix, we use the Inverse Wishart distribution with identity scale matrix and $p + 6$ degrees of freedom to reflect prior beliefs of near zero residual covariances, as is done in (Muthén and Asparouhov, 2012). Finally, we set large variance normal priors for the $\alpha$ parameters, $\alpha \sim N(0, 10^2)$.

2.4 Implementation

In the models mentioned before, the parameter vector $\Theta$ may contain population parameters such as $\alpha$, $\Lambda$, $\Phi$, $\Psi$, $\Omega$ or latent variables that can potentially capture individual characteristics such as $Z = \{z_i\}_{i=1}^n$ or $U = \{u_i\}_{i=1}^n$. Denote the former by $\theta$ and the latter by $X$ such that $\Theta = (\theta, X)$. Inference may be based on the augmented likelihood containing both parameters and latent variables $f(Y|\theta, X)$, although in some cases the latter can be integrated out to obtain $f(Y|\theta)$, e.g. when all the variables are continuous and the model follows Equations (3), (5), (7) or (8). But even in those cases, the posterior is typically not available in closed form and MCMC schemes can be used to draw samples from the posterior distribution and carry out Bayesian inference tasks. In this paper we use the Hamiltonian MCMC algorithm (Neal, 2011) as implemented in Stan (Carpenter et al., 2017). The samples from the posterior of $\Theta$ can be transformed into samples from the posterior of $M_r(\Theta)$, which can in turn be used to obtain Monte Carlo estimates of quantities such as the posterior probability of one drug having a greater MCDA score than another.

3 Model Assessment

3.1 Fit and predictive performance on mixed type data

In this section we propose a model assessment framework suitable for choosing between the models defined so far. We recommend complementing the goodness-of-fit assessment, which can be done using posterior predictive p-values (PPP values) (Meng, 1994), with the evaluation of the out-of-sample predictive performance through indices such as scoring rules (Dawid and Musio, 2015; Gneiting and Raftery, 2007). Our motivation for this dual assessment is to avoid overfit, which occurs in cases where the gains in goodness of fit are based on finding circumstantial patterns of the data that do not replicate in new unseen data. In line with Vamvourellis et al. (2021) we evaluate out-of-sample predictive performance using the log scoring rule through cross-validation.

The use with PPP values and log scores in the context of benefit risk analysis is not always straightforward, especially in cases of mixed type data. For example, in PPP values, it is not easy to identify a discrepancy function that operates on both covariance matrices and response patterns, typically used in continuous and categorical data respectively. The
approach we take, in line with previous work by Moustaki (1996), is to monitor PPP values and log scores separately for each data type, i.e. categorical and the continuous observations. This approach may also be helpful in identifying weak areas of models and suggesting potential modifications. In the following two sections we provide details on the computations of PPP values and log scores.

3.2 PPP values

As mentioned earlier, PPP values are quite common in the Bayesian setting, which is an absolute measure of in-sample performance. A model is considered to not fit the data if it achieves a PPP value that is close to zero. Nevertheless, PPP values do not have the same properties as traditional p-values and are only viewed as fit indices.

An essential part of the PPP value is its discrepancy function $D(Y, \Theta)$ that measures how far from the data $Y$ a value of the parameter vector $\Theta$ is. Given a discrepancy and samples from a suitable MCMC algorithm, the PPP value is calculated as follows:

1. At each (or some) of the MCMC samples $\theta_m$, $m = 1, \ldots, M$, do the following:
   
   (a) Compute $D(Y, \Theta_m)$.
   
   (b) Draw $\tilde{Y}$ having the same size as $Y$ using the current value $\Theta_m$ in Equation (2) or (7) (depending on which model is under consideration).
   
   (c) Calculate $D(\tilde{Y}, \Theta_m)$ and $d_m = I[D(Y, \Theta_m) < D(\tilde{Y}, \Theta_m)]$, where $I[\cdot]$ is an indicator function.

2. Return PPP = $\frac{1}{M} \sum_{m=1}^{M} d_m$.

A standard option for a discrepancy function $D(\cdot)$ for continuous data is the likelihood ratio test statistic between the factor (restricted covariance) and the saturated (unrestricted covariance) models (see e.g. Scheines, Hoijtink, and Boomsma, 1999),

$$D(Y, \Theta) = (n - 1) \left\{ \log |\Sigma(\Theta)| + \text{tr} \left[ S(Y)\Sigma^{-1}(\Theta) \right] - \log |S(Y)| - p \right\},$$

where $S(Y)$ and $\Sigma(\Theta)$ are the sample- and model-implied variance-covariance matrix respectively. Furthermore, $|\cdot|$, $\text{tr}(\cdot)$ denote the determinant and trace of a matrix respectively.

In the case of binary data, it is more convenient to reformulate the model in terms of response patterns and their observed frequencies. For binary items there are $R = 2^p$ possible response patterns, denoted by $y_r$, with corresponding observed frequencies denoted by $O_r$ where $r = 1, \ldots, R$. The probability of occurrence of a response pattern, based
on a logistic model with a parameter vector $\Theta$, can be calculated from the following equation using the fact that the $p$
variables are conditionally independent given $Z$ and, if applicable, $U$.

$$
\pi_r(\theta) = \int \prod_{j=1}^{p} \text{Bernoulli} \left( \{ y_{r, j} \mid \sigma(\eta_{r, j}) \} \right) f(Z) f(U) dU dU,
$$

(9)

In Equation (9) above, $\sigma(\eta_{r, j})$ is defined in (4), and $Z$ and $U$ are the latent components in the model considered. The integral in (9) can be computed using Monte Carlo. Having calculated the expected response patterns, a common discrepancy measure to contrast them with their observed counterparts is the $G^2$ statistic, see, for example, Sinharay (2005), defined as

$$
D(Y, \Theta) = \sum_{r=1}^{R} O_r \log \left( \frac{O_r}{n \pi_r(\Theta)} \right).
$$

3.3 Scoring Rules

The use of scoring rules aims to supplement the goodness-of-fit indices, which provide an absolute type of assessment, by a comparative assessment among the models considered. The predictive distribution of each model plays a crucial role in the calculation of scoring rules, as in PPP values, but there is a key difference: in scoring rules the predictive distribution is no longer obtained based on the entire dataset $Y$, but instead on a subset of it, the training sample $Y_{tr}$. The predictive distribution is then contrasted against the actual observations of the test sample $Y_{te}$, which is the complement of the training sample. More specifically, we define the predictive distribution as

$$
f(Y_{te} \mid Y_{tr}) = \int f(Y_{te} \mid \Theta) \pi(\Theta \mid Y_{tr}) d\Theta.
$$

A common choice for a scoring rule is the log score, small values of which indicate good performance, defined as

$$
LS(Y_{te}) = -\log f(Y_{te} \mid Y_{tr}).
$$

The log score is among a class of scoring rules with the desired property of being strictly proper. Strict propriety for a scoring rule ensures that the optimal model among the ones considered will be uniquely identified.

