

Evidence Synthesis Methods for Overcoming Data Scarcity in Child Health Research.

A Focus on Antiemetic Medications for
Preventing Chemotherapy-Induced Nausea and
Vomiting in Children.

Appendices

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1 Chapter One Appendix

1.1 Protocol

1.1.1 Plain English summary of research

Background

Chemotherapy is a cancer treatment that can cause nausea (feeling sick) and vomiting (being sick). These unpleasant side effects are a problem for children and young people who are being treated for cancer, even though there are effective anti-sickness medicines available.

Clinical trials investigate how well these anti-sickness medications work. However, there are many more trials in adults than in children, meaning we know less about how well different anti-sickness medicines prevent nausea and vomiting in children and young people.

Children and young people are therefore not always given the best anti-sickness medicines and sometimes must wait years before new anti-sickness medicines given to adults become available for them. This means that children and young people often continue to feel and be sick during their chemotherapy treatment.

Aims

This research aims to find out which medicines work best at stopping nausea and vomiting in children and young people being treated for cancer, by gathering, reviewing and analysing all the clinical trials that investigate this.

When there is not enough evidence from these clinical trials to understand which anti-sickness medicines work best, I will see if research done with adults could improve our understanding of how well these anti-sickness medicines stop nausea and vomiting in children and young people.

Design and methods

I will use data from clinical trials done in children and young people to compare each anti-sickness medicine with every other, to find out which works best. Where there are no or few clinical trials comparing certain anti-sickness medicines in children and young people, I will find clinical trials comparing them in adults and use statistical methods to see if the data from these adult trials can be used to reliably predict how well they work in children and young people.

I will also ask for the 'raw' patient data from clinical trials and use this to improve understanding of outcomes such as nausea and explore whether some patients might benefit more from anti-sickness

medicines than others.

Patient public involvement

I will work with patients (primary school age or older, or adults who were treated for cancer when they were a child or young person) and carers who have experienced nausea and vomiting during cancer treatment. Together we will prioritise which outcomes the project will look at, decide how to share the findings with patients and their families and present the findings at a conference. This will involve face-to-face activities and online meetings.

To help young people and adults be involved, I will provide training for them on the research methods used in the PhD project. I will work with everyone involved to understand how we could learn from their experience of being part of the team, to improve such projects in the future.

Anticipated impact

Findings will provide information to help healthcare providers decide which medicines to prescribe. They will help patients and carers to understand their treatment options, without the need for more clinical trials in children. Evidence from adult trials may, in future, help to reach conclusions about new anti-sickness medicines for children and young people sooner, and minimise the amount of evidence needed in children and young people; as, instead, smaller clinical trials could be used to confirm findings.

Dissemination

To ensure findings reach those affected by childhood cancers, I will work with patients and their carers to create two short animation films and an easy-to-read summary, which will be shared in hospital wards and cancer charities to reach a wider patient group. To reach healthcare providers and researchers, I will publish the findings as peer-reviewed journal articles and present at relevant conferences.

1.1.2 Background

What problem is being addressed?

Nausea and vomiting are common side effects of many cancer treatments that continue to be a problem for children undergoing treatment for malignancies. These side effects have profound physical consequences, including dehydration, electrolyte imbalance, weight loss, anorexia, weakness and increased susceptibility to infection (Phillips RS, 2016). They also have an adverse psychological

impact; in particular, nausea is commonly identified as being a distressing aspect of chemotherapy treatment (Hedstrom M, 2003). The use of more intensive chemotherapy agents means that ~70% of paediatric patients receiving chemotherapy still experience these side effects, despite the development of new antiemetic therapies (Dupuis et al., 2017).

Chemotherapy-induced nausea and vomiting (CINV) is described in three clinical phases: anticipatory, prior to chemotherapy administration, acute, within 24 hours of chemotherapy administration and delayed, 1 to 7 days after chemotherapy administration. As anticipatory CINV appears to be a conditioned response to previous CINV experienced in the acute and delayed phases, adequately controlling these from the first chemotherapy administration may prevent subsequent anticipatory CINV (Phillips et al., 2010, Phillips RS, 2016).

CINV can be prevented through the appropriate use of antiemetic therapies, including benzodiazepines, cannabinoids, corticosteroids and 5-HT₃ antagonists, cyclizine, dopamine blockers, levomepromazine and NK1 antagonists. These have different modes of action, effectiveness and side effect profiles (Patel et al., 2019)(Phillips RS, 2016).

Most research supporting the use of these agents for the prevention of CINV has been conducted in adults. The efficacy, safety, and dosing of these therapies, whilst well-established in adults, cannot simply be assumed in children due to potential differences in the way that medicines are absorbed, distributed, metabolised, and excreted in the body (Gamalo-Siebers et al., 2017). Randomised controlled trials (RCTs) including children are therefore important in establishing the exposure-response relationship and providing sufficient evidence to support safe and effective use in children. However, recruiting children to supportive care RCTs is challenging, even in paediatric oncology, where trial enrolment is historically high. Fewer patients are eligible for inclusion due to lower disease incidence in children (Agency, 2018)(Gamalo-Siebers et al., 2017), and children, young people and/or their parents/carers may not wish to participate in trials assessing a drug of unknown efficacy.

Due to fewer RCTs comparing antiemetics in paediatric populations, much less is known about the relative efficacy of these therapies in children, including optimal dosing and scheduling. Existing studies in paediatric populations lack direct comparisons between different agents and classes and often report outcomes differently. Furthermore, most outcomes relate to vomiting, rather than nausea, which may be more distressing to patients (Phillips RS, 2016).

The overall picture of which antiemetics are most effective at preventing CINV in childhood remains incomplete, and estimates of efficacy, imprecise. This has resulted in variation and inconsistencies in

prescribing, often based on clinician experience and personal preference, rather than research-based evidence(Phillips RS, 2016)(Ruggiero et al., 2018). Furthermore, new and potentially more effective treatments, e.g. aprepitant (Agency, 2008)(Agency, 2015) are usually licensed in adults many years before children have access to the same therapy(Agency, 2018).

How will this research fill an evidence gap

This research will provide better estimates of the relative effects of different antiemetic medications for preventing CINV in children and young people undergoing treatment for cancer by using a systematic review and Bayesian network meta-analysis (NMA). These methods will make ‘indirect’ comparisons between treatments, where head-to-head trials do not exist, thus reducing the need for additional paediatric RCTs.

Where data from children are sparse, Bayesian methods will be used to borrow strength from the information in adult trials to make inferences about antiemetic efficacy in children and young people. This could improve the certainty of the relative effect estimates in children, and if these methods are shown to be reliable, be used alongside confirmatory trials in the future to reach faster and more robust conclusions regarding the paediatric efficacy of antiemetics already approved for use in adults.

To further maximise the usefulness of the existing evidence, IPD will be sought from recent RCTs of antiemetics in children and adults. These data will be used to estimate treatment efficacy for multiple outcomes simultaneously, to improve our understanding of poorly reported outcomes relating to nausea. IPD will also be used to explore who might benefit most from antiemetic therapies, i.e., how patient characteristics, such as age and emetogenicity of chemotherapy, alter treatment effect.

The methodologies considered within this PhD project will inform the development of a framework for extrapolating efficacy data from adult trials to children, which may be applied in other fields of paediatric medicine, where RCTs are equally lacking.

Why is the research important to improve the health/well-being of the patients/ health care services?

This proposed research will make an important contribution to improving the lives of children with cancer by supporting better-informed decisions about which antiemetics to prescribe and for whom.

Prevention of CINV is important as it is one of the most distressing symptoms for children undergoing cancer treatment and is associated with a significant deterioration in quality of life (Hedstrom M,

2003). The James Lind Alliance priority setting partnership for Teenage and Young Adult Cancer (2018)(Alliance), identified ‘understanding what interventions can reduce adverse short-term and long-term effects of cancer treatment’ as a top two priority for future research.

Patient public involvement (PPI) done to support the development of this application suggests that some children undergo several rounds of chemotherapy, trying many different antiemetics/combinations of antiemetics, before their CINV is controlled. One parent said, “*My son had a lot of problems getting anti-sickness right, I don’t think we ever did, in the five years of (chemotherapy) treatment*”. Another parent said, “*My daughter had nine cycles of chemo(therapy)... three of them needed a post-chemo hospital admission for IV (intra-venous) fluids because she couldn’t stop vomiting*”, highlighting the significant difficulties faced by patients and their families.

The PPI work also highlighted that antiemetics can be associated with side effects, and even for those patients for whom antiemetics are effective, CINV may still be experienced with sub-optimal medication scheduling.

RCTs comparing all available antiemetics for the prevention of CINV in children would take many years to conduct and require substantial resources and costs. To address these important issues sooner, there is a need for alternative approaches and improved methods which make best use of existing research.

Review of existing evidence

This PhD will build on two Cochrane reviews(Phillips et al., 2010)(Phillips RS, 2016), addressing the unanswered questions these raise. The 2010 Cochrane review made direct comparisons using data from 28 studies to assess the efficacy of antiemetic medication for anticipatory, acute, and delayed nausea and vomiting in children and young people receiving chemotherapy. An update was published in 2016, which included eight additional studies, but conclusions remained largely unchanged.

The 2016 Cochrane review suggested that 5-HT₃ antagonists (more modern antiemetics) were more effective than older antiemetics (even when combined with a steroid). Of the 5-HT₃ antagonists, granisetron and palonosetron may be more effective than ondansetron, but this was based on limited evidence, and the authors cautioned against firm conclusions. Overall, direct comparisons of different antiemetics and classes of antiemetics were lacking, and data were sparse. There is no complete or clear picture of which antiemetics are most effective in preventing CINV in children and young adults, including which doses and/or treatment schedules are optimal. The review also highlighted a

need to clarify the role of new agents to prevent CINV. The scarcity of data in this paediatric population highlights the need for alternative methods (Nikolaidis G.F 2021) to maximise the usefulness of the existing evidence base.

In 2020, an IPD pooled analysis (Dupuis LL, 2020) of RCTs of aprepitant or fosaprepitant for prevention of CINV in paediatric patients, applied regression modelling to assess factors, e.g., patient age, *associated* with CINV control when receiving moderate or highly emetogenic chemotherapy. The research did not investigate whether *interactions* exist between patient characteristics and the antiemetics; therefore, it remains unknown the extent to which patient characteristics alter the relative efficacy of these medications in children and young people. To address this and determine which patients may benefit from most antiemetics, an IPD approach investigating interactions is needed.

1.1.3 Research Aims

The proposed project aims to identify and synthesise clinical trial evidence on the efficacy of eight modern antiemetic medications for the prevention of CINV in children and young people using NMA to determine which agents work best and for whom. Where paediatric evidence is lacking, the project will use Bayesian methods to determine the appropriateness of using data from adults to make inferences about the efficacy of these medications in children and young people.

Specifically, this project will consider the following:

Stage one (using aggregate data from RCTs of eight modern antiemetic medications):

1. What is the relative efficacy and ranking of eight modern antiemetics for preventing CINV in children and young people being treated for cancer?
2. Can adult clinical trial data be used to supplement paediatric trial data and improve the certainty of relative effect estimates in children and young people?
3. Can adult clinical trial data be used to reliably predict the relative effect in the paediatric population for antiemetic therapies not yet licenced to treat CINV in children and young people?

Stage two (using patient-level data from recent RCTs):

4. How effective are antiemetic medications at preventing *both* nausea and vomiting in children and young people?

5. A) Do patient-level characteristics, such as cancer type, sex, age and emetogenicity of chemotherapy, alter antiemetic efficacy in children and young people?

B) Do patient-level characteristics alter antiemetic efficacy differently in adults and children/ young people, and if so, how can this information be used to improve predictions of relative effect in the paediatric population?

Findings will inform the development of a generalised framework for incorporating adult research evidence with paediatric research evidence to support decision-making.

1.1.4 Project Plan

Stage one (analysis of aggregate data)

Stage one of this PhD will use the published aggregate data from RCTs of modern antiemetics for the prevention of CINV in children and adults. As older antiemetics have been found to be less effective than newer agents in children (Phillips RS, 2016), the focus will be on those modern antiemetics currently recommended for children: Ondansetron, Dexamethasone, Aprepitant, Fosaprepitant, Levomepromazine, Metoclopramide, Palonosetron and Olanzapine (Group, 2018) (Dupuis et al., 2014) (Patel et al., 2017). A clinical advisory panel will be consulted to confirm these choices.

The systematic reviews will be registered, following best practice ((CRD), 2008), and be reported in accordance with the relevant Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(s).

Identifying clinical trials

Relevant RCTs identified using a systematic bibliographic search of databases and trial registers will be screened for inclusion against pre-defined criteria. Two reviewers will independently screen in two stages, firstly of the title and abstract to identify potentially relevant RCTs and full texts.

Assessing risk of bias

RCTs will be critically appraised independently by two researchers using the Cochrane Risk of Bias tool version 2 (Higgins, 2019).

Outcomes

Preparatory work has identified the following outcomes reported in clinical trial publications.

Complete control (i.e., zero episodes) or partial control (one or two episodes) of:

- anticipatory nausea/vomiting (before chemotherapy)
- acute nausea/vomiting (up to 24 hours after chemotherapy)
- delayed nausea/vomiting (after 24 hours after chemotherapy)
- side effects of antiemetic medications, e.g., dry mouth, constipation, indigestion (reported in clinical trials)

Which outcomes matter most to patients?

To prioritise these outcomes for analysis, I will consult patients and their carers to understand which matter most to them. This will be done during:

- 1) A face-to-face advisory meeting (~2 hours), at the University of York, inviting four local carers of patients and or adults who were treated for cancer when they were a child.
- 2) An online meeting, over Zoom (~1 hour, to avoid Zoom fatigue), inviting four adolescents (aged 12-18).
- 3) A play-based group activity held at Leeds Children's Hospital, inviting four children of primary school age (aged 5-11) undergoing cancer treatment. Candlelighters charity, who support Yorkshire families facing children's cancer, is experienced in working using creative methods with this group and will help to facilitate the activity. Methods will be informed by the training course 'Research with children and young people'.

If the outcomes that patients and their carers deem important are not reported in clinical trial publications but have been recorded in the trials, IPD may offer an opportunity to explore these additional outcomes.

Question 1: What is the relative efficacy and ranking of eight modern antiemetics for preventing chemotherapy-induced nausea and vomiting in children and young people being treated for cancer?

Using only RCTs in children, I will apply Bayesian NMA to produce a coherent set of estimates of the efficacy of any treatment in the network, relative to any other, for each outcome.

Data analysis methods

Antiemetic efficacy for the outcomes will be analysed on an intention-to-treat basis, that is, participants will be analysed according to allocated treatment, irrespective of whether the treatment was received.

Analyses will be conducted using a Bayesian Markov chain Monte Carlo method (implemented in OpenBUGS through R). Where there is both direct and indirect evidence, i.e. where there is a loop in the network, I will check the assumption of evidence consistency, i.e. that the estimates derived from the direct evidence do not contradict those derived from the indirect evidence (Dias S, 2018).

