# A BAYESIAN NETWORK META-ANALYSIS FOR INTEGRATING INDIVIDUAL PATIENT DATA FROM TWO ARMS TRIALS, AND AGGREGATE DATA FROM TWO AND SINGLE ARM TRIALS

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## Introduction

In the past, only published evidence from RCTs were combined in meta-analysis (MA) or in network MA (NMA) to assess the efficacy of a treatment or a network of treatments, respectively. Within the published literature, trial outcomes are typically presented as aggregate data (AD), which provides a summarized view of the average treatment effect [1,2]. The synthesis of evidence from RCTs has long been regarded as the benchmark approach, as the random allocation of treatments helps mitigate the potential influence of confounding factors.

However, in same circumstances where randomized evidence is limited, it is important to keep into account also other sources of evidence, such as single-arm trials [3] or individual patient data (IPD).
In fact, in the last years there is a growing interest in including all the available evidence (from RCTs, single-arm trials, IPD, …) in order to assess the comparative effects of different treatments, with more generalizable and transferable results.
Up to now, many methodological developments have been proposed to integrate in NMA different sources of evidence. For example, Begg and colleagues [4] proposed advancements in MA techniques to enable the integration of single-arm trials and RCTs on the AD level. Then, this approach was improved by Thom et al [5] using a mixture of AD and IPD in a NMA contrast-based setting, using baseline values as references. Hong et colleagues [6] developed an arm-based NMA method, which parametrize absolute treatment effects across trial arms, also allowing single-arm trials to be incorporated into a synthesis of RCTs in a Bayesian NMA context using AD. Then, Singh et al [7] proposed a method to synthesize IPD from single and two arms trial and AD from two arms trials.
However, a method to synthetize in a NMA evidence from two arms IPD, single-arm AD and two arms AD is

still lacking. In this study, we extend Singh et al [7] methodology to address this limitation. Then, we applied the proposed methodology to a case study, performing a Bayesian NMA to evaluate the efficacy in term of readmission and major complications of the Enhanced Recovery after Surgery (ERAS) program for patients with peritoneal surface malignancies undergoing cytoreductive surgery (CRS) with or without Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

**Aim**

This study aims to develop an arm-based Bayesian NMA framework to combine evidence coming from IPD studies with two arms and AD from studies with one and two arms.

**Methods**

We applied a three-level hierarchical Bayesian NMA, to capture heterogeneity across studies, while accounting for within-study variability. We used data from two-arms IPD, AD on RCTs and AD on single-arm trial. Four Markov Chain Monte Carlo (MCMC) chains are employed to estimate the model parameters and derive posterior distributions of treatment effects. The number of iterations was set to 2000, the warmup was set to 1000, and the thinning rate was set to 1. In the case study, only dichotomous outcomes Y were considered. For the studies with IPD, the probability of the event was modelled as $logit(p_{ijk}) = \theta_k + v_{jk}$, for i=1,..,#participants, j=1,…,# IPD trials, k=1,…,#treatments. Then, we assumed $Y_{ijk} \sim Bernouilli(p_{ijk})$. On the other hand, for the AD we modelled $logit(p_{jk}) = \theta_k + v_{jk}$, for $j=N^{IPD}+1,\ldots,$# AD trials, k=1,…,#treatments, and we assumed that the number of successes in trial j for treatment k followed a Binomial distribution, with parameters $n_{jk}$ (sample size) and $p_{jk}$. Non-informative priors were defined, in particular $\theta_k \sim N(0,10^2)$, $v_{jk} \sim N(0,\tau^2)$, $\tau \sim U(0,2)$. Furthermore, we assigned a Cholesky vague prior to the unstructured variance-covariance matrix for studies with two-arms, both AD and IPD.

For the case study, we included in the NMA retrospective and prospective cohort studies, case-control studies and RCTs comparing ERAS program adoption with standard perioperative care for CRS combined or not with HIPEC for peritoneal surface malignancies. The IPD about unpublished experience of two Italian institutes that currently apply the ERAS protocol in this setting were also included. Stan and R were used to conduct the analyses.