Quite often, and in most of the Bayesian models considered in this paper, the log score is not available in closed form since the same holds for the posterior. Instead, samples from the predictive distribution are available that allow an approximation of it. A standard approach is the mixtures-of-parameters (MP); see, for example, (Krüger, Lerch, Thorarinsdottir, and Gneiting, 2021) and in particular Table 1 of its supplementary material for a list of papers where this approximation was used. In general the MP approximation for the test data point $Y_{te}$ uses the following Monte Carlo approximation on the conditional predictive density $f(Y_{te} \mid \Theta)$, which is required in closed form, given samples
$\Theta_{m=1}^M$ from the posterior $\pi(\Theta|Y^{tr})$

$$LS(Y_i^{te}) = -\log \int f(Y_i^{te}|\Theta)\pi(\Theta|Y^{tr})d\Theta \approx -\log \left\{ \frac{1}{M} \sum_{m=1}^M f(Y_i^{te}|\Theta_m) \right\}.$$ 

For the mixed type data setting of this paper let us illustrate the MP approximation of the log score assuming that the data for each individual consist of some continuous ($C$) and some binary ($B$) observations, i.e. $Y_i = (C_i, B_i)$. Under the models of Section 2.2, $C_i$ and $B_i$ would be distributed according to the Normal and Bernoulli distributions respectively, and be independent conditional on $\Theta$. The MP approximation of the log score can then be formulated in the following way, taking advantage of the independence between $C$ and $B$ conditional on $\Theta,$

$$LS(Y_i^{te}) = -\log \int f(Y_i^{te}|\Theta)\pi(\Theta|Y^{tr})d\Theta = -\log \int f(C_i^{te}|\Theta)f(B_i^{te}|\Theta)\pi(\Theta|Y^{tr})d\Theta,$$

which leads to the Monte Carlo approximation

$$LS(Y_i^{te}) \approx -\log \left\{ \frac{1}{M} \sum_{m=1}^M N(C_i^{te}|M_c(\Theta), V_c(\Theta)) \times \pi_r(\Theta) \right\}$$

where $N(X|\mu, V)$ denotes the probability density function of the $N(\mu, V)$ distribution, $M_c(\Theta)$ and $V_c(\Theta)$ are the mean and variance of the predictive distribution for the continuous data point $C_i^{te}$ and $\pi_r(\Theta)$ is the probability of the response pattern observed in the binary data points $B_i.$ Similar formulations are possible for other types of data, e.g. ordinal or counts. We conclude this section by noting that so far we have assumed a single split between the training and test data. In order to limit the effect of peculiar splits, cross validation may be used.

### 4 Sequential Benefit Risk Analysis

#### 4.1 Motivation

As noted earlier in the paper, the MCDA score for a drug or treatment depends not only on the choice of the model for the data, but also on the data that have been made available by that time and have been used to estimate the relevant unknown parameters. For example, should more data become available, these estimates will change and so will the MCDA score. It would therefore be helpful, in the context of a benefit risk analysis, to consider a statistical inference paradigm of sequential nature, so that we can monitor potential fluctuations in the MCDA scores of different drugs and, most importantly, on differences thereof.

In terms of notation, we first assume a time order in the available data to mimic a scenario where the data are collected in real time. Ideally the time order could be the actual chronological order the data were collected, if such time stamps were recorded, otherwise a random order can be considered. The estimation procedure should ensure that this time
order has no impact on the estimates based on all the data, but the evolution of these estimates can be quite informative. We denote by \( f(y_{i:t} \mid \Theta) \) the likelihood function, according to the models in Section 2.2, based on the observations up to time \( t \), where \( t = 1, \ldots, n \). Given the Bayesian paradigm and the priors \( \pi(\Theta) \) of Section 2.3, we therefore get the sequence of posteriors \( \pi(\Theta \mid y_{i:t}) \) and consequently \( \pi(M_r(\Theta) \mid y_{i:t}) \).

### 4.2 Sequential Monte Carlo for Benefit Risk Analysis

The use of SMC algorithms for static models in Bayesian inference was initially suggested by (Chopin, 2002) and presented in more formal and general context in (Del Moral, Doucet, and Jasra, 2006); see also (Dai, Heng, Jacob, and Whiteley, 2020) for a recent work that also includes a thorough review of more specific approaches to different applications over recent years. The aim is to eventually obtain weighted or unweighted samples from the posterior distribution, although the process includes sampling from a number of intermediate distributions thus forming a sequence from the prior to the posterior. There are different ways to form the path from the prior to the posterior distributions. Here we focus on the so-called path of partial posteriors or else data-tempering approach, which is highly informative in the context of benefit risk analysis since it involves sampling from \( \pi(\Theta \mid y_{i:t}) \) for all \( t = 1, \ldots, n \).

The choice of the SMC algorithm also depends on the model and in particular the presence of latent variables in addition to static parameters. If it is possible to integrate out the latent variables analytically and obtain a likelihood function of the form \( f(Y \mid \theta) \) it is possible to use the Iterated Batch Importance Sampling algorithm (IBIS) of (Chopin, 2002). For the more general case including categorical variables, in which latent variables can no longer be integrated out and we rely on the augmented likelihood \( f(Y \mid \Theta) \), more involved schemes are needed such as the SMC \(^2\) algorithm of (Chopin, Jacob, and Papaspiliopoulos, 2012) or the modified IBIS scheme used in (Vamvourellis, Kalogeropoulos, and Moustaki, 2022).