I will compare models that assume all studies estimate the same effect (common/fixed-effect), to models where effects of studies are assumed to be exchangeable or similar (random-effects models), using the deviance information criterion and taking into account any lack of fit for individual data points and changes in the estimated heterogeneity. The ability of each model to predict the observed data will be checked graphically and by comparing the mean residual deviance to the number of unconstrained data points (which should be roughly equal if the model predicts the data well) (Dias S, 2018). Using the favoured model(s), a treatment ranking (from best to worst) will be produced for each outcome.

Networks may be disconnected, and where connected, data may be sparse. If this occurs, I will consider alternative methods, such as a class model, where similar treatments are grouped and assumed to have a similar effect. I will consult the clinical advisory panel to determine whether these assumptions are appropriate.

Exploring heterogeneity

The efficacy of different doses and scheduling of antiemetic therapies will be explored through their inclusion as separate nodes in the NMA.

Question 2: Can data from clinical trials in adults be used to supplement paediatric trial data and improve the certainty of relative effect estimates in children and young people?

Using RCTs in children and adults, I will apply a Bayesian (NMA) information-sharing model to extrapolate evidence from the adults to the children's network.

Preliminary investigations during my pre-doctoral fellowship

I have established that comparisons with few data in the children's network have corresponding clinical trials in adults, e.g. granisetron and dexamethasone vs palonosetron and dexamethasone (Phillips RS, 2016, Patel et al., 2019, Roila et al., 2016)(Sutherland et al., 2018),(Popovic et al., 2014) (supplemental material, figure 1), indicating an opportunity for information sharing between the networks.

Several different information-sharing models exist, each using a different main assumption to relate evidence on children and adults (Nikolaidis G.F 2021). The decision which to apply has been informed by preparatory comparison models using aggregate data from RCTs of aprepitant vs. placebo.

Results suggested a model relating the relative effect estimates in adults and children using a 'functional relationship' (e.g., through meta-regression) is likely to be most appropriate, as it allows data from clinical trials in adults to provide additional evidence for the paediatric population, without assuming that the relative efficacy is identical. Instead, differences in clinical response between the two populations are estimated, given the data.

I also identified a difference in baseline risk between RCTs of adults and children. Binary outcomes will therefore be analysed using risk ratios, as this measure is less susceptible to differences in the distribution of prognostic factors across trials compared to odds ratios (Higgins JPT).

Data analysis methods

I will use a 'functional relationship' model (Nikolaidis G.F 2021) to analyse the primary efficacy outcomes and one side effect of antiemetics in OpenBUGS through R (and consider an extension to this model that prevents the data from the children from affecting the estimate of the adult

population). The appropriateness of applying these models will be assessed by their ability to predict the observed data (described in Question 1).

I will determine whether information sharing has improved the certainty of the estimates of relative efficacy of antiemetics in the paediatric populations, by comparing estimates with those from the NMA, including children only. Should antiemetic efficacy remain uncertain in children, the information generated should help inform prioritisation of future clinical trials.

Question 3: Can data from clinical trials in adults be used to reliably predict the relative effect in the paediatric population for antiemetic therapies not yet licenced to treat CINV in children and young people?

A case study of olanzapine (an antipsychotic medication approved for use to treat CINV in adults but not children) will explore whether adult data can reliably predict the relative effect in children and young people.

Data analysis methods

I will use the model applied in question two to quantify differences in the clinical response between adults and children for every treatment comparison present in both of the networks and determine whether these differences are similar or fall within a certain range, across treatment comparisons or classes of treatments.

If the clinical response between adults and children is similar across treatment comparisons*, I will use this information, along with the relative treatment effects of olanzapine in adults, to estimate a prediction interval of the treatment effect we would expect to see in a new trial of olanzapine in children.

To assess the reliability of predictions, I will compare the estimate to the treatment effects from two recent paediatric RCTs of olanzapine (and others completed during my PhD). I will discuss with clinical experts how this evidence could support future approval of new antiemetic therapies in children and young people, with confirmatory research instead of full clinical trial programmes.

*Should the clinical response between adults and children be too dissimilar (advice on this will be sought from the clinical advisory panel), extrapolation may be appropriate. In this case, I would use the information generated to make recommendations for the priority of future clinical trials.

Stage two (analysis of individual participant data)

In stage two of this PhD, IPD will be obtained from recent RCTs of aprepitant, fosaprepitant, and olanzapine in adults and children (identified through systematic searches in stage one. Recent trials are prioritised as IPD is more likely to be available.

Acquiring individual participant data

Trial investigators will be asked whether willing to share clinical trial data. IPD on patient characteristics and outcomes, including those deemed important to patients and their carers, but not reported in clinical trial publications, will be requested.

From publicly funded RCTs, I have received in principle agreements to share data from 5/5 trials in children and 5/16 in adults. All IPD will be provided in an anonymous standardised format (or recoded as required).

Eleven industry-funded RCTs (9 in adults and 2 in children) are held within the Merck data repository. An application for access to these data (drafted during my pre-doctoral fellowship) will be submitted at the beginning of the PhD. The Merck data sharing policy states that sometimes IPD from trials needs to be analysed within the company's data sharing platform. If the case, estimates (and covariances where required) will be derived for each study and exported to be analysed with the other trials.

A secure online transfer will be used to receive data, which will then be held in a password-protected area of the CRD server for the duration of the project. Access to the data will be limited to myself and project supervisors. Copying data to laptop computers or memory sticks will be prohibited.

Assessing consistency with publications and the quality of the data.

Baseline data and primary outcomes will be compared to those in trial publications for consistency. IPD quality will be assessed by examining the integrity of randomisation and missing data patterns. IPD from clinical trials judged to be of insufficient quality or completeness will be excluded from the analyses.

Question 4: How effective are antiemetic medications at preventing both nausea and vomiting in children and young people?

Nausea outcomes are less commonly reported in clinical trials of children and young people than vomiting (2/5 paediatric RCT publications of aprepitant report no outcomes related to nausea). These outcomes may be present in the IPD; however, if they are missing, estimating treatment efficacy for multiple outcomes (i.e., the probability of preventing outcomes relating to both nausea *and* vomiting) may help to improve our understanding of antiemetic efficacy for preventing nausea in children and young people. This is because, if outcomes are missing in certain trials, the synthesis of one outcome utilises (via correlation) available data from the other outcome and vice versa.

The analyses estimate both between-study correlation, as the outcomes may be more similar from one trial compared to another and within-study correlation, as individuals contribute to both outcomes, within a study; the latter requires IPD to estimate.

These analyses will use IPD from the RCTs in children. Outcomes patients and carers deemed important in stage one, but are not reported in clinical trial publications, will also be prioritised in these analyses (should they be available in the IPD).

Data analysis methods

I will explore using bivariate IPD meta-analysis (Riley et al., 2015) (using the R package ‘mvmeta’(Gasparini et al., 2012)) or Bayesian multivariate NMA methods (implementing code from (Achana FA, 2014)(Owen, 2020) in OpenBUGS through R).

**If required, I will explore alternative methods of dealing with missing data, such as multiple imputation.

Question 5: Do patient-level characteristics, such as cancer type, sex, age and emetogenicity of chemotherapy, alter antiemetic efficacy in children and young people?

I will firstly use IPD from the RCTs in children to estimate within and between study heterogeneity in the treatment effect (if the full IPD are not available, then summary data (interaction coefficients), will be requested from clinical trials). I will then consider incorporating aggregate data into these analyses, as these may improve the precision of the results (Donegan et al., 2013).

Data analysis methods

I will use Bayesian IPD network meta-regression (using the package ‘multinma’ in STAN through R(Phillippo, 2021)) to regress patient-level characteristics (covariates) against patient-level outcomes within each study and estimate a ‘treatment-covariate interaction’, i.e., the extent treatment effect varies between individuals with and without a characteristic. This will be done for the efficacy outcomes and one side effect of antiemetics, which were prioritised by patients and their families in stage one.

I will then explore the use of multi-level network meta-regression (ML-NMR) (using the package ‘multinma’ in STAN through R)(Phillippo, 2020) to incorporate aggregate data (from trials where IPD is not available, including those used to address question one) into these analyses. This will require baseline characteristics of interest to be reported in clinical trial publications.

Question 6: Do patient-level characteristics alter antiemetic efficacy differently in adults and children/ young people, and if so, how can this information be used to improve predictions of relative effect in the paediatric population?

Here, I will explore methods for sharing information between adult and children’s IPD networks. As in question five, these analyses will consider IPD only before considering the incorporation of aggregate data. IPD from RCTs in both adults and children will be used.

Data analysis methods

I will use the models applied in question five to explore treatment-covariate interactions using IPD from RCTs in adults. I will compare the interaction estimates with those from children to determine whether they are similar and consult with the clinical advisory panel on the extent any differences would matter in practice.

I will then explore the possibility of incorporating aggregate data into the analyses to understand if differences in treatment-covariate interactions between adults and children are consistent across treatment comparisons.

Following this, I will explore how this information could be used to improve predictions of new antiemetic therapies, such as olanzapine. This may involve including information from the adults’ network as a prior distribution for the regression coefficient in the children’s network, and then using the children’s network to produce a prediction interval (or separate prediction interval for each subgroup).

Developing a framework for incorporating adult clinical trial information

The consideration and application of methods during this project will inform the development of a framework for incorporating relevant evidence from studies in adult populations with evidence from paediatric studies in extended networks to inform paediatric decision-making.

Interpreting the findings from a patient perspective

To understand what the findings mean to patients, I will hold two online meetings, inviting four carers of patients and/or adults who were treated for cancer when they were a child (providing an involvement opportunity to adults who were unable to travel to the University of York). The first meeting (in year three) will develop a rapport with those involved and share project achievements and interim findings. I will begin conversations about how patients and their carers might use the information arising from the research.

The second meeting (in year four) will discuss what difference the final findings would make for patients in practice, and based on this, which information should be included in short animation films and easy-to-read summaries. Two additional meetings following the same format will involve four young people (aged 12-18).

I will not involve primary school-aged children in these activities, as an understanding of potentially complex findings will be required. Instead, I will invite four children to watch the animated film during an online event and ask their views on the content and animation. The Candlelighters charity will help to facilitate this event.

Dissemination of findings

PPI during the development of this grant application have informed these methods.

Patients and carers

To ensure patients and carers are aware of their treatment options, I will create two short animation films to share the findings (one for adolescents/ adults and one adapted for children of primary school age) and an easy-to-read summary to be shared in hospital wards/clinics (the content of these will be informed by PPI). I will also talk at a Bone Cancer Research Trust event to reach individuals who may not usually engage with academic research.

Cancer charities

I will engage with cancer charities, including contacts at Candlelighters, to share the animation films via their websites and social media channels.

Healthcare professionals

To reach healthcare professionals so that findings can support better-informed decisions about which antiemetics to prescribe and for whom, I will submit presentations to conferences, including a co-presentation with a patient (young person or adult with personal experience of CINV) or carer at the Childhood Cancer Conference.

I will connect and share findings with paediatric oncology units in the UK and Ireland through the Children's Cancer and Leukaemia Group (CCLG) professionals' network and produce an open-access, peer-reviewed publication.

Academic and research audiences

To reach an academic audience who may apply the methods of this project in other fields, I will publish findings in peer-reviewed journal articles, including an article using the clinical work as an example of the application of the methods. I will also submit presentations to the International Society of Paediatric Oncology (SIOP), the Multinational Association of Supportive Care in Cancer (MASCC).

Funders

The outputs of the Fellowship will be fed back to the NIHR Academy.

1.1.5 Ethics

This PhD project will collect and synthesise data from previous clinical trials in which the trial investigators have already obtained ethical approval and informed consent. IPD will be obtained and held securely. Therefore, I anticipate (as for other CRD IPD projects), formal ethical approval will not be required. This will be confirmed with the Chair of the University of York Department of Health Sciences Ethics Committee, prior to starting.

PPI does not require formal ethical approval; however, due to the sensitive nature of the topic, I will gain consent from children who are involved, letting them know that they are not required to take part in the activity, and I will ensure carers are comfortable with their involvement in the activity. Participants of all meetings will be provided with support as required.

1.1.6 Success Criteria

Sufficient recruitment to PPI meetings and activities.

I will advertise opportunities early in the fellowship and consider methods to improve the recruitment of young people. Individuals involved in the development of this grant application have expressed an interest in being involved in this proposed PhD project.

Obtaining sufficient IPD

IPD will be requested early in the research process. Undertaking the fellowship over five years will also help to ensure there is sufficient time to obtain and analyse IPD. In principle, agreements from trial investigators have been obtained during my pre-doctoral fellowship.

1.1.7 Patient and Public Involvement.

Five parents of children who had undergone treatment for cancer and one adult with experience of CINV as a young person have been involved in the development of this grant application, four who attended an online advisory meeting and two who reviewed the plain English summary of this application. The involvement was funded by the Research Design Service for Yorkshire and the Humber.

The advisory meeting sought to understand whether those involved considered the proposed research valuable, how they would feel about being involved in aspects of the research project (including how they would like to learn about research methods as part of the involvement) and how they would like to hear about the results of the study.

The experiences shared in this meeting have reconfirmed the importance of effective management of nausea and vomiting and informed the methods and approaches to be used in engaging patients and carers in the research (Table 1).

Table 1. Feedback shared during an advisory meeting and the impact this has had on the method of this proposed PhD project.

Feedback	Impact on methods in the PhD project
Adolescents may feel influenced by the presence of carers and should have an opportunity to be treated as individuals.	Meetings with adolescents will be held separately from their parents
Adolescents have time commitments associated with school, and travelling to a venue may be a barrier to recruitment.	Meetings with adolescents will be held online
Advertising at events such as ‘Find your Sense of Tumour’ organised by the Teenage Cancer Trust may improve recruitment of adolescents.	PPI recruitment will involve advertising at this event
Training about systematic reviews and network meta-analysis would be valuable as the topic area is challenging. People learn differently	Training will be delivered through a variety of methods to accommodate individual learning styles.
Short animation videos summarising the findings of the study would be helpful for both children and parents, as these are more easily shared with friends on social media.	Dissemination of findings will include a short animation film for adults as well as children.

Of those involved in this preparatory activity, three have expressed interest in being involved in the research proposed.

How will the public be actively involved in the proposed research, including any training and support provided?

I will continue to involve both carers and patients who have experience of CINV to prioritise the project outcomes and to interpret and disseminate the findings. I will advertise involvement opportunities on social media platforms for local and national children’s cancer charities (Candlelighters, CCLG and the Teenage Cancer Trust). I will invite individuals to work with me through the fellowship, but will recruit separately for each meeting if retention is an issue.

I will provide information packs prior to involvement (including for carers when activities involve children), detailing the purpose of the project, project plan, anticipated time commitment and nature of the involvement and payments and reimbursements.

Training

Teaching on systematic reviews and network meta-analysis will involve:

- A document/ short informational video prior to the meeting and a short presentation within the meeting, explaining what a systematic review is/ what are their limitations.
- A glossary of common 'jargon'.
- An opportunity to send in questions beforehand, to be answered at the start of the PPI meeting.