**Results**

In total, 8391 articles related to CRS with or without HIPEC were identified. After eliminating duplicates, 6891 abstracts underwent evaluation and screening for eligibility. Ultimately, the NMA included 24 AD studies, encompassing 5131 patients. Among these, 7 studies focused on CRS + HIPEC (6 RCTs and 1 one-arm), while 17 two arms studies investigated CRS alone. Furthermore, two Italian studies with two-arms IPD were also included, with a total of 127 patients. Results show that the adherence to ERAS program could help in minimizing postoperative complications and in avoiding readmissions (Figure 1).

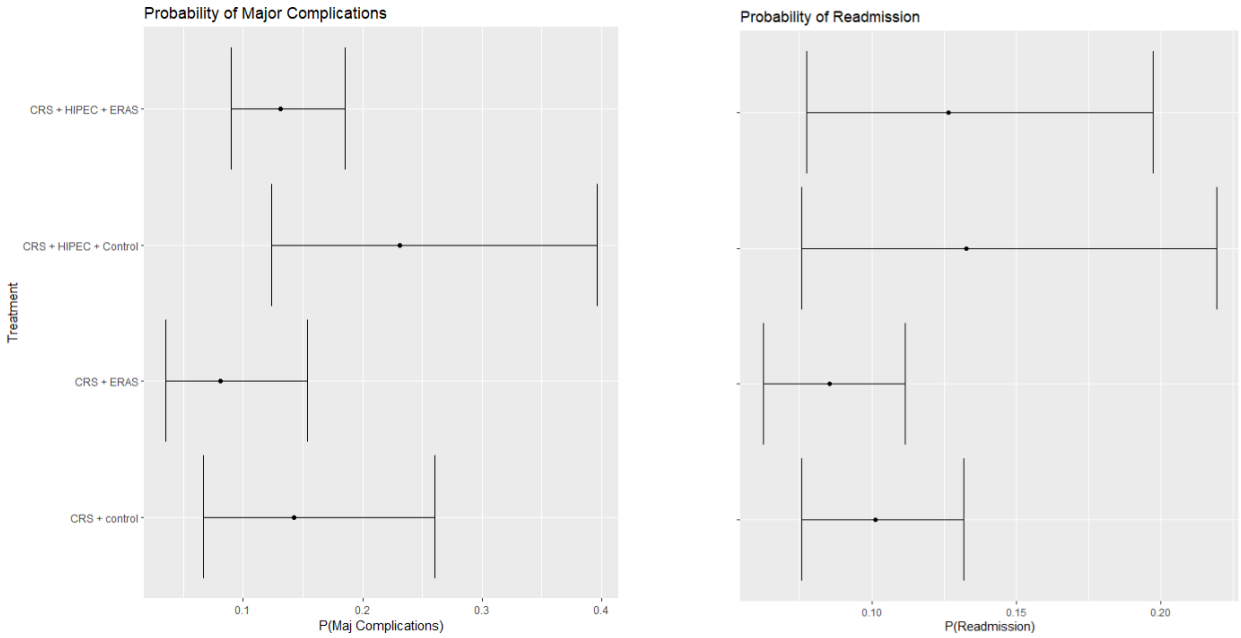


*Figure 1: Probability of Major complications and Readmission for each treatment arm.*

## Conclusion

The proposed Bayesian NMA framework provides a valuable tool for decision-making in healthcare. By synthesizing a wide range of evidence, it enables researchers and policymakers to make informed choices regarding the relative effectiveness and safety of different interventions. The framework's flexibility and ability to integrate diverse data types, i.e. from single-arm and two arms studies, both with IPD and AD, make it a versatile tool for evidence synthesis and comparative effectiveness research. The application of such proposed framework in the case study, suggests that the implementation of the ERAS protocol in patients affected by peritoneal surface malignancies undergoing CRS with or without HIPEC could provide improvements in health outcomes.

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