#### 4.2.1 The standard IBIS algorithm

For the former case, in the presence of a likelihood depending only on \( \theta \), the IBIS procedure is presented in Algorithm 1. The algorithm is a rather direct application of (Chopin, 2002), beginning by drawing \( N_\theta \) samples of the parameter vector \( \theta \) from the prior distribution, called \( \theta \) particles and denoted with \( \{\theta^m\}_{m=1}^{N_\theta} \). At each time \( i \), or else data point, the particle weights are computed using the likelihood function \( \omega^m_i = f(y_{1:i} \mid y_{1:i-1} \theta^m) \). The weighted draws of the \( \theta \) particles, \( \{\theta^m, \omega^m_i\}_{i=1}^{N_\theta} \) at time \( i \) can be used to evaluate summaries of the posterior \( \pi(\theta \mid y_{1:i}) \). More specifically,
Algorithm 1 IBIS

Sample $\theta^m$, for $m = 1,\ldots,N_\theta$ from $\pi(\theta)$ and set $\omega^m = 1$. All operations are assumed to be repeated for all $m \in 1:N_\theta$.

Then at time $i = 1,\ldots,n$:

1: Compute the incremental weights and their weighted average

$$u_i(\theta^m) = f(y_i|y_{i:i-1},\theta^m) = f(y_i|\theta^m), \quad L_i = \frac{1}{\sum_{m=1}^{N_\theta} \omega^m} \times \sum_{m=1}^{N_\theta} \omega^m u_i(\theta^m).$$

2: Update the importance weights

$$\omega^m = \omega^m u_i(\theta^m).$$

3: if $\text{ESS}(\omega) < \gamma$ then

4: procedure RESAMPLE($\theta, \omega$)

5: return $\theta$

6: procedure JITTER($\theta^m, y_{1:i}$) using an MCMC algorithm

7: return $\tilde{\theta}^m$

8: $(\theta^m, \omega^m) = (\tilde{\theta}^m, 1)$

expectations with respect to that posterior, $E[g(\theta)|y_{1:i}]$, can be computed using the estimator

$$\sum_m \frac{\omega^m g(\theta^m)}{\omega^m} \rightarrow E[g(\theta)|y_{1:i}].$$

(Chopin, 2004) shows consistency and asymptotic normality of this estimator as $N_\theta \rightarrow \infty$ for all appropriately integrable $g(\cdot)$. Moreover, a very useful by-product of the IBIS algorithm is the ability to compute the model evidence $f(y_{1:i})$, to calculate Bayes factors. Computing the following quantity in step 1 in Algorithm 1 yields a consistent and asymptotically normal estimator of $f(y_i|y_{i:i-1})$

$$\frac{1}{\sum_{m=1}^{N_\theta} \omega^m} \sum_{m=1}^{N_\theta} \omega^m u_i(\theta^m) \rightarrow f(y_i|y_{i:i-1}).$$

In other words, the output of the IBIS output allows the calculation of all the summaries often obtained from the MCMC outputs, such as the posterior mean, mode, or median, 95% credible intervals, samples from the predictive distribution, but for all the posteriors $\pi(\theta|y_{1:i})$, $i = 1,\ldots,n$. Moreover it provides estimates of the model evidence for all $i$.

Note that if we were to only propagate the particles according to steps 1 and 2 of the (IBIS) Algorithm 1, the weights of the particles will eventually deteriorate with very few, or even one, of them dominating the others, which will lead to inaccurate estimates of the posterior summaries. One index that measures the quality of the weighted $\theta$ particles is
the effective sample size (ESS)

$$\text{ESS}(\omega) = \left( \frac{\sum_{m=1}^{N_\theta} \omega_m}{\sum_{m=1}^{N_\theta} (\omega_m)^2} \right)^2. $$

The protocol of the IBIS algorithm requires monitoring a degeneracy criterion, which is typically to check if the ESS is less than a pre-specified threshold $\gamma$, the violation of which triggers a two-step procedure to improve the quality of the $\theta$ particles. The first step of this procedure is to resample the $\theta$ particles with replacement, e.g. via the Multinomial distribution with the normalised weights as probabilities. At that point, we reset all weights to 1 but we end up having multiple copies of the $\theta$ particles with high weights, whereas some $\theta$ particles with low weights are removed. The purpose of this step is to drop $\theta$ particles of low weights and focus on the ones with high weights. This can be particularly helpful in the presence of local modes, since the $\theta$ particles that can potentially get trapped there will eventually be removed if the density at those modes is low. The second step of this procedure, called jittering, is to apply a MCMC algorithm with initial value at each $\theta^m$ particle to sample from the posterior given data up to that point. The MCMC algorithm is run for a few iterations and the last value of the MCMC chain, denoted by $\tilde{\theta}^m$, becomes the new value $\theta^m$. The purpose of jittering is to avoid having exact multiple copies in the set of $\theta$ particles and the use of MCMC ensures that the desirable asymptotic properties of the IBIS output are not violated; see (Chopin, 2002, 2004; Del Moral et al., 2006) for details on the relevant theory.

Hence, in order to fully define the IBIS algorithm, it necessary to provide an MCMC algorithm to sample from the posteriors $\pi(\theta|y_{1:i})$ for all $i$. In this paper, as mentioned earlier, we proceed with Hamiltonian MCMC. The code used for this paper, which is provided in the accompanying repository,\(^1\) combines the IBIS algorithm with the use of PyStan, the Python interface of the Stan language.

From a computational point of view, the most expensive step of the IBIS algorithm is the jittering step that requires to run an MCMC routine for a few iterations per $\theta$ particle. This is roughly equivalent to running several MCMC algorithms based on the smaller dataset $y_{1:i}$ for some $i$. Nevertheless, note that jittering is more likely to occur when, in the transition between $\pi(\theta|y_{1:i-1})$ and $\pi(\theta|y_{1:i})$, these two posteriors are substantially different. As a consequence, most jittering steps tend to take place for small $i$s, where the learning curve is steeper, and become less frequent as $i$ increases. This suggests that the computational cost of the IBIS algorithm is typically larger than running a single MCMC algorithm on the full data $y_{1:n}$ but usually not by much. The difference can often be eliminated by using parallel computing; more specifically running the MCMC chains of the jittering step in parallel for each $\theta$ particle.