Material will be adapted for young people as needed.

Evaluating patient, public involvement and reporting study progress

I will request feedback forms after each activity (adapted for children involved) and provide regular updates of interim findings. A final online evaluation meeting for adults and young people will reflect on how we learn from the experience of those involved, to improve such projects in the future. This may be sufficient to warrant a specific academic report, which will be completed following the GRIPP2 template.

Support for those involved.

Dr Bob Phillips (see research support section) will support the PPI meetings. Bob has extensive experience in facilitating these activities and providing support to children and young people who are undergoing treatment for cancer, and their families. PPI contributors may be on or post-treatment and will therefore have ongoing access to emotional support within their follow-up (which is lifelong for those treated for cancer at less than 18 years). For face-to-face meetings with adults, I will budget for childcare costs to support adults with younger children.

1.1.8 Research support

Professor Sofia Dias.

Sofia Dias is a professor in health technology assessment. She is a statistician specialising in Bayesian evidence synthesis methods, with a particular interest in methods for network meta-analysis. Sofia has previously supervised a PhD student to completion at the University of Bristol.

Sofia will support me in developing and applying Bayesian network meta-analysis models and interpreting the outputs from statistical analyses. She will provide technical support and guide my learning of relevant statistical software packages. She will also support me to apply my research

methodology training within the PhD and to consolidate my learning through relevant departmental projects.

Dr Bob Phillips.

Bob Phillips is a senior clinical academic at the Centre for Reviews and Dissemination (CRD) and an honorary consultant in paediatric and teenage-young adult (TYA) oncology at Leeds Children's Hospital. Bob Phillips specialises in supportive care management, translation of research into clinical practice and evidence synthesis, including IPD meta-analysis. Bob has previously supervised three PhD students to completion; one at the University of Melbourne, one at the University of York and one at the University of Leeds, with a fourth due to complete this 2021.

Bob Phillips will provide clinical and methodological support throughout the PhD Specifically, supporting me in managing the collection and analysis of IPD and in interpreting the findings of the PhD from a clinical perspective, including how the findings may influence current clinical practice.

Bob will also help to facilitate the PPI activities as well as provide support to children and young people who are undergoing treatment for cancer.

Professor Lesley Stewart

Lesley Stewart is Director of the Centre for Reviews and Dissemination and specialises in evidence synthesis, particularly systematic review and IPD meta-analysis. Lesley previously supervised my NIHR Systematic Review Training Fellowship and will provide additional methodological support and mentorship, particularly in the collection, evaluation and synthesis of IPD.

Dr Amy Mitchell, Dr Hugh Bishop and Mrs. Eloise Neumann

Amy Mitchell is a Consultant Paediatric and Adolescent Oncologist at Oxford University Hospital; Hugh Bishop is a Consultant Paediatric Oncologist at Royal Aberdeen Children's Hospital, and Eloise Neumann is an advanced clinical practitioner at Birmingham Children's Hospital. They will form a clinical advisory panel that will support key decisions made in the project, such as whether additional

antiemetic agents should be considered for inclusion and will provide guidance on the interpretation and translation of findings into clinical practice.

1.2 Definition of CINV

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of chemotherapy treatment, characterised by nausea and vomiting occurring either before, in anticipation of chemotherapy, or during or after, as a result of receiving the chemotherapy (Gupta et al., 2021a). To define these individual side effects going forward, vomiting or ‘emesis’ is defined as the involuntary, forceful expulsion of stomach contents through the mouth (Janelins et al., 2013) and nausea, ‘an unpleasant painless subjective feeling that one will imminently vomit’ (Hasler and Chey, 2003).

1.2.1 Classification of CINV

Chemotherapy-induced nausea and vomiting (CINV) is often described in three clinical phases. Acute CINV can occur from the point of chemotherapy administration, up to 24 hours after (Chang, 2015). Chemotherapy in children is often given in cycles, with treatment delivered in ‘blocks’, often 1-3 days in length, and then a period without treatment whilst the body recovers (DeVita et al., 2018). As such, the length of the ‘acute phase’ can vary depending on the length of the chemotherapy block. For example, if chemotherapy is given over a two-day period, the length of the acute phase could be three days. Delayed CINV then occurs from 24 hours after chemotherapy administration ends, up to 7 days afterwards. Finally, anticipatory CINV can occur prior to chemotherapy administration and is often a result of poor control of CINV within previous cycles of chemotherapy. It may be triggered by sights and smells of treatment rooms or by emotions such as anxiety about receiving chemotherapy treatment (Chang, 2015).

1.2.2 Pathophysiology of CINV

The exact mechanisms by which chemotherapy causes nausea and vomiting are not fully understood. Vomiting is thought to be the result of stimulation of a neuronal area of the brain, sometimes referred to as the 'vomiting centre'. It is located within the fourth ventricle of the brain, on the dorsal surface of the medulla oblongata (Zhong et al., 2021, Chang, 2015) and can receive signals from a region next to the vomiting centre referred to as the chemoreceptor trigger zone (CTZ), or from other natural pathways, namely the vagal afferent pathways, cortisol pathways and vestibular-labyrinthine apparatus, either directly, or indirectly via the CTZ (Gupta et al., 2021b, Chang, 2015). The CTZ and vagal afferent pathways are likely to play a role in initiating acute and delayed vomiting. The CTZ can detect chemicals circulating within the blood, including chemotherapy, as it lacks a blood-brain barrier, and vagal afferent pathways relay information on the physiological state of the gastrointestinal tract, which can become damaged as a result of chemotherapy treatment (Chang, 2015). The cortisol pathway may then play a role in anticipatory vomiting, as this pathway is triggered by smells, sights, and emotions (Chang, 2015) (Agrawal and Feusner, 2022). Vomiting can also be initiated by the vestibular-labyrinthine apparatus of the inner ear, which is responsible for motion sickness (Chang, 2015); however, the pathway is likely less important in the initiation of CIV.

Chemotherapy (and/or other concomitant medication) is thought to trigger nausea through irritation of the gut, or through other treatment-related side effects such as indigestion or constipation (Chang, 2015). Nausea also includes a significant psychological component (Singh et al., 2016). Similar pathways that initiate vomiting are also thought to initiate nausea (Singh et al., 2016) and in both cases, the pathways are activated by a range of neurotransmitters including serotonin (5-HT), histamine, neurokinin-1 (NK-1), acetylcholine and dopamine (H₁) (Agrawal and Feusner, 2022).

The vomiting centre and CTZ have receptors to detect these neurotransmitters, and to prevent nausea and vomiting, it is these receptors that antiemetic medications aim to block (Hesketh, 2008). However, as there is no single pathway involved in causing nausea and vomiting, and the relative contribution of each pathway is unknown, it is thought that a single antiemetic agent may not be effective against CINV (Chang, 2015) and more often, antiemetic medications are given in combination with others (Phillips et al., 2016).

1.3 Classification of emetogenicity of chemotherapy.

The extent to which children receiving chemotherapy experience CINV can vary depending on the ‘emetogenicity’ of the chemotherapy agent. This emetogenic potential can be broadly categorised into ‘low’, a chemotherapy causing a 10-30% incidence of emesis in the absence of prophylaxis (anti-emetic (or anti-sickness) medication), ‘moderate’, a chemotherapy causing a 30-90% incidence of emesis in absence of prophylaxis and ‘high’ a chemotherapy causing over a 90% incidence in the absence of prophylaxis (Paw Cho Sing et al., 2019).

However, it is important to note that this categorisation is not an exact science and the emetogenic potential of chemotherapies in children is informed by limited data and is periodically under review (Paw Cho Sing et al., 2019).

2 Chapter Two Appendix

2.1 Report of patient public involvement in the development of an NIHR doctoral fellowship application.

This public involvement work has been previously uploaded to the PURE database at the University of York, a system that captures research activities and outputs; therefore, some of the text within this report will closely align, if not be identical to that reported on this online system.

NIHR Research Design Service for Yorkshire and the Humber RDSYH Public Involvement Funds – Call 7: Report of patient public involvement in the development of a NIHR doctoral fellowship application.

Pharmacological intervention for the prevention of chemotherapy-induced nausea and vomiting in children and young people undergoing treatment for cancer: a systematic review and Bayesian network meta-analysis with extrapolation of adult clinical trial information.

Ruth Walker

Pre-doctoral Fellow, University of York.

2.1.1 Introduction

Using chemotherapy to treat cancer in children and young people can cause nausea (a feeling that one might be sick) and vomiting. These unpleasant symptoms continue to be a problem despite better anti-sickness drugs.

Clinical trials investigating the use of anti-sickness drugs are more common in adults, and we know less about how well they work in children and young people. This means that children and young people are not always prescribed the most effective anti-sickness medications when being treated for cancer. Adults often have access to new medications before they are made available for children.

Funding received from the NIHR Research Design Service for Yorkshire and the Humber has been used to conduct PPI to develop a grant application for round 6 NIHR Doctoral fellowship, to investigate the use of anti-sickness medication to prevent chemotherapy-induced nausea and vomiting in children and young people.

In this doctoral fellowship, I will identify and combine evidence from clinical trials comparing how well anti-sickness medications prevent nausea and vomiting in children and young people undergoing cancer treatment. Using data from these clinical trials, I will compare each anti-sickness medication with every other.

Where there are few or no clinical trials comparing medications in children and young people, I will identify clinical trials comparing how well anti-sickness medications prevent of nausea and vomiting in adults and use statistical methods to investigate whether data from clinical trials can be safely used to predict how well anti-sickness medications work in children and young people.

I will discuss how this information could be used to reach conclusions about anti-sickness medications for children and young people undergoing cancer treatment sooner, with confirmatory research rather than a full clinical trials programme.

2.1.2 Aims

Patients and the public were involved to facilitate the development of a grant application for round 6 NIHR Doctoral Fellowship in July 2021.

The purpose of this involvement was to understand:

- Whether, based on people's experience, the research would be considered valuable.
- How people would feel about being involved in aspects of the doctoral fellowship, such as designing the study, interpreting the findings and disseminating the results and how, as researchers, we could facilitate this involvement.
- How patients and the public would like to hear about the results of the study, once it is completed and whether my current plans to disseminate the findings of the research are likely to be effective or whether alternative methods would be better.
- Whether the plain English summary in my doctoral fellowship application is understandable to a lay audience, and whether any improvements could be made to the language.

2.1.3 Methods

2.1.3.1 Recruitment

I sought to involve people with experience of chemotherapy-induced nausea and vomiting (CINV), either from personal experience when being treated for cancer when they were a child or young person, or as a family member or carer of a child being treated for cancer. To reach these people, I advertised on social media platforms for local and national children's cancer charities (Candlelighters and Children's Cancer and Leukaemia Group (CCLG)).

Those who expressed an interest in being involved were sent an information sheet, which provided further details of my study, what the involvement would entail, the impact the

involvement would have on my grant application and information about reimbursement we would provide for being involved.

Four adults were recruited to be involved in an advisory meeting. Attempts were also made to recruit four young people; however, this was not successful. A further two adults were involved to provide written feedback on the plain English summary in my doctoral grant application.

2.1.3.2 Description of activity

Advisory meeting

The advisory meeting took place later in the evening, over Zoom and ran for one hour. The time was agreed to allow parents with younger children to attend after their children had gone to bed. Dial-in numbers were provided for those who do not have a stable internet connection; however, these were not required. Those who attended were also asked prior to the session if they were comfortable with the meeting being recorded, to allow time to focus on what was being said in the meeting, as opposed to making notes.

Dr Bob Phillips, a senior clinical academic at the Centre for Reviews and Dissemination (CRD) and an honorary consultant in paediatric and teenage-young adult (TYA) oncology at Leeds Children's Hospital, attended to help facilitate the meeting. Dr Bob Philips has extensive experience in providing support to children and young people who are undergoing treatment for cancer, as well as their families.

The meeting started with some brief introductions and an explanation of the methods that will be used in my doctoral fellowship, assisted by PowerPoint slides. The group were then asked three main questions:

- Whether they consider the research valuable
- How they would feel about being involved in aspects of the research project (including how they would like to learn about research methods as part of the involvement)
- How they would like to hear about the results of the study.

After this main discussion, I explained how information shared in the meeting would be used to inform my grant application, when I would be making the application and when I would expect to hear whether it has been successful. Participants were thanked for their time, and the meeting was concluded.

Written feedback on Doctoral Fellowship application

The plain English summary was sent via email to two adults who agreed to review the document and provide written feedback. Specifically, I asked for feedback on whether the language used is appropriate or whether there is any language that would make it more understandable. Feedback was received three weeks after it was initially sent.

2.1.4 Contributions made by the patients and the public

The experiences shared in this meeting have reconfirmed the importance of this proposed PhD fellowship, as they suggested that some children are undergoing several rounds of chemotherapy and trying many different antiemetics or combinations of antiemetics, before their CINV is brought under control. One parent shared that for their child, CINV was never completely controlled, despite trying different antiemetic medications. The PPI also highlighted that antiemetics can be associated with side effects, and for patients for whom antiemetics are effective, CINV may still be experienced if the scheduling of their medication is not optimal. Parents also expressed that they were not aware of all the antiemetic treatment options that are available to prevent CINV on the NHS.

The feedback from the meeting has informed the methods for my doctoral fellowship in the following ways:

- Involvement meetings with adolescents will be held separately from their parents, as adolescents may feel influenced by the presence of carers and should have an opportunity to be treated as individuals.

- Involvement meetings with adolescents will be held online, as time commitments associated with school and travelling to a venue may be a barrier to the recruitment of adolescents.
- Training about systematic reviews and network meta-analysis would be valuable and should be delivered through a variety of methods to accommodate individual learning styles. The following methods were thought to be valuable:
 - A document/ short informational video prior to the meeting and a short presentation within the meeting, explaining what a systematic review is/ what are their limitations.
 - A glossary of common 'jargon'.
 - An opportunity to send in questions beforehand, to be answered at the start of the PPI meeting.
- Short animation videos summarising the findings of the study would be helpful for both children and parents, as these are more easily shared on social media.

The language in my plain English summary has been adapted based on the feedback provided. As per one suggestion, I have also made it clearer how I intend the results of the study to be used in practice.

2.1.5 Evaluation of the involvement of the patients and the public

A feedback form was sent to each person involved to assess how they experienced the involvement activities and whether anything that could be improved. Feedback was largely positive. One person who reviewed the plain English summary said that they would have preferred to have spoken to me over the phone or over Zoom, as all communication was done via email. If my doctoral fellowship is awarded, I will endeavour to offer an option of a phone call or online meeting to talk through the involvement activities and any details of the research that people may be unsure of.

2.1.6 Difficulties encountered

I was unable to recruit any teenagers to be involved in these activities to inform my grant application. I discussed this briefly with those who attended the online advisory meeting. Advice was to advertise at events such as 'Find your Sense of Tumour' organised by the Teenage Cancer Trust, as this may improve recruitment of adolescents. I will incorporate this into my recruitment strategy if the doctoral fellowship application is successful.

2.1.7 How will patient and public involvement be taken forward?

I will continue to involve both carers and patients who have experience of CINV in meetings focusing on design, interpretation, and dissemination. Patients may be children, primary school-aged and older or adults who were treated for cancer when they were a child or young person.

I will involve patients and the public to determine which of the efficacy outcomes matter most to them and whether particular adverse event outcomes should be prioritised. Meetings with adults and teenagers will be held separately, and to involve young children, I will run activities that involve methods of play. Adults and teenagers with experience of CINV will also be involved to understand what the findings of the research mean to patients and their families, and how the findings might matter to them in practice. Finally, I will co-present the findings of the research with a patient or their family member at the Childhood Cancer Conference.

So that those adults and teenagers involved in these activities understand the research method being used, I will provide training about systematic reviews and network meta-analysis. See the section 'Contributions made by the patients and the public' for more details on the methods of teaching.

N.B. I will hear whether the doctoral fellowship application has been successful in November 2021.

2.1.8 Appendix: Breakdown of costs

Section: Payment & Reward

Item: Fees to individuals

Quantity: 3 x Cost: £50 = £150.00

Notes: For involvement in the advisory meeting (a task or activity likely to require some preparation.)
One participant did not wish to receive payment

Quantity: 2 x Cost: £25 = £50

Notes: For involvement to review my plain English summary (a task or activity requiring little or no preparation and which equates to approximately one hour of activity or less).

2.2 Search strategy

Appendices: Search Strategies

Ovid MEDLINE(R) ALL

via Ovid <http://ovidsp.ovid.com/>

Date range searched: <1946 to July 20, 2022>

Date searched: 21 July 2022

Records retrieved: 1466

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.

- 1 Vomiting/ci (8383)
- 2 Nausea/ci (8647)
- 3 Anorexia/ci (1265)
- 4 (CINV or CANV).ti,ab,kw. (1125)
- 5 ((chemo* or cisplatin*) adj2 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)),ti,ab,kw. (3823)
- 6 or/1-5 (14469)
- 7 Neoplasms/dt (84822)
- 8 exp Antineoplastic Protocols/ (156410)
- 9 Antineoplastic Agents/ (311873)
- 10 exp Chemoradiotherapy/ (18933)
- 11 exp Chemotherapy, Adjuvant/ (45294)
- 12 Consolidation Chemotherapy/ (713)
- 13 Electrochemotherapy/ (766)
- 14 Induction Chemotherapy/ (3611)
- 15 Maintenance Chemotherapy/ (2107)
- 16 Photochemotherapy/ (24328)

- 17 (chemo* or radiochemotherap* or radio-chemotherap* or electrochemotherap* or electro-chemotherap* or photochemotherap* or photo-chemotherap*).ti,ab,kw. (764376)
- 18 ((neoplasm* or cancer* or malignan* or metasta* or tumor* or carcinoma* or adenocarcinoma* or oncolog* or leuk?emia* or adenoma* or lymphoma* or melanoma* or sarcoma* or myeloma* or blastoma* or mesenchymoma* or mesothelioma* or thymoma* or hepatoma* or hepatoblastoma* or glioma* or ganglioglioma* or glioblastoma* or neuroblastoma* or retinoblastoma* or meningioma* or seminoma* or carcinosarcoma* or angiosarcoma* or chondrosarcoma* or cholangiocarcinoma* or medulloblastoma* or astrocytoma* or ependymoma* or germinoma* or craniopharyngioma*) adj5 (drug* or agent* or treat* or therap* or pill*1 or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)).ti,ab,kw. (1100451)
- 19 ((antineoplas* or anti-neoplas* or anticancer or anti-cancer or antitumor* or anti-tumor*) adj5 (drug* or agent* or treat* or therap* or pill*1 or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)).ti,ab,kw. (152892)
- 20 or/7-19 (1818644)
- 21 Vomiting, Anticipatory/ (231)
- 22 Vomiting/ (24846)
- 23 Nausea/ (17120)
- 24 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*).ti,ab,kw. (231244)
- 25 Antiemetics/ (9710)
- 26 (antiemetic* or anti-emetic* or antiemetogenic* or anti-emetogenic*).ti,ab,kw. (10012)
- 27 or/21-26 (246202)
- 28 20 and 27 (30828)
- 29 6 or 28 (37821)
- 30 Dexamethasone/ (54533)
- 31 (dexameth* or decacort* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or "7s5i7g3jql" or decadron or diodex or baycadron or ciprodex or dextenza or dioptril or "hidex 6-day taper" or maxitrol or neofordex or ozurdex or "taperdex 12 day taper" or "taperdex 6 day taper" or "taperdex 7-day taper" or tobradex or "zcort 7 day taper").ti,ab,kw,m,nm. (79156)
- 32 Ondansetron/ (3262)
- 33 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedatron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or "gr 38032f" or gr-38032f or gr38032f or nmh84ozk2b or "sn 307" or sn-307 or sn307 or "sud 002" or "sud002" or suda 002" or suda002).ti,ab,kw,m,nm. (5263)
- 34 Aprepitant/ (708)
- 35 (aprepitant or emend or "l 754030" or l-754030 or l754030 or "mk 0517" or "mk 0869" or "mk 869" or mk-0517 or mk-0869 or mk-869 or mk0517 or mk0869 or mk869 or Cinvanti or Ivemend).ti,ab,kw,m,nm. (1495)
- 36 Metoclopramide/ (4952)

- 37 (metoclopramide* or "5yna80e9to" or cerucal or "l4yeb44i46" or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or Metozolv ODT).ti,ab,kw,m,nm. (7229)
- 38 Serotonin 5-HT₃ Receptor Antagonists/ (837)
- 39 ("serotonin 5-ht₃ receptor antagonist*" or "5 ht₃ antagonist*" or "5-ht₃ antagonist*" or "serotonin 5 ht₃ receptor antagonist*" or "5-hydroxytryptamine₃" or "5-hydroxytryptamine type 3–receptor antagonist" or "5-hydroxytryptamine 3 (5-HT₃)-receptor antagonist").ti,ab,kw,m,nm. (2101)
- 40 Neurokinin-1 Receptor Antagonists/ (2125)
- 41 (("neurokinin 1" or neurokinin-1 or "neuroleukin 1" or neuroleukin-1 or "substance p receptor" or "tachykinin receptor 1") adj3 (antagonist* or blocker*)).ti,ab,kw,m,nm. (2691)
- 42 Palonosetron/ (452)
- 43 (palonosetron* or "2-qhbiqo" or "23310d4i19" or "2ucb21er4v" or "5d06587d6r" or aloxi* or onicit* or "rs 25233*" or "rs 25259").ti,ab,kw,m,nm. (950)
- 44 Methotrimeprazine/ (798)
- 45 (methotrimeprazine or "9g0law7atq" or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiscerine or tizercine or tizertsin or nozinan or levoprome or detenler or himamin or levotomin).ti,ab,kw,m,nm. (1089)
- 46 Olanzapine/ (6076)
- 47 (Olanzapine or "ly 17005*" or "n7u69t4szr" or "x7s6q4mhcb" or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis).ti,ab,kw,m,nm. (10158)
- 48 Lorazepam/ (2998)
- 49 (Lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or novo-lorazem or nu loraz or nu-loraz or o26fzp769l or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy-4036 or wy4036 or loreev).ti,ab,kw,m,nm. (5024)
- 50 *Cannabinoids/ (6925)
- 51 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).ti,ab,kw,m,nm. (386)
- 52 Granisetron/ (1134)
- 53 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6170j8" or "brl 43694*" or kytril or wzg3j2mcol).ti,ab,kw,m,nm. (1811)
- 54 Tropisetron/ (899)
- 55 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205 -930" or "ics 205930" or "ics-205-930" or ics-205930 or "indole 3 carboxylic acid tropine ester" or "indole-3-carboxylic acid tropine ester" or navoban).ti,ab,kw,m,nm. (1597)
- 56 or/30-55 (118704)
- 57 29 and 56 (4783)
- 58 animals/ not (animals and humans).sh. (5004269)
- 59 57 not 58 (4388)
- 60 randomized controlled trial.pt. (575128)

61 controlled clinical trial.pt. (94983)
 62 randomized.ab. (571392)
 63 placebo.ab. (230783)
 64 clinical trials as topic.sh. (200281)
 65 randomly.ab. (388745)
 66 trial.ti. (268284)
 67 or/60-66 (1465544)
 68 59 and 67 (1662)
 69 letter/ or letter.ti. (1228511)
 70 exp historical article/ (408663)
 71 news/ (213488)
 72 or/69-71 (1836800)
 73 68 not 72 (1638)
 74 limit 73 to english language (1472)
 75 remove duplicates from 74 (1466)

Key:

/ or .sh. = indexing term (Medical Subject Heading: MeSH)

exp = exploded indexing term (MeSH)

* before an indexing term = focussed indexing term

/ci = indexing term with chemically induced subheading

/dt = indexing term with drug therapy subheading

* or \$ = truncation

ti,ab,kw = terms in either title, abstract, keyword fields

rn = registry number/name of substance field

nm = name of substance word field

adj3 = terms within three words of each other (any order)

? = optional wild card character for zero or one letters

pt = publication type

Embase

via Ovid <http://ovidsp.ovid.com/>

Date range searched: <1974 to 2022 July 20>

Date searched: 21 July 2022

Records retrieved: 1665

The Embase strategy below includes the Cochrane Embase RCT filter (Ovid format).

Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Info Libr J.* 2019 Jul 22. doi: 10.1111/hir.12269

- 1 exp "chemotherapy induced nausea and vomiting"/ (9667)
- 2 "anticipatory nausea and vomiting"/dt, pc (63)
- 3 (CINV or CANV).ti,ab,kw. (2293)
- 4 ((chemo* or cisplatin*) adj2 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)).ti,ab,kw. (6224)
- 5 or/1-4 (13279)
- 6 dexamethasone/ (172723)
- 7 (dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or "7s5i7g3jql" or decadron or diodex or baycadron or ciprodex or dextenza or dioptril or "hidex 6-day taper" or maxitrol or neofordex or ozurdex or "taperdex 12 day taper" or "taperdex 6 day taper" or "taperdex 7-day taper" or tobradex or "zcort 7 day taper").ti,ab,kw,tn,du. (187777)
- 8 ondansetron/ (20258)
- 9 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedatron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or "gr 38032f" or gr-38032f or gr38032f or nmh84ozk2b or "sn 307" or sn-307 or sn307 or "sud 002" or "sud002" or suda 002" or suda002).ti,ab,kw,tn,du. (20678)
- 10 aprepitant/ (3728)
- 11 (aprepitant or emend or "l 754030" or l-754030 or l754030 or "mk 0517" or "mk 0869" or "mk 869" or mk-0517 or mk-0869 or mk-869 or mk0517 or mk0869 or mk869 or Cinvanti or Ivemend).ti,ab,kw,tn,du. (4182)
- 12 metoclopramide/ (26560)
- 13 (metoclopramide* or "5yna80e9to" or cerucal or "l4yeb44i46" or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or Metozolv ODT).ti,ab,kw,tn,du. (27230)
- 14 serotonin 3 antagonist/ (4097)
- 15 ("serotonin 5-HT3 receptor antagonist*" or "5 HT3 antagonist*" or "5-HT3 antagonist*" or "serotonin 5 HT3 receptor antagonist*" or "5-hydroxytryptamine3" or "5-hydroxytryptamine type 3-receptor antagonist" or "5-hydroxytryptamine 3 (5-HT3)-receptor antagonist").ti,ab,kw,tn,du. (2142)
- 16 neurokinin 1 receptor antagonist/ (2546)
- 17 (("neurokinin 1" or neurokinin-1 or "neuroleukin 1" or neuroleukin-1 or "substance p receptor" or "tachykinin receptor 1") adj3 (antagonist* or blocker*)).ti,ab,kw,tn,du. (1437)
- 18 palonosetron/ (2230)

- 19 (palonosetron* or "2-qhbqo" or "23310d4i19" or "2ucb21er4v" or "5d06587d6r" or aloxi* or onicit* or "rs 25233*" or "rs 25259").ti,ab,kw,tn,du. (3094)
- 20 levomepromazine/ (5645)
- 21 (methotrimeprazine or "9g0law7atq" or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiserin or tizerine or tizertsin or nozinan or levoprome or detenler or himamin or levotomin).ti,ab,kw,tn,du. (5718)
- 22 olanzapine/ (37592)
- 23 (olanzapine or "ly 17005*" or "n7u69t4szz" or "x7s6q4mhcb" or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis).ti,ab,kw,tn,du. (38408)
- 24 lorazepam/ (29066)
- 25 (Lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or novo - lorazem or nu loraz or nu-loraz or o26fzp7691 or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy-4036 or wy4036 or loreev).ti,ab,kw,tn,du. (29549)
- 26 nabilone/ (1515)
- 27 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).ti,ab,kw,tn,du. (1587)
- 28 granisetron/ (5705)
- 29 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6170j8" or "brl 43694*" or kytril or wzg3j2mcol).ti,ab,kw,tn,du. (5926)
- 30 tropisetron/ (3640)
- 31 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205 -930" or "ics 205930" or "ics-205-930" or ics-205930 or "indole 3 carboxylic acid tropine ester" or "indole-3-carboxylic acid tropine ester" or navoban).ti,ab,kw,tn,du. (3789)
- 32 or/6-31 (299910)
- 33 5 and 32 (6164)
- 34 animal/ (1581240)
- 35 exp animal experiment/ (2866742)
- 36 nonhuman/ (6963299)
- 37 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6188089)
- 38 or/34-37 (9814788)
- 39 exp human/ (23853513)
- 40 human experiment/ (585050)
- 41 39 or 40 (23855599)
- 42 38 not (38 and 41) (6993986)
- 43 33 not 42 (5861)
- 44 randomized controlled trial/ (718648)

- 45 controlled clinical trial/ (466843)
- 46 Random\$.ti,ab,ot. (1812093)
- 47 randomization/ (94417)
- 48 intermethod comparison/ (285216)
- 49 placebo.ti,ab,ot. (343836)
- 50 (compare or compared or comparison).ti,ot. (569607)
- 51 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2531536)
- 52 (open adj label).ti,ab,ot. (98237)
- 53 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,ot. (258614)
- 54 double blind procedure/ (196941)
- 55 parallel group\$1.ti,ab,ot. (29695)
- 56 (crossover or cross over).ti,ab,ot. (117253)
- 57 ((assign\$ or match or matched or allocation) adj5 (alternate or group or groups or intervention or interventions or patient or patients or subject or subjects or participant or participants)).ti,ab,ot. (383771)
- 58 (assigned or allocated).ti,ab,ot. (452561)
- 59 (controlled adj7 (study or design or trial)).ti,ab,ot. (413249)
- 60 (volunteer or volunteers).ti,ab,ot. (269167)
- 61 or/44-60 (5363427)
- 62 43 and 61 (2539)
- 63 (conference or letter or note).pt. (7366598)
- 64 62 not 63 (1801)
- 65 limit 64 to english language (1677)
- 66 remove duplicates from 65 (1665)

Key:

/ or .sh. = indexing term (Emtree subject heading)

exp = exploded indexing term (Emtree)