\(^1\)https://github.com/...???
4.2.2 The modified IBIS algorithm to include latent variables

The IBIS approach taken in the continuous data is not directly applicable in cases where binary or ordinal data are available, because, in such cases, we cannot integrate out the latent variables $X$; instead, we work with the augmented likelihood $f(Y|\theta, X)$. There are two potential routes in order to construct a sequential Monte Carlo scheme in such cases. The first is to pursue the development of a scheme in the spirit of the SMC$^2$ of (Chopin et al., 2012). SMC$^2$ focuses mostly on the case of Markov-dependent latent variables and combines the IBIS algorithm with the pseudo-marginal framework of Andrieu and Roberts (2009) and, more specifically, the particle MCMC algorithm (Andrieu, Doucet, and Holenstein, 2010). The second route is to consider an IBIS algorithm on the higher dimensional parameter vector $\Theta$ as is done in (Vamvourellis et al., 2022). In this paper we proceed along the lines of the latter and tailor the methodology to the mixed type data setting of benefit risk analysis. Note that the developed approach requires a single $X$ particle for each $\theta$ particle, as opposed to $N_z$ particles in the SMC$^2$ framework.

In order to use the augmented likelihood we need to augment the set of particles in the IBIS algorithm to include the latent variables as well. For each data point $y_i$ we draw latent variable particles $\{X_i^m\}_{m=1}^{N_\theta}$ from a proposal distribution $q(.)$ and compute the weights according to $u_m = f(y_i|\theta^m, z_i^m)$.

The simplest and most standard choice for the proposal distribution is the prior $q(z) = \pi(z)$, which leads to the standard IBIS algorithm. However, this results in schemes where jittering is triggered very often (Vamvourellis et al., 2022) thus making the scheme less appealing. A much better performance is attained when if the proposal is an approximation of the posterior of $X_i$, which in our context simplifies to $\pi(X_i|y_i, \theta^m)$. The Laplace or the Variational Bayes (Blei, Kucukelbir, and McAuliffe, 2017) approximations can be used for this purpose. In this paper we proceed with the former, which we denote as $\pi^L(X_i|y_i, \theta^m)$. The IBIS procedure is presented in Algorithm 2.

The incremental weight in Algorithm 2 can be computed as follows:

$$u_i(\theta^m, z_i^m) = \frac{f(y_i|y_{1:i-1}, \theta^m, z_i^m)\pi(z_i^m|\theta^m)}{p^L(z_i^m|y_i, \theta^m)} = \frac{f(y_i|\theta^m, z_i^m)\pi(z_i^m|\theta^m)}{p^L(z_i^m|y_i, \theta^m)}$$

where

$$f(y_i|\alpha^m, \Lambda^m, \Psi^m, z_i^m) = \prod_{j=1}^{c} N\left(y_{i,1:c}(\alpha^m + z_i^m \Lambda^m)_{ij}, \psi^2_j\right) \cdot \prod_{j=p-c+1}^{p} \text{Bernoulli}\{y_{ij} | \sigma[(\alpha^m + z_i^m \Lambda^m)_{ij}]\}$$

$$\pi(z_i^m|\Phi^m) = N(z_i|0, \Phi^m) \quad \text{(prior for } z_i)$$

$$p^L(z_i^m|y_i, \theta^m) = N(z_i|\mu^L, \Sigma^L) \quad \text{(Laplace approximation)}$$
Algorithm 2 IBIS-Laplace for Benefit Risk Analysis

Sample $\theta^m$ from $p(\theta)$ and store and set $\omega^m = 1$. All operations are assumed to be repeated for all $m \in 1 : N_\theta$.

Then for point $i = 1 : N$:

1: Sample $z^m_i \sim p^L(z_i | y_i, \theta^m)$ using the Laplace approximation.

2: Compute and store $\eta^m_i$ along with $\theta^m_i$ and $z^m_i$ as $\eta(z_i, \theta) = \alpha + z_i \Lambda'$ so that every time we refer to $(\theta^m_i, z^m_i)$ we also have access to the associated $\eta^m_i$. We also compute and store the associated MCDA scores $M_r(\eta^m_i)$ using formula (1) where $r$ refers to the treatment assigned to subject $i$.

3: Update $z^m_i = z^m_i$.

4: Compute the incremental weights and their weighted average

$$ u_i(\theta^m, z^m_i) = \frac{f(y_i | y_{1:i-1}, \theta^m, z^m_i) \pi(z^m_i | \theta^m)}{p^L(z^m_i | y_i, \theta^m)} , \quad L_i = \frac{1}{\sum_{m=1}^{N_\theta} \omega^m} \sum_{m=1}^{N_\theta} \omega^m u_i(\theta^m, z^m_i), $$

5: Update the importance weights

$$ \omega^m = \omega^m u_i(\theta^m, z^m_i). $$

6: if $\text{ESS}(\omega) < \gamma$ then

7: procedure RESAMPLE($\theta, z_{1:i}, \omega$)

8: return $\theta, z_i$

9: procedure JITTER($\theta^m, z^m_{1:i}, y_{1:i}$) using an HMC algorithm with

10: return $\tilde{\theta}^m, \tilde{z}^m_{1:i}$

11: $(\theta^m, z^m_{1:i}, \omega^m) = (\tilde{\theta}^m, \tilde{z}^m_{1:i}, 1)$

with $N(x|A, B)$ denoting the probability density function of a random variable $x$ based on the $N(A, B)$ and, similarly, Bernoulli$(y_{ij}|P)$ denotes the probability mass function of the Bernoulli($P$) distribution. The last formula is given by the Laplace approximation of the posterior $\pi(z^m_i | y_i, \theta^m)$. Further simplifications may be possible depending on the model. Appendix A contains details for EZ models with separate independent factors for the continuous and binary variables.