* before an indexing term = focussed indexing term

* or \$ = truncation

ti,ab,kw = terms in either title, abstract or keyword fields

adj3 = terms within three words of each other (any order)

? = optional wild card character for zero or one letters

tn = drug trade name field
 du = drug index terms field
 ot = original title
 pt = publication type

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley <http://onlinelibrary.wiley.com/>

Date range: Issue 7 of 12, 2022

Date searched: 21 July 2022

Records retrieved: 3160

- #1 [mh ^Vomiting/ci] 1683
- #2 [mh ^Nausea/ci] 2200
- #3 [mh ^Anorexia/ci] 102
- #4 (CINV or CANV):ti,ab,kw 717
- #5 ((chemo* or cisplatin*) NEAR/2 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)):ti,ab,kw 2822
- #6 {OR #1-#5} 4988
- #7 [mh ^Neoplasms/dt] 1844
- #8 [mh "Antineoplastic Protocols"] 15260
- #9 [mh ^"Antineoplastic Agents"] 7166
- #10 [mh Chemoradiotherapy] 1179
- #11 [mh "Chemotherapy, Adjuvant"] 4126
- #12 [mh ^"Consolidation Chemotherapy"] 108
- #13 [mh ^Electrochemotherapy] 12
- #14 [mh ^"Induction Chemotherapy"] 456
- #15 [mh ^"Maintenance Chemotherapy"] 458
- #16 [mh ^Photochemotherapy]993
- #17 (chemo* or radiochemotherap* or electrochemotherap* or photochemotherap*):ti,ab,kw 100741
- #18 ((neoplasm* or cancer* or malignan* or metasta* or tumo*r* or carcinoma* or adenocarcinoma* or oncolog* or leuk*emia* or adenoma* or lymphoma* or melanoma* or sarcoma* or myeloma* or blastoma* or mesenchymoma* or mesothelioma* or thymoma* or hepatoma* or hepatoblastoma* or glioma* or ganglioglioma* or glioblastoma* or neuroblastoma* or retinoblastoma* or meningioma* or seminoma* or carcinosarcoma* or angiosarcoma* or chondrosarcoma* or cholangiocarcinoma* or medulloblastoma* or astrocytoma* or ependymoma* or germinoma* or craniopharyngioma*) NEAR/5 (drug* or agent* or treat* or therap* or pill*1 or capsule* or topical* or medicine* or medication* or

- tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)):ti,ab,kw 133192
- #19 ((antineoplas* or anti NEXT neoplas* or anticancer or anti NEXT cancer or antitumo*r or anti NEXT tumo*r) NEAR/5 (drug* or agent* or treat* or therap* or pill*1 or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)):ti,ab,kw 26828
- #20 (Patel et al.-#19) 173529
- #21 [mh ^"Vomiting, Anticipatory"] 31
- #22 [mh ^Vomiting] 3737
- #23 [mh ^Nausea] 4001
- #24 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*):ti,ab,kw72679
- #25 [mh ^Antiemetics] 2369
- #26 (antiemetic* or anti NEXT emetic* or antiemetogenic* or anti NEXT emetogenic*):ti,ab,kw 6420
- #27 {OR #21-#26} 73441
- #28 #20 and #27 15862
- #29 #6 or #28 17447
- #30 [mh ^Dexamethasone] 5050
- #31 (dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or "7s5i7g3jql" or decadron or diodex or baycadron or ciprodex or dextenza or dioptrrol or "hidex 6-day taper" or maxitrol or neofordex or ozurdex or "taperdex 12 day taper" or "taperdex 6 day taper" or "taperdex 7-day taper" or tobradex or "zcort 7 day taper"):ti,ab,kw 13819
- #32 [mh ^Ondansetron] 1380
- #33 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedantron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or "gr 38032f" or gr38032f or nmh84ozk2b or "sn 307" or sn307 or "sud 002" or "sud002or suda 002" or suda002):ti,ab,kw 3971
- #34 [mh ^Aprepitant] 334
- #35 (aprepitant or emend or "l 754030" or l754030 or "mk 0517" or "mk 0869" or "mk 869" or mk0517 or mk0869 or mk869 or cinvanti or ivemend):ti,ab,kw 806
- #36 [mh ^Metoclopramide] 1182
- #37 (metoclopramide* or "5yna80e9to" or cerucal or "l4yeb44i46" or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or "Metozolv ODT"):ti,ab,kw 3114
- #38 [mh ^"Serotonin 5-HT3 Receptor Antagonists"] 81
- #39 ("serotonin 5-ht3 receptor antagonist*" or "5 ht3 antagonist*" or "serotonin 5 ht3 receptor antagonist*" or "5-hydroxytryptamine3" or "5-hydroxytryptamine type 3-receptor antagonist" or "5-hydroxytryptamine 3 (5-HT3)-receptor antagonist"):ti,ab,kw 297

- #40 [mh ^"Neurokinin-1 Receptor Antagonists"] 152
- #41 (("neurokinin 1" or "neuroleukin 1" or "substance p receptor" or "tachykinin receptor 1") NEAR/3 (antagonist* or blocker*)):ti,ab,kw 356
- #42 [mh ^Palonosetron] 221
- #43 (palonosetron* or "2-qhbiqo" or "23310d4i19" or "2ucb21er4v" or "5d06587d6r" or aloxi* or onicit* or "rs 25233*" or "rs 25259"):ti,ab,kw 705
- #44 [mh ^Methotrimeprazine] 36
- #45 (methotrimeprazine or "9g0law7atq" or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiscerin or tizercine or tizertsin or nozinan or levoprome or detenler or hirmamin or levotomin):ti,ab,kw 113
- #46 [mh ^Olanzapine] 1353
- #47 (olanzapine or "ly 17005*" or "n7u69t4szz" or "x7s6q4mhcb" or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis):ti,ab,kw 3684
- #48 [mh ^Lorazepam]839
- #49 (lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or nu loraz or o26fzp769l or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy4036 or loreev):ti,ab,kw 2036
- #50 [mh ^Cannabinoids] 119
- #51 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514):ti,ab,kw 164
- #52 [mh ^Granisetron] 447
- #53 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6l70j8" or "brl 43694*" or kytril or wzg3j2mcol):ti,ab,kw 1206
- #54 [mh ^Tropisetron] 194
- #55 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205930" or "indole 3 carboxylic acid tropine ester" or navoban):ti,ab,kw 450
- #56 {OR #30-#55} 25893
- #57 #29 and #56 in Trials 3160

Key:

mh = exploded indexing term (MeSH)

mh ^ = unexploded indexing term (MeSH)

/ci = indexing term with chemically induced subheading

/dt = indexing term with drug therapy subheading

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

Cochrane Databases of Systematic Reviews (CDSR)

via Wiley <http://onlinelibrary.wiley.com/>

Date range: Issue 7 of 12, 2022

Date searched: 21 July 2022

Records retrieved: 12

- #1 [mh ^Vomiting/ci] 1683
- #2 [mh ^Nausea/ci] 2200
- #3 [mh ^Anorexia/ci] 102
- #4 (CINV or CANV):ti,ab,kw 717
- #5 ((chemo* or cisplatin*) NEAR/2 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)):ti,ab,kw 2822
- #6 {OR #1-#5} 4988
- #7 [mh ^Neoplasms/dt] 1844
- #8 [mh "Antineoplastic Protocols"] 15260
- #9 [mh ^"Antineoplastic Agents"] 7166
- #10 [mh Chemoradiotherapy] 1179
- #11 [mh "Chemotherapy, Adjuvant"] 4126
- #12 [mh ^"Consolidation Chemotherapy"] 108
- #13 [mh ^Electrochemotherapy] 12
- #14 [mh ^"Induction Chemotherapy"] 456
- #15 [mh ^"Maintenance Chemotherapy"] 458
- #16 [mh ^Photochemotherapy]993
- #17 (chemo* or radiochemotherap* or electrochemotherap* or photochemotherap*):ti,ab,kw 100741
- #18 ((neoplasm* or cancer* or malignan* or metasta* or tumor* or carcinoma* or adenocarcinoma* or oncolog* or leuk*emia* or adenoma* or lymphoma* or melanoma* or sarcoma* or myeloma* or blastoma* or mesenchymoma* or mesothelioma* or thymoma* or hepatoma* or hepatoblastoma* or glioma* or ganglioglioma* or glioblastoma* or neuroblastoma* or retinoblastoma* or meningioma* or seminoma* or carcinosarcoma* or angiosarcoma* or chondrosarcoma* or cholangiocarcinoma* or medulloblastoma* or astrocytoma* or ependymoma* or germinoma* or craniopharyngioma*) NEAR/5 (drug* or agent* or treat* or therap* or pill*1 or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)):ti,ab,kw 133192

- #19 ((antineoplas* or anti NEXT neoplas* or anticancer or anti NEXT cancer or antitumo*r or anti NEXT tumo*r) NEAR/5 (drug* or agent* or treat* or therap* or pill*1 or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)):ti,ab,kw 26828
- #20 (Patel et al.-#19) 173529
- #21 [mh ^"Vomiting, Anticipatory"] 31
- #22 [mh ^Vomiting] 3737
- #23 [mh ^Nausea] 4001
- #24 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*):ti,ab,kw72679
- #25 [mh ^Antiemetics] 2369
- #26 (antiemetic* or anti NEXT emetic* or antiemetogenic* or anti NEXT emetogenic*):ti,ab,kw 6420
- #27 {OR #21-#26} 73441
- #28 #20 and #27 15862
- #29 #6 or #28 17447
- #30 [mh ^Dexamethasone] 5050
- #31 (dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or "7s5i7g3jql" or decadron or diodex or baycadron or ciprodex or dextenza or dioptrol or "hidex 6-day taper" or maxitrol or neofordex or ozurdex or "taperdex 12 day taper" or "taperdex 6 day taper" or "taperdex 7-day taper" or tobradex or "zcort 7 day taper"):ti,ab,kw 13819
- #32 [mh ^Ondansetron] 1380
- #33 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedantron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or "gr 38032f" or gr38032f or nmh84ozk2b or "sn 307" or sn307 or "sud 002" or "sud002or suda 002" or suda002):ti,ab,kw 3971
- #34 [mh ^Aprepitant] 334
- #35 (aprepitant or emend or "l 754030" or l754030 or "mk 0517" or "mk 0869" or "mk 869" or mk0517 or mk0869 or mk869 or cinvanti or ivemend):ti,ab,kw 806
- #36 [mh ^Metoclopramide] 1182
- #37 (metoclopramide* or "5yna80e9to" or cerucal or "l4yeb44i46" or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or "Metozolv ODT"):ti,ab,kw 3114
- #38 [mh ^"Serotonin 5-HT3 Receptor Antagonists"] 81
- #39 ("serotonin 5-ht3 receptor antagonist*" or "5 ht3 antagonist*" or "serotonin 5 ht3 receptor antagonist*" or "5-hydroxytryptamine3" or "5-hydroxytryptamine type 3-receptor antagonist" or "5-hydroxytryptamine 3 (5-HT3)-receptor antagonist"):ti,ab,kw 297
- #40 [mh ^"Neurokinin-1 Receptor Antagonists"] 152

- #41 ((("neurokinin 1" or "neuroleukin 1" or "substance p receptor" or "tachykinin receptor 1") NEAR/3 (antagonist* or blocker*)):ti,ab,kw 356
- #42 [mh ^Palonosetron] 221
- #43 (palonosetron* or "2-qhbiqo" or "23310d4i19" or "2ucb21er4v" or "5d06587d6r" or aloxi* or onicit* or "rs 25233*" or "rs 25259"):ti,ab,kw 705
- #44 [mh ^Methotrimeprazine] 36
- #45 (methotrimeprazine or "9g0law7atq" or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiserin or tizercine or tizertsin or nozinan or levoprome or detenler or himnamin or levotomin):ti,ab,kw 113
- #46 [mh ^Olanzapine] 1353
- #47 (olanzapine or "ly 17005*" or "n7u69t4szz" or "x7s6q4mhcb" or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis):ti,ab,kw 3684
- #48 [mh ^Lorazepam]839
- #49 (lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or nu loraz or o26fzp769l or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy4036 or loreev):ti,ab,kw 2036
- #50 [mh ^Cannabinoids] 119
- #51 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514):ti,ab,kw 164
- #52 [mh ^Granisetron] 447
- #53 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6170j8" or "brl 43694*" or kytril or wzg3j2mcol):ti,ab,kw 1206
- #54 [mh ^Tropisetron] 194
- #55 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205930" or "indole 3 carboxylic acid tropine ester" or navoban):ti,ab,kw 450
- #56 {OR #30-#55} 25893
- #57 #29 and #56 in Cochrane Reviews 12

Key:

mh = exploded indexing term (MeSH)

mh ^ = unexploded indexing term (MeSH)

/ci = indexing term with chemically induced subheading

/dt = indexing term with drug therapy subheading

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

Health Technology Assessment (HTA)

via <https://www.crd.york.ac.uk/CRDWeb/>

Date range searched: Inception to March 2018

Date searched: 21 July 2022

Records retrieved: 6

- 1 MeSH DESCRIPTOR Vomiting WITH QUALIFIER CI IN HTA 2
- 2 MeSH DESCRIPTOR Nausea WITH QUALIFIER CI IN HTA 2
- 3 MeSH DESCRIPTOR Anorexia WITH QUALIFIER CI IN HTA 0
- 4 (CINV or CANV) IN HTA2
- 5 ((chemo* or cisplatin*) NEAR2 (nausea* or vomit* or sick* or emesis or emesis or emetic* or emetogenic* or hyperemesis or anorex*)) IN HTA 15
- 6 #1 OR #2 OR #3 OR #4 OR #5 16
- 7 MeSH DESCRIPTOR Neoplasms WITH QUALIFIER DT IN HTA 13
- 8 MeSH DESCRIPTOR Antineoplastic Protocols EXPLODE ALL TREES IN HTA 147
- 9 MeSH DESCRIPTOR Antineoplastic Agents IN HTA 374
- 10 MeSH DESCRIPTOR Chemoradiotherapy EXPLODE ALL TREES IN HTA 1
- 11 MeSH DESCRIPTOR Chemotherapy, Adjuvant EXPLODE ALL TREES IN HTA 58
- 12 MeSH DESCRIPTOR Consolidation Chemotherapy IN HTA 0
- 13 MeSH DESCRIPTOR Electrochemotherapy IN HTA 2
- 14 MeSH DESCRIPTOR Induction Chemotherapy IN HTA 2
- 15 MeSH DESCRIPTOR Maintenance Chemotherapy IN HTA 1
- 16 MeSH DESCRIPTOR Photochemotherapy IN HTA 66
- 17 (chemo* or radiochemotherap* or radio-chemotherap* or electrochemotherap* or electro-chemotherap* or photochemotherap* or photo-chemotherap*) IN HTA 730
- 18 ((neoplasm* or cancer* or malignan* or metasta* or tumor* or tumour* or carcinoma* or adenocarcinoma* or oncolog* or leukaemia* or leukemia* or adenoma* or lymphoma* or melanoma* or sarcoma* or myeloma* or blastoma* or mesenchymoma* or mesothelioma* or thymoma* or hepatoma* or hepatoblastoma* or glioma* or ganglioglioma* or glioblastoma* or neuroblastoma* or retinoblastoma* or meningioma* or seminoma* or carcinosarcoma* or angiosarcoma* or chondrosarcoma* or cholangiocarcinoma* or medulloblastoma* or astrocytoma* or ependymoma* or germinoma* or craniopharyngioma*) NEAR5 (drug* or agent* or treat* or therap* or pill* or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)) IN HTA 1061

19 ((antineoplas* or anti-neoplas* or anticancer or anti-cancer or antitumor or anti-tumor or antitumour or anti-tumour) NEAR5 (drug* or agent* or treat* or therap* or pill* or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)) IN HTA 531

20 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 1607

21 MeSH DESCRIPTOR Vomiting, Anticipatory IN HTA 0

22 MeSH DESCRIPTOR Vomiting IN HTA 16

23 MeSH DESCRIPTOR Nausea IN HTA 16

24 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*) IN HTA 195

25 MeSH DESCRIPTOR Antiemetics IN HTA 11

26 (antiemetic* or anti-emetic* or antiemetogenic* or anti-emetogenic*) 281

27 #21 OR #22 OR #23 OR #24 OR #25 OR #26 460

28 #20 AND #27 38

29 #6 OR #28 39

30 MeSH DESCRIPTOR Dexamethasone IN HTA 20

31 (dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or 7s5i7g3jql or decadron or diodex or baycadron or ciprodex or dextenza or dioptril or hidex 6-day taper or maxitrol or neofordex or ozurdex or taperdex 12 day taper or taperdex 6 day taper or taperdex 7-day taper or tobradex or zcort 7 day taper) IN HTA 40

32 MeSH DESCRIPTOR Ondansetron IN HTA 3

33 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedantron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or gr 38032f or gr-38032f or gr38032f or nmh84ozk2b or sn 307 or sn-307 or sn307 or sud 002 or sud002 or suda 002 or suda002) IN HTA 11

34 MeSH DESCRIPTOR Aprepitant IN HTA 0

35 (aprepitant or emend or l 754030 or l-754030 or l754030 or mk 0517 or mk 0869 or mk 869 or mk-0517 or mk-0869 or mk-869 or mk0517 or mk0869 or mk869 or Cinvanti or Ivemend) IN HTA 2

36 MeSH DESCRIPTOR Metoclopramide IN HTA 0

37 (metoclopramide* or 5yna80e9to or cerucal or l4yeb44i46 or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or Metozolv ODT) IN HTA 4

38 MeSH DESCRIPTOR Serotonin 5-HT3 Receptor Antagonists IN HTA 1

39 (serotonin 5-ht3 receptor antagonist* or 5 ht3 antagonist* or 5-ht3 antagonist* or serotonin 5 ht3 receptor antagonist* or 5-hydroxytryptamine3 or 5-hydroxytryptamine type 3-receptor antagonist) IN HTA 7

40 MeSH DESCRIPTOR Neurokinin-1 Receptor Antagonists IN HTA 0

- 41 ((neurokinin 1 or neurokinin-1 or neuroleukin 1 or neuroleukin-1 or substance p receptor or tachykinin receptor 1) NEAR3 (antagonist* or blocker*)) IN HTA 0
- 42 MeSH DESCRIPTOR Palonosetron IN HTA 0
- 43 (palonosetron* or 2-qhbiqo or 23310d4i19 or 2ucb21er4v or 5d06587d6r or aloxi* or onicit* or rs 25233* or rs 25259) IN HTA 4
- 44 MeSH DESCRIPTOR Methotrimeprazine IN HTA 0
- 45 (methotrimeprazine or 9g0law7atq or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiserin or tizercine or tizertsin or Nozinan or levoprome or detenler or himamin or levotomin) IN HTA 1
- 46 MeSH DESCRIPTOR Olanzapine IN HTA 0
- 47 (Olanzapine or ly 17005* or n7u69t4szz or x7s6q4mhcb or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis) IN HTA 23
- 48 MeSH DESCRIPTOR Lorazepam IN HTA 1
- 49 (Lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or novo-lorazem or nu loraz or nu-loraz or o26fzp769l or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy-4036 or wy4036 or loreev) IN HTA 5
- 50 MeSH DESCRIPTOR Cannabinoids IN HTA 8
- 51 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514) IN HTA 6
- 52 MeSH DESCRIPTOR Granisetron IN HTA 1
- 53 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6170j8" or "brl 43694*" or kytril or wzg3j2mcol) IN HTA 4
- 54 MeSH DESCRIPTOR Tropisetron IN HTA 0
- 55 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205930" or "indole 3 carboxylic acid tropine ester" or navoban) IN HTA 1
- 56 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 96
- 57 #29 AND #56 6

Key:

MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)

EXPLODE ALL TREES = exploded indexing term (MeSH)

WITH QUALIFIER CI = indexing term with chemically induced subheading

WITH QUALIFIER DT indexing term with drug therapy subheading

* = truncation

NEAR2 = terms within three words of each other (only in the order specified)

International HTA database

via <https://database.inahta.org/>

Date range: Inception – 21 July 2022

Date searched: 21 July 2022

Records retrieved: 57

((("Tropisetron"[mh]) OR (((Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205930" or "indole 3 carboxylic acid tropine ester" or navoban))) OR (((Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6170j8" or "brl 43694*" or kytril or wzg3j2mcol))) OR ("Granisetron"[mh]) OR ((("Dexamethasone"[mh]) OR ("Ondansetron"[mh]) OR ("Aprepitant"[mh]) OR ("Metoclopramide"[mh]) OR ("Serotonin 5-HT3 Receptor Antagonists"[mh]) OR ("Neurokinin-1 Receptor Antagonists"[mh]) OR ("Palonosetron"[mh]) OR ("Methotrimeprazine"[mh]) OR ("Olanzapin"[mh]) OR ("Lorazepam"[mh]) OR ("Cannabinoids"[mh]) OR ((dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or "7s5i7g3jql" or decadron or diodex or baycadron or ciprodex or dextenza or dioptril or "hidex 6-day taper" or maxitrol or neofordex or ozurdex or "taperdex 12 day taper" or "taperdex 6 day taper" or "taperdex 7-day taper" or tobradex or "zcort 7 day taper"))) OR ((ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedatron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or "gr 38032f" or gr-38032f or gr38032f or nmh84ozk2b or "sn 307" or sn-307 or sn307 or "sud 002" or "sud002 or suda 002" or suda002)) OR ((aprepitant or emend or "l 754030" or l-754030 or l754030 or "mk 0517" or "mk 0869" or "mk 869" or mk-0517 or mk-0869 or mk-869 or mk0517 or mk0869 or mk869 or Cinvanti or Ivemend)) OR ((metoclopramide* or "5yna80e9to" or cerucal or "l4yeb44i46" or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or Metozolv ODT)) OR ((("serotonin 5-ht3 receptor antagonist*" or "5 ht3 antagonist*" or "5-ht3 antagonist*" or "serotonin 5 ht3 receptor antagonist*" or "5-hydroxytryptamine3" or "5-hydroxytryptamine type 3–receptor antagonist")) OR ((("neurokinin 1" or neurokinin-1 or "neuroleukin 1" or neuroleukin-1 or "substance p receptor" or "tachykinin receptor 1")) OR ((palonosetron* or "2-qhbiqo" or "23310d4i19" or "2ucb21er4v" or "5d06587d6r" or aloxi* or onicit* or "rs 25233*" or "rs 25259")) OR ((methotrimeprazine or "9g0law7atq" or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiserin or tizercine or tizertsin or Nozinan or levoprome or detenler or himamin or levotomin)) OR ((Olanzapine or "ly 17005*" or "n7u69t4szz" or "x7s6q4mhcb" or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis)) OR ((Lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or novo - lorazem or nu loraz or nu-loraz or o26fzp769l or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy-4036 or wy4036 or loreev)) OR ((nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514)))) AND (((CINV OR CANV)) OR ((chemo* OR cisplatin* OR radiochemotherap* OR radio-chemotherap* OR electrochemotherap* OR electro-chemotherap* OR photochemotherap* OR photo-chemotherap*)) OR ((nausea* OR vomit* OR sick* OR emesia OR emesis OR emetic* OR emetogenic* OR hyperemesis OR anorex*)) OR ((antiemetic* OR anti-emetic* OR antiemetogenic* OR anti-emetogenic*)) OR ((neoplasm* OR cancer* OR malignan* OR metasta* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR oncolog* OR leukaemia* OR leukemia* OR adenoma* OR lymphoma* OR melanoma* OR sarcoma* OR myeloma* OR blastoma* OR mesenchymoma* OR mesothelioma* OR thymoma* OR hepatoma* OR hepatoblastoma* OR glioma* OR ganglioglioma* OR glioblastoma* OR neuroblastoma* OR retinoblastoma* OR meningioma* OR seminoma* OR carcinosarcoma* OR angiosarcoma* OR chondrosarcoma* OR cholangiocarcinoma* OR medulloblastoma* OR astrocytoma* OR ependymoma* OR germinoma* OR craniopharyngioma*))))

Key:

[mh] = indexing term: Medical Subject Heading (MeSH)

* = truncation

ClinicalTrials.gov

via <https://clinicaltrials.gov/>

Date searched: 21 July 2022

Records retrieved: 232

Advanced search screen was used. 2 separate searches were used, retrieving 232 records in total, which were imported into EndNote 20 and deduplicated.

1. **Condition or Disease:** (CINV OR CANV)

Other Terms: (Dexamethasone OR Ondansetron OR Aprepitant OR Metoclopramide OR Serotonin "5-HT3 Receptor Antagonists" OR "Neurokinin-1 Receptor Antagonists" OR Palonosetron OR Methotrimeprazine OR Olanzapine OR Lorazepam OR Nabilone OR Granisetron OR Tropisetron) =
74 hits

2. **Condition or Disease:** (chemo* OR cisplatin* OR neoplasm* OR cancer* OR malignan* OR metasta* OR tumor* OR tumour OR oncolog*) AND (vomit* OR sick* OR emesia OR emesis OR emetic* OR emetogenic* OR hyperemesis OR anorex*)

Other Terms: (Dexamethasone OR Ondansetron OR Aprepitant OR Metoclopramide OR Serotonin "5-HT3 Receptor Antagonists" OR "Neurokinin-1 Receptor Antagonists" OR Palonosetron OR Methotrimeprazine OR Olanzapine OR Lorazepam OR Nabilone OR Granisetron OR Tropisetron) =
157 hits

WHO International Clinical Trials Registry Platform (ICTRP)

via <https://trialsearch.who.int/AdvSearch.aspx>

Date searched: 21 July 2022

Records retrieved: 409

Advanced search screen used. 2 separate searches were used, retrieving 399 records in total, which were imported into EndNote 20 and deduplicated.

1. Advanced Search

Condition: (chemo* OR cisplatin* OR neoplasm* OR cancer* OR malignan* OR metasta* OR tumor* OR tumour* OR oncolog*) AND (vomit* OR sick* OR emesia OR emesis OR emetic* OR emetogenic* OR hyperemesis OR anorex*)

Intervention: (Dexamethasone OR Ondansetron OR Aprepitant OR Metoclopramide OR Serotonin "5-HT3 Receptor Antagonists" OR "Neurokinin-1 Receptor Antagonists" OR Palonosetron OR Methotrimeprazine OR Olanzapine OR Lorazepam OR Nabilone OR Granisetron OR Tropisetron)

Recruitment Status: ALL = **302 records for 174 trials found**

2. Advanced Search

Title: (chemo* OR cisplatin* OR neoplasm* OR cancer* OR malignan* OR metasta* OR tumor* OR tumour* OR oncolog*)

Condition: (vomit* OR sick* OR emesia OR emesis OR emetic* OR emetogenic* OR hyperemesis OR anorex*)

Intervention: (Dexamethasone OR Ondansetron OR Aprepitant OR Metoclopramide OR Serotonin "5-HT3 Receptor Antagonists" OR "Neurokinin-1 Receptor Antagonists" OR Palonosetron OR Methotrimeprazine OR Olanzapine OR Lorazepam OR Nabilone OR Granisetron OR Tropisetron)

Recruitment Status: ALL = 351 records for 235 trials found

Key:

* = truncation

ProQuest Dissertations & Theses A&I

via <https://www.proquest.com/>

Date range: 1743 - Present

Date searched: 21 July 2022

Records retrieved: 37

TI,AB,SU((chemo* OR cisplatin* OR neoplasm* OR cancer* OR malignan* OR metasta* OR tumor* OR tumour OR oncolog*) AND (vomit* OR sick* OR emesia OR emesis OR emetic* OR emetogenic* OR hyperemesis OR anorex*)) AND TI,AB,SU(Dexamethasone OR Ondansetron OR Aprepitant OR Metoclopramide OR Serotonin "5-HT3 Receptor Antagonists" OR "Neurokinin-1 Receptor Antagonists" OR Palonosetron OR Methotrimeprazine OR Olanzapine OR Lorazepam OR Nabilone OR Granisetron OR Tropisetron)

Key:

TI,AB,SU = in title, abstract or subject field

* = truncation

Database of Abstracts of Reviews of Effects (DARE)

via <https://www.crd.york.ac.uk/CRDWeb/>

Date range searched: Inception to December 2014

Date searched: 21 July 2022

Records retrieved: 33

1	MeSH DESCRIPTOR Vomiting WITH QUALIFIER CI IN DARE	44
2	MeSH DESCRIPTOR Nausea WITH QUALIFIER CI IN DARE	55

3	MeSH DESCRIPTOR Anorexia WITH QUALIFIER CI IN DARE	2
4	(CINV or CANV) IN DARE	3
5	((chemo* or cisplatin*) NEAR2 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)) IN DARE	39
6	#1 OR #2 OR #3 OR #4 OR #5	82
7	MeSH DESCRIPTOR Neoplasms WITH QUALIFIER DT IN DARE	227
8	MeSH DESCRIPTOR Antineoplastic Protocols EXPLODE ALL TREES IN DARE	588
9	MeSH DESCRIPTOR Antineoplastic Agents IN DARE	684
10	MeSH DESCRIPTOR Chemoradiotherapy EXPLODE ALL TREES IN DARE	88
11	MeSH DESCRIPTOR Chemotherapy, Adjuvant EXPLODE ALL TREES IN DARE	317
12	MeSH DESCRIPTOR Consolidation Chemotherapy IN DARE	1
13	MeSH DESCRIPTOR Electrochemotherapy IN DARE	4
14	MeSH DESCRIPTOR Induction Chemotherapy IN DARE	13
15	MeSH DESCRIPTOR Maintenance Chemotherapy IN DARE	13
16	MeSH DESCRIPTOR Photochemotherapy IN DARE	43
17	(chemo* or radiochemotherap* or radio-chemotherap* or electrochemotherap* or electro-chemotherap* or photochemotherap* or photo-chemotherap*) IN DARE	2219
18	((neoplasm* or cancer* or malignan* or metasta* or tumor* or tumour* or carcinoma* or adenocarcinoma* or oncolog* or leukaemia* or leukemia* or adenoma* or lymphoma* or melanoma* or sarcoma* or myeloma* or blastoma* or mesenchymoma* or mesothelioma* or thymoma* or hepatoma* or hepatoblastoma* or glioma* or ganglioglioma* or glioblastoma* or neuroblastoma* or retinoblastoma* or meningioma* or seminoma* or carcinosarcoma* or angiosarcoma* or chondrosarcoma* or cholangiocarcinoma* or medulloblastoma* or astrocytoma* or ependymoma* or germinoma* or craniopharyngioma*) NEAR5 (drug* or agent* or treat* or therap* or pill* or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)) IN DARE	3233
19	((antineoplas* or anti-neoplas* or anticancer or anti-cancer or antitumor or anti-tumor or antitumour or anti-tumour) NEAR5 (drug* or agent* or treat* or therap* or pill* or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)) IN DARE	1333
20	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	4045
21	MeSH DESCRIPTOR Vomiting, Anticipatory IN DARE	2
22	MeSH DESCRIPTOR Vomiting IN DARE	105
23	MeSH DESCRIPTOR Nausea IN DARE	105
24	(nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*) IN DARE	1448
25	MeSH DESCRIPTOR Antiemetics IN DARE	107