5 Rosiglitazone Case Study

We now demonstrate our proposed framework by applying it to the study of Rosiglitazone treatment for type 2 diabetes. We first give an overview of the clinical trial setup and the data that was collected as a result of it, and lay out the MCDA framework and the parameter choices within. In Section 5.2 we describe in detail the range of models we
consider and demonstrate the proposed model choice methodology. In Section 5.3 we compute the final MCDA scores based on the estimated parameters of the chosen model. Finally, in Section 5.4, we present our proposed sequential framework. Specifically, since we do not have a dedicated sequential dataset we create one synthetically to highlight the benefits of the sequential clinical trial design.

5.1 Data and MCDA Setup

We analyse data from a clinical trial in which three different treatments were administered over a 12-week period and the difference in health outcomes was compared before and after the treatment. The data consists of 449 diabetic subjects that received one of three treatments under examination: Metformin (MET), Rosiglitazone (RSG) and a combination of the two (AVM), marketed under the commercial name ‘Avandia’. The sample sizes for each group were as follows: 146 subjects were given MET, 153 were given RSG, and 150 were given AVM.

We employed the MCDA methodology to arrive at a comprehensive score for each treatment reflecting their corresponding benefit risk profiles. The targeted efficacy outcome was a reduction of the haemoglobin and glucose levels detected in the bloodstream of each subject at the end of the treatment, compared to the level observed in the pre-treatment screening. Measurements for both haemoglobin and glucose difference from the baseline were taken on a continuous scale. The treatments under consideration are known to have relatively mild side effects, the most common of which are nausea and vomiting. For our case study we consulted with researchers who studied the drugs before and landed on 4 adverse events of note: diarrhoea, nausea, vomiting, and dyspepsia, encoded as binary outcomes that were equal to 0 unless a patient experienced the event at least once during the trial. Overall, our data consisted of 8 columns, one for the anonymised subject id, one for treatment received, two for the efficacy continuous outcomes, and four for the binary adverse events.

In this study, we adopted all the MCDA parameters, such as the partial value functions and the specified ranges of the variables in question, in consultation with researchers who have conducted similar studies of Rosiglitazone in the past using MCDA. The ranges and weights for each outcome are presented in Table 1.

Note that the continuous variables, the first two items, indicate the difference in measured haemoglobin and glucose levels respectively, at the end of the study versus at the beginning. The binary adverse events, last 4 items, measure the probability of experiencing the event in question at least once during the course of the treatment.
| Name          | Type    | Outcome Range | MCDA Weight |
|---------------|---------|---------------|-------------|
| haemoglobin   | continuous | [-6, 3]    | 0.592       |
| glucose       | continuous | [-15, 7.5] | 0.118       |
| prob(diarrhoea) | binary | [0.10, 0.35] | 0.089       |
| prob(nausea)  | binary   | [0.10, 0.25] | 0.178       |
| prob(vomiting) | binary  | [0.10, 0.20] | 0.018       |
| prob(dyspepsia) | binary | [0.10, 0.25] | 0.005       |

Table 1: Outcomes of interest and MCDA parameters.

5.2 Model Choice

Given the data and the MCDA scores, it is important to design an appropriate model in order to extract the relevant population parameters of interest. We consider a range of different models and utilise the proposed model assessment framework to choose between them. Focus is given on CFA models with two factors and a structure such that the first factor loads onto the efficacy variables and the second loads onto the risk variables, as shown in Table 2.

\[
\Lambda_{1} \quad \Lambda_{2}
\]

\[
\begin{array}{cccc}
1 & 0 \\
x & 0 \\
0 & x \\
0 & x \\
0 & x \\
0 & x
\end{array}
\]

Table 2: Hypothesised factor loading structure: the first factor $z_1$ loads onto the efficacy variables, the first two items, and the second factor $z_2$ loads onto the risk variables, last four items.

The models considered are the full saturated model, with full covariance matrix (SAT), and the independence model where the covariance matrix $S$ is fixed to be diagonal (IND). Then we considered four factor models where one factor loads to the first two items, being the efficacy variables which are continuous variables, and the second factor loads to
the remaining 4 items, the adverse events which are binary variables. The first model is the EZ model with independent factors (EZ1), and the second is the same model with correlated factors (EZ2). The approximate zero model includes a model with correlated errors for the binary data, without cross loadings (AZ1), and with cross loadings (AZ2). For all the above models, we fit also the version (denoted by ‘-p’) where the covariance structured is assumed to be common amongst the three groups. Among these options, the model that fits the data the best has to be the one with the highest predictive performance for out-of-sample data. The results are summarised in Table 3 and Table 4 for the combined log scores. Before proceeding one should also check that the model selected achieves a reasonable PPP value, typically values greater than 0.1 are not problematic and values around 0.5 indicate excellent fit. The PPP values for the top four models are shown in Table 5.

The collective results, presented in Table 3, lead to the following conclusions. First, pooling the covariance parameters results in higher predictive performance for the binary data and lower performance for the continuous data. We can verify that by comparing models in pairs while recalling that lower scoring rules indicate a better predictive performance. For example, we see that SAT underperforms SAT-p in both continuous and binary scoring rules by about 1 and 2 units respectively, EZ1 underperforms EZ1-p in both continuous and binary scoring rules by about 5 and 9 units respectively, and finally IND underperforms IND-p in both continuous and binary scoring rules by about 6 and 1 units respectively. When the covariance estimates of each of the three groups are reasonably close, as seems to be the case here, pooling benefits predictive accuracy; whereas in the opposite case the pooled model will underperform.

Second, the results suggest that the saturated model overfits the data leading to lower out-of-sample performance than the more parsimonious models. To verify that, observe that the best performing saturated model amongst all the versions (SAT, SAT-p, IND, IND-p) is SAT-p, and it is still underperforming the worst performing factor model, EZ1, by about 1 unit in the continuous part and about 6 units in the binary part. Third, we suspect that the benefits and risks are not substantially correlated, since EZ1-p fits better than EZ2-p. Recall that EZ1 is the same model as EZ2 except that the factors are assumed independent. Furthermore, we see that there is non-trivial correlation within the benefit items, and within the risk items respectively, since the IND scores worse than SAT while at the same time IND-p scores worse than SAT-p. Finally, we see the power of model parsimony as the most parsimonious of the models, EZ1-p, turns out to be the best in terms of predictive performance of all models. Before moving on with the model of choice, EZ1-p, we also confirm that it achieves a satisfactory fit. In Table 5 we compare the PPP values for all the best models so far, and confirm that all of them, including the top pick, EZ1-p, demonstrate excellent fit with PPP values near 0.5 for both continuous and binary.
In any case, the importance of model choice and assessment becomes clear. While all the models presented here are plausible, there could be substantial differences between them as far as predictive performance is concerned. Since we will be basing our final analysis on the estimated parameters of the model, choosing a model with good predictive performance is crucial to protect the validity of the final results.

| Model | Continuous-LS | Binary-LS |
|-------|---------------|-----------|
| SAT   | 1,746.65      | 573.10    |
| SAT-p | 1,742.56      | 570.91    |
| EZ1   | 1,745.47      | 564.36    |
| EZ1-p | 1,742.25      | 555.36    |
| EZ2-p | 1,742.30      | 558.53    |
| AZ1-p | 1,742.25      | 557.56    |
| AZ2-p | 1,742.31      | 558.51    |
| IND   | 1,818.57      | 576.37    |
| IND-p | 1,818.42      | 575.07    |

Table 3: Summary of out-of-sample predictive performance for all candidate models using scoring rules. Sum of log scores (LS) of 3-fold cross validation for continuous and binary data respectively.

In Table 6 we also present the parameter estimates for EZ1-p, the chosen model, on the basis of goodness of fit and out-of-sample predictive performance.

5.3 MCDA Scores

Our goal is to compute the final benefit risk score, including the parameter uncertainty that is propagated from the Bayesian model. Having access to samples from the posterior distributions of the parameters allow us to compute any metric of interest, including the MCDA scores. For each sample from the posterior $\alpha_m^r$ for treatment $r$ we compute the implied sample $s_r^m$ from the posterior of the MCDA score as follows: $s_r^m = \sum_j w_j \cdot u_j(\alpha_{jr})$. We run the batch MCMC algorithm to draw 1,000 samples from the posterior distribution of $\alpha$ and the implied posterior distribution of the scores $s_r$ for $r = 1, 2, 3$ representing the three treatment groups MET, RSG, and AVM respectively. The scores’ posterior
| Model | Combined Log-Score |
|-------|--------------------|
| SAT   | 2,344.11           |
| SAT-p | 2,339.14           |
| EZ1   | 2,335.68           |
| EZ1-p | 2,322.25           |
| EZ2-p | 2,324.49           |
| AZ1-p | 2,324.51           |
| AZ2-p | 2,324.52           |
| IND   | 2,419.31           |
| IND-p | 2,418.11           |

Table 4: Summary of out-of-sample predictive performance for all candidate models using scoring rules. Sum of log scores of 3-fold cross validation for continuous and binary data respectively.

| Model       | Continuous-PPP | Binary-PPP |
|-------------|----------------|------------|
| EZ1-p       | 0.49           | 0.36       |
| EZ2-p       | 0.49           | 0.37       |
| AZ1-p       | 0.42           | 0.35       |
| AZ2-p       | 0.44           | 0.39       |

Table 5: Model Fit Metrics for the best performing models.
| Parameter | 95% Coverage | Post. Mean | Post. Median |
|-----------|--------------|------------|--------------|
| $\Lambda_{[2,1]}$ | [1.45, 2.15] | 1.78 | 1.78 |
| $\Lambda_{[3,2]}$ | [0.05, 0.98] | 0.46 | 0.45 |
| $\Lambda_{[4,2]}$ | [-1.21, 0.40] | -0.39 | -0.37 |
| $\Lambda_{[5,2]}$ | [-1.43, 3.46] | 2.15 | 2.23 |
| $\Lambda_{[6,2]}$ | [-1.67, 3.71] | 2.36 | 2.44 |
| $\alpha^\text{AVM}_1$ | [-2.49, -2.10] | -2.30 | -2.30 |
| $\alpha^\text{AVM}_2$ | [-4.48, -3.62] | -4.05 | -4.05 |
| $\alpha^\text{AVM}_3$ | [-2.42, -1.40] | -1.87 | -1.86 |
| $\alpha^\text{AVM}_4$ | [-2.94, -1.70] | -2.27 | -2.25 |
| $\alpha^\text{AVM}_5$ | [-4.08, -1.88] | -2.83 | -2.78 |
| $\alpha^\text{AVM}_6$ | [-7.29, -3.60] | -5.19 | -5.10 |
| $\alpha^\text{MET}_1$ | [-2.03, -1.64] | -1.83 | -1.83 |
| $\alpha^\text{MET}_2$ | [-3.41, -2.49] | -2.95 | -2.95 |
| $\alpha^\text{MET}_3$ | [-1.85, -0.97] | -1.39 | -1.39 |
| $\alpha^\text{MET}_4$ | [-3.31, -1.96] | -2.58 | -2.56 |
| $\alpha^\text{MET}_5$ | [-4.91, -2.38] | -3.45 | -3.38 |
| $\alpha^\text{MET}_6$ | [-7.23, -3.63] | -5.17 | -5.07 |
| $\alpha^\text{RSG}_1$ | [-1.79, -1.41] | -1.60 | -1.60 |
| $\alpha^\text{RSG}_2$ | [-3.25, -2.38] | -2.81 | -2.81 |
| $\alpha^\text{RSG}_3$ | [-3.42, -2.08] | -2.70 | -2.68 |
| $\alpha^\text{RSG}_4$ | [-3.15, -1.87] | -2.44 | -2.42 |
| $\alpha^\text{RSG}_5$ | [-5.80, -2.87] | -4.11 | -4.04 |
| $\alpha^\text{RSG}_6$ | [-9.13, -4.53] | -6.55 | -6.45 |

Table 6: True values, 95% coverage success rate, and bias of point estimators out of 100 replications.
density distributions are shown in Figure 1. As we can see, AVM has higher mean scores compared to both RSG and MET. We computed the posterior probability that \( P(s_{AVM} > s_{MET}) = 0.99 \) and that \( P(s_{AVM} > s_{RSG}) = 0.99 \).