26 (antiemetic* or anti-emetic* or antiemetogenic* or anti-emetogenic*) IN DARE 151

27 #21 OR #22 OR #23 OR #24 OR #25 OR #26 1462

28 #20 AND #27 254

29 #6 OR #28 281

30 MeSH DESCRIPTOR Dexamethasone IN DARE 79

31 (dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or 7s5i7g3jql or decadron or diodex or baycadron or ciprodex or dextenza or dioptril or hidex 6-day taper or maxitrol or neofordex or ozurdex or taperdex 12 day taper or taperdex 6 day taper or taperdex 7-day taper or tobradex or zcort 7 day taper) IN DARE 204

32 MeSH DESCRIPTOR Ondansetron IN DARE 25

33 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedantron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or gr 38032f or gr-38032f or gr38032f or nmh84ozk2b or sn 307 or sn-307 or sn307 or sud 002 or sud002 or suda 002 or suda002) IN DARE 64

34 MeSH DESCRIPTOR Aprepitant IN DARE 0

35 (aprepitant or emend or l 754030 or l-754030 or l754030 or mk 0517 or mk 0869 or mk 869 or mk-0517 or mk-0869 or mk-869 or mk0517 or mk0869 or mk869 or Cinvanti or Ivemend) IN DARE 3

36 MeSH DESCRIPTOR Metoclopramide IN DARE 22

37 (metoclopramide* or 5yna80e9to or cerucal or l4yeb44i46 or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or Metozolv ODT) IN DARE 71

38 MeSH DESCRIPTOR Serotonin 5-HT3 Receptor Antagonists IN DARE 16

39 (serotonin 5-ht3 receptor antagonist* or 5 ht3 antagonist* or 5-ht3 antagonist* or serotonin 5 ht3 receptor antagonist* or 5-hydroxytryptamine3 or 5-hydroxytryptamine type 3-receptor antagonist) IN DARE 23

40 MeSH DESCRIPTOR Neurokinin-1 Receptor Antagonists IN DARE 1

41 ((neurokinin 1 or neurokinin-1 or neuroleukin 1 or neuroleukin-1 or substance p receptor or tachykinin receptor 1) NEAR3 (antagonist* or blocker*)) IN DARE 2

42 MeSH DESCRIPTOR Palonosetron IN DARE 0

43 (palonosetron* or 2-qhbiqo or 23310d4i19 or 2ucb21er4v or 5d06587d6r or aloxi* or onicit* or rs 25233* or rs 25259) IN DARE 4

44 MeSH DESCRIPTOR Methotrimeprazine IN DARE 0

45 (methotrimeprazine or 9g0law7atq or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiserin or tizercine or tizertsin or Nozinan or levoprome or detenler or himamin or levotomin) IN DARE 13

46 MeSH DESCRIPTOR Olanzapine IN DARE 0

47 (Olanzapine or ly 17005* or n7u69t4szz or x7s6q4mhcb or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis) IN DARE 172

- 48 MeSH DESCRIPTOR Lorazepam IN DARE 7
- 49 (Lorazepam* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazepam or novo-lorazepam or nu lorazepam or nu-lorazepam or o26fzp7691 or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy-4036 or wy4036 or loreev) IN DARE 63
- 50 MeSH DESCRIPTOR Cannabinoids IN DARE 12
- 51 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514) IN DARE 6
- 52 MeSH DESCRIPTOR Granisetron IN DARE 7
- 53 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6170j8" or "bri 43694*" or kytril or wzg3j2mcol) IN DARE 26
- 54 MeSH DESCRIPTOR Tropisetron IN DARE 0
- 55 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205930" or "indole 3 carboxylic acid tropine ester" or navoban) IN DARE 26
- 56 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 543
- 57 #29 AND #56 33

Key:

MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)

EXPLODE ALL TREES = exploded indexing term (MeSH)

WITH QUALIFIER CI = indexing term with chemically induced subheading

WITH QUALIFIER DT indexing term with drug therapy subheading

* = truncation

NEAR2 = terms within three words of each other (only in the order specified)

Epistemonikos

via <https://www.epistemonikos.org/>

Date range searched: Inception to 21 July 2022

Date searched: 21 July 2022

Records retrieved: 183

((chemo* OR cisplatin* OR neoplasm* OR cancer* OR malignan* OR metasta* OR tumor* OR tumour OR oncolog*) AND (vomit* OR sick* OR emesia OR emesis OR emetic* OR emetogenic* OR hyperemesis OR anorex*)) AND (Dexamethasone OR Ondansetron OR Aprepitant OR Metoclopramide OR Serotonin "5-HT3 Receptor Antagonists" OR "Neurokinin-1 Receptor Antagonists" OR Palonosetron OR Methotrimeprazine OR Olanzapine OR Lorazepam OR Nabilone OR Granisetron OR Tropisetron)

183 results when narrowed to publication type: systematic reviews

Key:

* = truncation

PROSPERO

via <https://www.crd.york.ac.uk/prosperto/#searchadvanced>

Date range searched: Inception to 21 July 2022

Date searched: 21 July 2022

Records retrieved: 54

- | | | |
|-----|---|------|
| #1 | MeSH DESCRIPTOR Vomiting WITH QUALIFIER CI | 0 |
| #2 | MeSH DESCRIPTOR Nausea WITH QUALIFIER CI | 0 |
| #3 | MeSH DESCRIPTOR Anorexia WITH QUALIFIER CI | 0 |
| #4 | (CINV or CANV) | 44 |
| #5 | ((chemo* or cisplatin*) NEAR2 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)) | 80 |
| #6 | #1 OR #2 OR #3 OR #4 OR #5 | 83 |
| #7 | MeSH DESCRIPTOR Neoplasms WITH QUALIFIER DT | 1 |
| #8 | MeSH DESCRIPTOR Antineoplastic Protocols EXPLODE ALL TREES | 70 |
| #9 | MeSH DESCRIPTOR Antineoplastic Agents | 178 |
| #10 | MeSH DESCRIPTOR Chemoradiotherapy EXPLODE ALL TREES | 71 |
| #11 | MeSH DESCRIPTOR Chemotherapy, Adjuvant EXPLODE ALL TREES | 88 |
| #12 | MeSH DESCRIPTOR Consolidation Chemotherapy | 4 |
| #13 | MeSH DESCRIPTOR Electrochemotherapy | 3 |
| #14 | MeSH DESCRIPTOR Induction Chemotherapy | 17 |
| #15 | MeSH DESCRIPTOR Maintenance Chemotherapy | 3 |
| #16 | MeSH DESCRIPTOR Photochemotherapy | 59 |
| #17 | (chemo* or radiochemotherap* or radio-chemotherap* or electrochemotherap* or electro-chemotherap* or photochemotherap* or photo-chemotherap*) | 7017 |
| #18 | ((neoplasm* or cancer* or malignan* or metasta* or tumor* or tumour* or carcinoma* or adenocarcinoma* or oncolog* or leukaemia* or leukemia* or adenoma* or lymphoma* or melanoma* or sarcoma* or myeloma* or blastoma* or mesenchymoma* or mesothelioma* or thymoma* or hepatoma* or hepatoblastoma* or glioma* or ganglioglioma* or glioblastoma* or neuroblastoma* or retinoblastoma* or meningioma* or seminoma* or carcinosarcoma* or angiosarcoma* or | |

- chondrosarcoma* or cholangiocarcinoma* or medulloblastoma* or astrocytoma* or ependymoma* or germinoma* or craniopharyngioma*) NEAR5 (drug* or agent* or treat* or therap* or pill* or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)) 8786
- #19 ((antineoplas* or anti-neoplas* or anticancer or anti-cancer or antitumor or anti-tumor or antitumour or anti-tumour) NEAR5 (drug* or agent* or treat* or therap* or pill* or capsule* or topical* or medicine* or medication* or tablet* or dose* or dosage* or pharmac* or inject* or intravenous* or monotherap* or immunotherap*)) 796
- #20 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
12472
- #21 MeSH DESCRIPTOR Vomiting, Anticipatory 0
- #22 MeSH DESCRIPTOR Vomiting 60
- #23 MeSH DESCRIPTOR Nausea 44
- #24 (nausea* or vomit* or sick* or emesia or emesis or emetic* or emetogenic* or hyperemesis or anorex*)
5688
- #25 MeSH DESCRIPTOR Antiemetics 52
- #26 (antiemetic* or anti-emetic* or antiemetogenic* or anti-emetogenic*) 237
- #27 #21 OR #22 OR #23 OR #24 OR #25 OR #26 5730
- #28 #20 AND #27 602
- #29 #6 OR #28 602
- #30 MeSH DESCRIPTOR Dexamethasone 50
- #31 (dexameth* or decaject* or decameth or decaspray or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or 7s5i7g3jql or decadron or diodex or baycadron or ciprodex or dextenza or dioptril or hidex 6-day taper or maxitrol or neofordex or ozurdex or taperdex 12 day taper or taperdex 6 day taper or taperdex 7-day taper or tobradex or zcort 7 day taper) 558
- #32 MeSH DESCRIPTOR Ondansetron9
- #33 (ondansetron or zofran or zophran or zofron or zophren or zofrene or zetron or avessaron or vomceran or zensana or emeset or zondamist or zuplenz or bryterol or cedantron or cellondan or ceramos or narfoz or onsia or sakisozin or setofilm or gr 38032f or gr-38032f or gr38032f or nmh84ozk2b or sn 307 or sn-307 or sn307 or sud 002 or sud002 or suda 002 or suda002) 56
- #34 MeSH DESCRIPTOR Aprepitant 2
- #35 (aprepitant or emend or l 754030 or l-754030 or l754030 or mk 0517 or mk 0869 or mk 869 or mk-0517 or mk-0869 or mk-869 or mk0517 or mk0869 or mk869 or Cinvanti or Ivemend) 23
- #36 MeSH DESCRIPTOR Metoclopramide 6
- #37 (metoclopramide* or 5yna80e9to or cerucal or l4yeb44i46 or maxolon or primperan or reglan or rimetin or w1792a2rvd or Gimoti or Reglan or Metozolv ODT) 63
- #38 MeSH DESCRIPTOR Serotonin 5-HT3 Receptor Antagonists 3

- #39 (serotonin 5-ht3 receptor antagonist* or 5 ht3 antagonist* or 5-ht3 antagonist* or serotonin 5 ht3 receptor antagonist* or 5-hydroxytryptamine3 or 5-hydroxytryptamine type 3-receptor antagonist)17
- #40 MeSH DESCRIPTOR Neurokinin-1 Receptor Antagonists 4
- #41 ((neurokinin 1 or neurokinin-1 or neuroleukin 1 or neuroleukin-1 or substance p receptor or tachykinin receptor 1) NEAR3 (antagonist* or blocker*)) 17
- #42 MeSH DESCRIPTOR Palonosetron 2
- #43 (palonosetron* or 2-qhbiqo or 23310d4i19 or 2ucb21er4v or 5d06587d6r or aloxi* or onicit* or rs 25233* or rs 25259) 24
- #44 MeSH DESCRIPTOR Methotrimeprazine 1
- #45 (methotrimeprazine or 9g0law7atq or levomeprazin or levomepromazine or levopromazine or methotrimeprazine or tiscercin or tizercine or tizertsin or Nozinan or levoprome or detenler or himamin or levotomin) 34
- #46 MeSH DESCRIPTOR Olanzapine 1
- #47 (Olanzapine or ly 17005* or n7u69t4szz or x7s6q4mhcb or zolafren or zyprexa or lybalvi or olazax or symbyax or zalasta or zypadhera or zydis) 209
- #48 MeSH DESCRIPTOR Lorazepam 2
- #49 (Lorazep* or ativan or donix or duralozam or durazolam or idalprem or laubeel or novo lorazem or novo-lorazem or nu loraz or nu-loraz or o26fzp769l or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tolid or "wy 4036" or wy-4036 or wy4036 or loreev) 87
- #50 MeSH DESCRIPTOR Cannabinoids 83
- #51 (nabilone or cesamet or cesametic or canemes or "compound 109514" or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514) 78
- #52 MeSH DESCRIPTOR Granisetron 1
- #53 (Granisetron or Sancuso or Sustol or "107007-99-8" or "318f6l70j8" or "brl 43694*" or kytril or wzg3j2mcol) 22
- #54 MeSH DESCRIPTOR Tropisetron 1
- #55 (Tropisetron or "6i819nik1w" or a19338q2yo or "ics 205 930" or "ics 205930" or "indole 3 carboxylic acid tropine ester" or navoban) 11
- #56 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 1062
- #57 #29 AND #56 54

Key:

MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)

EXPLODE ALL TREES = exploded indexing term (MeSH)

WITH QUALIFIER CI = indexing term with chemically induced subheading

WITH QUALIFIER DT indexing term with drug therapy subheading

* = truncation

NEAR2 = terms within three words of each other (only in the order specified)

2.3 Data Dictionary for Individual Participant Data

This data dictionary is based upon templates from previous IPD synthesis projects conducted within the Centre for Reviews and Dissemination, for example, Rogers et al. 2020 (Rodgers et al., 2020); therefore, the coding system used closely matches that within this publication.



Antiemetics for the prevention of chemotherapy-induced nausea and vomiting.

This Word document details a suggested coding system, which will hopefully minimise any risk of your trial coding being misinterpreted. The document sets out the variables I aim to collect, the names of each and how they will be coded in the combined dataset.

If possible, please supply your trial data using the suggested coding in the coding document. Should some of your data not fit with the suggested format, please indicate this by clearly highlighting it either in the data file or in a separate document or email.

Please do not include any codes or labels that could potentially identify any participants, such as names, locations/address details or dates of birth.