5.4 Sequential Analysis

In our data the subjects were pre-allocated according to a random algorithm to one of the three treatment arms ahead of the trial. For illustration purposes we now analyse the same data as if the allocation to the treatment arms was done sequentially. Specifically, we shuffled all subjects and then inter-weaved them cycling through the groups as shown in Table 7. We will demonstrate what could have been done differently if we conducted a sequential design trial, rather than a traditional pre-specified one.

To demonstrate the use of the sequential paradigm, we run our analysis inputting one subject at a time. Since we didn’t have access to the original order that the subjects were treated in, we randomised the order before interweaving the treatment groups so that we cycle through all three groups at a similar rate as we analyse one data point at a time.
Table 7: Schematic sequential schedule of synthetic reordering of the original clinical trial data.

| New Index | Subject ID | Group |
|-----------|------------|-------|
| 1         | 324        | AVM   |
| 2         | 422        | MET   |
| 3         | 124        | RSG   |
| 4         | 121        | AVM   |
| 5         | 224        | MET   |
| 6         | 231        | RSG   |
| 7         | ...        | ...   |

We computed the MCDA score of the parameters at each data point, looking for potential early stopping points for any of the treatments. In particular, we monitored the probability $P(s_{AVM} > s_{MET})$ at each data point and found that it converged to 0.99 within the first 198 patients. Of those patients, the effective sample size exposed to either AVM or MET is two-thirds as per the schedule (Table 7). That means that we were able to conclude that AVM is better than MET using information from only 66 of 150 patients, which represents about 43% of the subject sample size. Similarly, we monitored $P(s_{AVM} > s_{RSG})$ which converged to 0.99 at within the first 300, as shown in Figure 2. This translates to reaching a conclusion using 66% of the sample size. Using the sequential paradigm we would have concluded the exposure at the 300th subject, removing the need to expose subjects to the less effective treatments. This way the trials would have reached the same conclusion faster and exposing fewer subjects. Alternatively, we could have allocated more subjects to RSG and MET in order to facilitate that comparison. As shown in Figure 3, we can also see a case of an inconclusive comparison between RSG and MET. Under a dynamic clinical trial it would be possible to monitor these probabilities and allocate patients away from treatment arms whose results have converged early, such as the AVM-RSG and AVM-MET comparisons, and into groups that require more data to become conclusive, such as RSG-MET as depicted in Figure 3.

We are also able to make a sequential chart of distribution of the MCDA population scores for each treatment. Figure 4 shows the posterior mean (lines) and the 95% central quantiles (shade bands) of the posterior distributions for the final MCDA population scores for each treatment, at each point in the trial. This way we can get a high level view of the evolution of the clinical trial results, and the progression of the uncertainty quantification as more data is gathered.
Figure 2: Sequentially updated probabilities of $P(S(\text{AVM}) > S(\text{MET}))$ and $P(S(\text{AVM}) > S(\text{RSG}))$. We see that the probabilities converge to 1 within the first 300 patients. A dynamic trial could either have concluded early or assigned the remaining patients to AVM given that it is considered a better treatment based on MCDA scores.

The lines indicate that AVM (in blue) is shown to have a higher predicted score early on, within the first 100 data points. However, the fact that the uncertainty bands around the posterior mean lines of the three treatments at that point remain fairly indistinguishable indicate that there is considerable uncertainty about which treatment is better at that point. We can also see that the AVM 95% band separates from the the other two bands after about the first 300 subjects while the other two treatments remain very close throughout. At that point we are almost certain that the AVM score is higher than those of RSG and MET.

6 Discussion

In this paper we introduce a comprehensive benefit risk framework for the assessment of clinical treatments. To holistically assess competing treatments it is important to use a framework that encompasses all aspects of the treatment.
Figure 3: Sequentially updated probabilities of $P(S({\text{AVM}}) > S({\text{MET}}))$ and $P(S({\text{AVM}}) > S({\text{RSG}}))$. We see that the probabilities converge to 1 within the first 300 patients. A dynamic trial could have concluded early based on this evidence or could have assigned the remaining patients to AVM given that it is considered a better treatment based on MCDA scores.

MCDA is a general framework that can be used in association with any statistical model and any types of data. It also allows for stakeholders, clinicians, policy makers, individual patients, or others, to express their preferences through the use of weights. MCDA rests on accurate estimation of the statistical parameters of interest, which are embedded in the data generation process.

For this purpose we introduce a range of models that accommodate mixed type data and a methodology to assess the model fit. The more modelling options, the more important it is to choose the model carefully. On the one hand, more flexible models are desired in ordered to capture more features of the data, such as the dependence amongst the items. On the other hand, the more flexible the model, the more susceptible it is to overfitting. It is vital to carefully check the model fit before using the parameter estimates further. In particular, a model that overfits can produce misleading estimates, which in turn can lead to false conclusions regarding the treatment. Robust model assessment frameworks
are needed, especially when there are multiple competing models to choose from. The introduced model assessment framework does not examine cross-dependencies between binary and continuous data when it comes to goodness of fit and predictive performance as this is not a straightforward task. Finding metrics to do so is an interesting open problem which is left for further research. In this paper, we proceeded requiring good performance on both marginal parts of the data in the absence of a better alternative in line with Moustaki (1996).

In this paper we also propose a sequential clinical trial framework that can be a meaningful improvement in the process of assessing clinical treatments. This framework uses normality assumptions to derive the formulas for the sequential scheme. A promising direction for future research would be to drop these assumptions. Another assumption of the framework is the linearity of the model; it would be interesting to extend it for the non-linear models.

Regarding model fit, an alternative assessment method is that of comparing the model evidence quantities of the candidate models. These quantities are a by-product of the sequential framework we propose, without which it would
be non-trivial to compute. To pick between the two approaches we reflect on the ultimate goal of our research: ranking the treatments from best to worse. In that regard we need to pick the model that matches reality the best and whose parameters map as well as possible to the desired variables of clinical interest. In other words, we are not looking for the right model, but the most useful one. Of the two methods at hand, predictive performance is the more practical and for this reason we go with predictive performance over model evidence as the framework of choice.

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to each $z$.

Those are computed as follows:

\section*{A Laplace Approximation}

To derive the Laplace approximation of (12) we need the first and second derivatives of (13) with respect to each $z$.
\[ \frac{\partial}{\partial z} \ell(z \mid y, \theta) = -z + \sum_{j=1}^{p} \left\{ \frac{y_j \frac{\partial}{\partial \pi_j} \pi_j(z, \theta)}{\pi_j(z, \theta)} - \frac{(1 - y_j) \frac{\partial}{\partial \pi_j} \pi_j(z, \theta)}{1 - \pi_j(z, \theta)} \right\} \]

\[ = -z + \sum_{j=1}^{p} \frac{\partial}{\partial z} \pi_j(z, \theta) \left\{ \frac{y_j}{\pi_j(z, \theta)} - \frac{1 - y_j}{1 - \pi_j(z, \theta)} \right\} \]

\[ \frac{\partial^2}{\partial z^2} \ell(z \mid y, \theta) = -1 + \sum_{j=1}^{p} \frac{\partial^2}{\partial z^2} \pi_j(z, \theta) \left\{ \frac{y_j}{\pi_j(z, \theta)} - \frac{1 - y_j}{1 - \pi_j(z, \theta)} \right\} \]

\[ + \sum_{j=1}^{p} \frac{\partial}{\partial z} \frac{\partial}{\partial \pi_j} \pi_j(z, \theta) \left[ - \frac{y_j \frac{\partial}{\partial \pi_j} \pi_j(z, \theta)}{\pi_j(z, \theta)^2} - \frac{(1 - y_j) \frac{\partial}{\partial \pi_j} \pi_j(z, \theta)}{(1 - \pi_j(z, \theta))^2} \right] \]

\[ = -1 + \sum_{j=1}^{p} \frac{\partial^2}{\partial z^2} \pi_j(z, \theta) \left\{ \frac{y_j}{\pi_j(z, \theta)} - \frac{1 - y_j}{1 - \pi_j(z, \theta)} \right\} \]

\[ - \sum_{j=1}^{p} \left( \frac{\partial}{\partial z} \pi_j(z, \theta) \right)^2 \left[ \frac{y_j}{\pi_j(z, \theta)^2} + \frac{1 - y_j}{1 - \pi_j(z, \theta)^2} \right]. \]

The above can also provide the Fisher’s information matrix \( I(z \mid \theta) \), as for \( \ell = 1, \ldots, k \), we get

\[ I(z \mid \theta) = -E \left\{ \frac{\partial^2}{\partial z^2} \ell(z \mid y, \theta) \right\} = 1 + \sum_{j=1}^{p} \left\{ \frac{\partial}{\partial z} \pi_j(z, \theta) \right\}^2 \left\{ \frac{1}{\pi_j(z, \theta)} + \frac{1}{1 - \pi_j(z, \theta)} \right\} \]

\[ = 1 + \sum_{j=1}^{p} \pi_j(z, \theta) \left\{ \frac{\partial}{\partial z} \pi_j(z, \theta) \right\}^2 \left\{ \frac{1}{1 - \pi_j(z, \theta)} \right\}. \]

It remains to calculate \( \pi_j(z, \theta) \) and \( \frac{\partial}{\partial z} \pi_j(z, \theta) \). Based on the model in (6) we get

\[ \pi_j(z, \theta) = \frac{\exp \left( \alpha_j + \sum_{\ell=1}^{k} z \beta_{j\ell} \right)}{1 + \exp \left( \alpha_j + \sum_{\ell=1}^{k} z \beta_{j\ell} \right)} \]

\[ \frac{\partial}{\partial z} \pi_j(z, \theta) = \frac{\exp \left( \alpha_j + \sum_{\ell=1}^{k} z \beta_{j\ell} \right) \beta_{j\ell}}{\left\{ 1 + \exp \left( \alpha_j + \sum_{\ell=1}^{k} z \beta_{j\ell} \right) \right\}^2}, \]

which we can plug in to (10) and (11).

\section{Modified IBIS using the Laplace approximation}

To simplify the exposition we reparameterise the model into a single factor model by integrating out the first factor that loads to the continuous variables. This is possible because with two continuous variables \( y_{1:2} \) and two corresponding loadings \( \beta_1, \beta_2 \) the first loading has to be constrained to a constant, say 1, for identifiability. This leaves only one loading which can be absorbed by the mean parameter without loss of generality. Hence the original two factor model is expressed in terms of a single factor model that loads onto the binary variables only. Since there are no cross loadings, the posterior of \( z \) becomes \( \pi(z \mid y_{3:6}, \theta) \) and depends only on the binary variables \( y_{3:6} \).

We aim to approximate the posterior \( \pi(z_m^i \mid y_{i,3:6}, \theta_m^i) \). In the exposition below we drop the subscripts and superscripts to simplify notation. The posterior is

\[ \pi(z_i \mid y_i, \theta) \propto \pi(z_i \mid y_i, \theta) \pi(z_i) = f(y_i \mid z_i, \theta) \exp(-\frac{1}{2}z_i z_i^T). \]
Without loss of generality, we suppress the notation setting $y_i = y$ and $z_i = z$ to simplify the notation. We then target the logarithm of (12),

$$
\ell(z \mid y, \theta) = \log f(y \mid z, \theta) - \frac{1}{2} z z^T = \sum_{j=1}^{p} [y_j \log \pi_j(z, \theta) + (1 - y_j) \log \{1 - \pi_j(z, \theta)\}] - \frac{1}{2} \sum_{\ell=1}^{k} z^2.
$$

In order to apply the Laplace approximation on (12) we need the first and second derivatives of (13) with respect each $z$ to obtain the Laplace approximation

$$
z \sim N \left\{ \arg \max_{z} \ell(z \mid y, \theta), \mathcal{I}(z \mid \theta)^{-1} \right\}
$$

where $\arg \max_{z} \ell(z \mid y, \theta)$ can be obtained via the Fisher's Scoring algorithm or any standard optimisation routine. Appendix A contains the full derivation.

We have implemented this algorithm in Python using Stan for the jittering component in the same way as in Section 2.