Whilst the Word document shows the preferred format to receive the data, IPD will be accepted in any usable format, provided I have the means of handling it. It is preferred that data be sent as Microsoft Excel spreadsheets (filenames ending in .xls or .xlsx). If this is not possible, other spreadsheet formats may be used, that can be read by Excel can be used instead, such as comma-separated files (.csv), tab-delimited files, or OpenDocument (.ods) spreadsheets.

If you are unable to recode your data into the suggested format, please prepare the data using your own coding and supply a coding document describing how each included variable is coded. If you anticipate any difficulties in preparing data, such as a lack of time or resources to code data, please don't hesitate to contact me.

Next steps:

Once the data is ready to share, please contact me and I can share the link to securely transfer the IPD using the University of York "DropOff Service" <https://www.york.ac.uk/it-services/services/dropoff/>, which is intended for secure transfer of large files to University of York Staff (the link for the data is then valid for 7 days from the point of request).

Spreadsheet/sheet 1 (Trial information): Please provide information on all patients even if individuals were excluded from analysis.	
Trial information	Suggested format
Treatment comparisons	Free text field – please specify: Control treatment arm: Active treatment arm: Active treatment arm 2 (If applicable):
Treatment dosage	Free text field – please specify: The dosage of antiemetics for all treatment arms of the trial: Control treatment arm: Active treatment arm: Active treatment arm 2 (If applicable):
Timing and scheduling of antiemetics given in trial	Free text field – please specify: The time of day and schedule of antiemetics for all treatment arms of the trial. Control treatment arm: Active treatment arm: Active treatment arm 2 (If applicable):
Anxiety scale used	Free text field – please specify: The scale(s) used to measure baseline anxiety levels if recorded in trial

Spreadsheet/sheet 1 (Trial information): Please provide information on all patients even if individuals were excluded from analysis.	
Trial information	Suggested format
	7 = not collected in trial
Nausea severity scale used	Free text field – please specify: The scale(s) used to measure severity of nausea if recorded in trial 7 = not collected in trial
Vomiting severity scale used	Free text field – please specify: The scale(s) used to measure severity of vomiting if recorded in trial 7 = not collected in trial
Quality of life scale used	Free text field – please specify: The scale(s) used to measure quality of life if recorded in trial 7 = not collected in trial
Complete control/response definition	Free text field – please specify: The definition of complete control within your trial
Partial control/response definition	Free text field – please specify: The definition of partial control within your trial
Acute phase definition	Free text field – please specify: The definition of acute phase within your trial
Delayed phase definition	Free text field – please specify: The definition of delayed phase within your trial

Spreadsheet/sheet 1 (Trial information): Please provide information on all patients even if individuals were excluded from analysis.	
Trial information	Suggested format
Overall phase definition	Free text field – please specify: The definition of overall phase within your trial

Spreadsheet/sheet 2 (Baseline data): Please provide information on all patients, even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Patient ID	PatID	Any unique coding may be used
Date of randomisation	DateRandom	Date in dd/mm/yyyy format
Age at baseline	AgeRand	Numeric value (in years) 77 = not collected in trial 99 = missing for this patient
Ethnicity	Ethnicity	11 = African-American 12 = Afro-Caribbean 13 = African or other Black ethnicity 21 = East Asian (e.g. Chinese/Japanese) 22 = South Asian (e.g. Indian/Pakistani) 31 = Hispanic or Latino

Spreadsheet/sheet 2 (Baseline data): Please provide information on all patients, even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		32 = Hispanic Black 33 = Hispanic White 41 = Middle Eastern or North African 51 = Native American or First Nations 52 = Pacific Islander 61 = White European or North American 62 = Other Caucasian / White 81 = Mixed ethnicity (any) 82 = Other 77 = Not collected in trial 99 = missing for this patient
Weight at baseline	Weight	Numeric value in kilogram (kg) 777 = not collected in trial 888 = NA BMI provided 999 = missing for this patient
Height at baseline	Height	Numeric value in metres (m) 777 = not collected in trial 888 = NA BMI provided 999 = missing for this woman

Spreadsheet/sheet 2 (Baseline data): Please provide information on all patients, even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Treatment arm assigned	Arm	0= Control arm 1= Active treatment arm 2= Active treatment arm 2 (if applicable) 9 = missing for this patient
Sex	Sex	0= Male 1= Female 7= not collected in trial 9 = missing for this patient
Primary diagnosis	Diagnosis	1= Leukaemia 2= Brain tumours 3=Lymphoma 4=Osteosarcoma 5=Ewing sarcoma 6=Rhabdomyosarcoma 7=Neuroblastoma 8=Wilms tumour

Spreadsheet/sheet 2 (Baseline data): Please provide information on all patients, even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		9=Germ cell tumours 10=Retinoblastoma 11=Liver tumours 12=Langerhans Cell Histiocytosis (LCH) 13=Other
Duration of illness	Duration	Numeric value in months 7= not recorded in this trial 9= missing for this patient
Type of chemotherapy	Chemo	Free text field 7= not recorded in this trial 9= missing for this patient
Emetogenicity of chemotherapy regimen	Emetogenicity	0=low emetogenicity 1= moderate emetogenicity 2= high emetogenicity 7= not recorded in this trial 9= missing for this patient
Duration of chemotherapy	ChemoBlock	0=single day 1=multi-day 7= not recorded in this trial

Spreadsheet/sheet 2 (Baseline data): Please provide information on all patients, even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		9= missing for this patient
ECOG performance status	ECOG	0=0-1 1= $\geq$ 2 7= not recorded in this trial 9= missing for this patient
Concomitant medication used (excluding rescue medication- see outcomes section)	ConcomitantMed	Free text field NA= none used for this patient 7= not records in this trial 9= missing for this patient
Prior exposure to chemotherapy	PriorExposure	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
History of motion sickness	MotionSickHist	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Previous experience of CINV	PriorCINV	0= no 1=yes

Spreadsheet/sheet 2 (Baseline data): Please provide information on all patients, even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		7= not recorded in this trial 9= missing for this patient
Anxiety levels at baseline	BaseAnxiety	Numeric value of any valid measurement scale (note scale used in sheet 1) 7777= not recorded in this trial 9999= missing for this patient
Reduced baseline sleep quality/quantity	BaselineSleep	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Reduced baseline sleep quality	BaselineSleepQoL	0= no 1=yes 7= not recorded in this trial 9= missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Patient ID	PatID	Any unique coding may be used
Treatment arm assigned	Arm	0= Control arm 1= Active treatment arm 2= Active treatment arm 2 (if applicable) 9 = missing for this patient
Acute phase outcomes (Note definition in sheet 1)		
Achieved control/response in acute phase	AcuteComControl	(Note definition in sheet 1) 0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Achieved partial control/response in acute phase	AcuteParControl	(Note definition in sheet 1) 0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Nausea in acute phase	AcuteNausea	0= no nausea 1= nausea 7= not recorded in this trial

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		9= missing for this patient
Nausea severity in acute phase	AcuteNausSev	Numeric value (any validated severity scale) 77= not recorded in this trial 999= missing for this patient
Length of time feeling nauseous in acute phase	AcuteNausLength	Numeric value in hours 77= not recorded in this trial 999= missing for this patient
Vomiting in acute phase	AcuteVomit	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Vomiting severity in acute phase	AcuteVomSev	Numeric value (any validated severity scale) 77= not recorded in this trial 999= missing for this patient
Required rescue medication in acute phase	AcuteRescue	0= no 1=yes 7= not recorded in this trial 9= missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Type of rescue medication used	AcuteRescueType	Free text field 7= not recorded in this trial 9= missing for this patient
Delayed phase outcomes (Note definition in sheet 1)		
Achieved complete control/response in delayed phase	DelayComControl	(Note definition in sheet 1) 0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Achieved partial control/response in delayed phase	DelayParControl	(Note definition in sheet 1) 0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Nausea in delayed phase	DelayNausea	0= no nausea 1= nausea 7= not recorded in this trial 9= missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Nausea severity in delayed phase	DelayNausSev	Numeric value (any validated severity scale) 77= not recorded in this trial 999= missing for this patient
Length of time feeling nauseous in delayed phase	DelayNausLength	Numeric value in hours 77= not recorded in this trial 999= missing for this patient
Vomiting in delayed phase	DelayVomit	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Vomiting severity in delayed phase	DelayVomSev	Numeric value (any validated severity scale) 77= not recorded in this trial 999= missing for this patient
Required rescue medication in delayed phase	DelayRescue	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Type of rescue medication used in delayed phase	DelayRescueType	Free text field 7= not recorded in this trial

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		9= missing for this patient
Overall phase outcomes (Note definition in sheet 1)		
Achieved complete control/response in overall phase	OverallComControl	(Note definition in sheet 1) 0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Achieved partial control/response in overall phase	OverallParControl	(Note definition in sheet 1) 0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Nausea in overall phase	OverallNausea	0= no nausea 1= nausea 7= not recorded in this trial 9= missing for this patient
Nausea severity in overall phase	OverallNausSev	Numeric value (any validated severity scale) 77= not recorded in this trial 999= missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Length of time feeling nauseous in overall phase	OverallNausLength	Numeric value in hours 77= not recorded in this trial 999= missing for this patient
Vomiting in overall phase	OverallVomit	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Vomiting severity in overall phase	OverallVomSev	Numeric value (any validated severity scale) 77= not recorded in this trial 999= missing for this patient
Required rescue medication used in overall phase	OverallRescue	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Type of rescue medication used in overall phase	OverallRescueType	Free text field 7= not recorded in this trial 9= missing for this patient
Outcomes related to quality of life		

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Quality of life	QoL	Numeric value (any validated QoL measure e.g., PedsQL) 77= not recorded in this trial 999= missing for this patient
Increased appetite	IncreaseAppetite	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Decreased appetite	DecreaseAppetite	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Increased sleep quantity	IncreaseSleep	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Decreased sleep quantity	DecreaseSleep	0= no 1=yes 7= not recorded in this trial 9= missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
Increased quality of sleep	IncreaseSleepQol	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Decreased quality of sleep	DecreaseSleepQol	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Increased nausea with motion (e.g., on car journeys)	MotionSick	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Anxiety	Anxiety	Numeric value of any valid measurement scale (note scale used in sheet 1) 7777= not recorded in this trial 9999= missing for this patient
Other & adverse event outcomes		
Anticipatory nausea or vomiting prior to subsequent cycles of chemotherapy	Anticipatory	0= no 1=yes 7= not recorded in this trial

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
		9= missing for this patient
Decreased fluid intake	Fluid	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Number of unscheduled hospital visits for hydration	HospHyd	Numeric value (number of unscheduled hospital visits for hydration) 777= not recorded in this trial 999= missing for this patient
Decreased food intake	FoodIntake	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Required Nasogastric tube	NGTube	0= no 1=yes 7= not recorded in this trial 9= missing for this patient
Discontinuation of study treatment	DisconTreat	0 = no discontinuation 1 = yes discontinued because of AE/side effects 2 = discontinued for reason other than side effects 3 = discontinued but reason not known

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
			7 = not recorded in trial 9 = missing for this patient
Death		Death	0 = No 1 = Yes 7 = not collected in trial 9 = missing for this patient
Adverse events	Drug-related adverse events	DrugRelAEs	Numeric value (total number of drug related AEs for this patient) 777= not recorded in this trial 999= missing for this patient
	Drug-related serious adverse events	DrugRelSAEs	Numeric value (total number of drug related SAEs for this patient) 777= not recorded in this trial 999= missing for this patient
	Drowsiness	Drowsy	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Dry mouth	DryMouth	0 = none recorded 1 = yes

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
			2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Water retention	WaterRet	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Dizziness	Dizzy	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Raised blood sugar levels	BloodSug	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Headache	Headache	0 = none recorded

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
			1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Fatigue	Fatigue	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Myalgia	Myalgia	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Abdominal pain	AbPain	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
	Gastritis	Gastritis	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Diarrhoea	Diarrhoea	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Constipation	Constipation	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
	Cough	Cough	0 = none recorded 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Hiccups	Hiccups	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Anaphylaxis	Anaphylax	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
	Anorexia	Anorexia	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Extrapyramidal Disorder	ExtraPhr	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Pruritus	Pruritus	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
	Sedation	Sedation	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Agitation	Agitation	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Pneumonia	Pneumonia	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
	Febrile neutropenia	FebNeut	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Neutropenia	Neutropenia	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Anaemia	Anaemia	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.			
Variable		Variable name in data file	Suggested coding
	Thrombocytopenia	Thrombocyt	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Mucositis	Mucositis	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Fever	Fever	0 = no 1 = yes 2= yes and thought to be related to study medication 7 = not recorded in trial 9 = missing for this patient
	Other	OtherAE	Free text (Note any other adverse event(s) experienced for this patient) NA = no other AE recorded for this patient 7= not recorded in this trial 9= missing for this patient

Spreadsheet/sheet 3 (Outcome data): Please provide information on all patients even if individuals were excluded from analysis.		
Variable	Variable name in data file	Suggested coding
SAEs	SAE	Free text (Note type of SAE(s) experienced by this patient) NA= No SAEs recorded for this patient 7= not recorded in this trial 9 = missing for this patient
Whether the patient was excluded from trial analysis	Exclusion	0 = not excluded 1 = excluded 9 = unknown
Reason for exclusion	ReasonExcluded	Free text (50 characters max) Please give brief description of reason for exclusion e.g. lost to follow up 8 = NA excluded

2.4 Data checking and harmonisation of Individual Participant Data

The IPD were checked and ‘harmonised’ using a standardised procedure (Figure 2-1) informed by processes recommended in Riley et al. 2022 (Riley et al., 2021). Two reviewers were involved in the data checking process: one who conducted the primary checking, and one who verified/checked the results of this.

The process ensured that the data was received, and stored correctly and was coded in line with the pre-specified data dictionary (included in the previous section of this appendix). Trial investigators were asked to confirm that variables missing from the dataset entirely were truly not collected by trial investigators, i.e. were systematically missing (Riley et al., 2021). The IPD was then examined for missing, implausible or inconsistent values. This included checking continuous variables, e.g. height and weight, fell within sensible limits, and participants did not have mutually exclusive events, e.g. those with no prior exposure to chemotherapy, should not have a history of CIN V.

Checks were also made to inform the risk of bias assessment. This involved checking the integrity of the randomisation process by graphically examining, where possible, the date of randomisation by treatment arm to look for obvious imbalances in allocation over time (or by days of the week). Baseline characteristics were then checked graphically for imbalances across treatment arms, and the proportion of missing outcome data by treatment arm was calculated for each variable to check that these were roughly equal. If patients were excluded from the analysis reported in a clinical trial publication (i.e. an intention-to-treat method was not applied), IPD were checked to ensure this outcome data was available and could be included in the IPD NMA. If access to the IPD impacted the original assessment of risk of bias, this was also communicated to the trial investigators.

Finally, summary statistics for baseline characteristics and outcome were generated to ensure that these agreed with the clinical trial publications and that any major differences were understood and/or discussed with trial investigators. Any problems and discrepancies were discussed and resolved with trial investigators, and a document summarising the final information held for each study and any amendments made to the original data was provided.

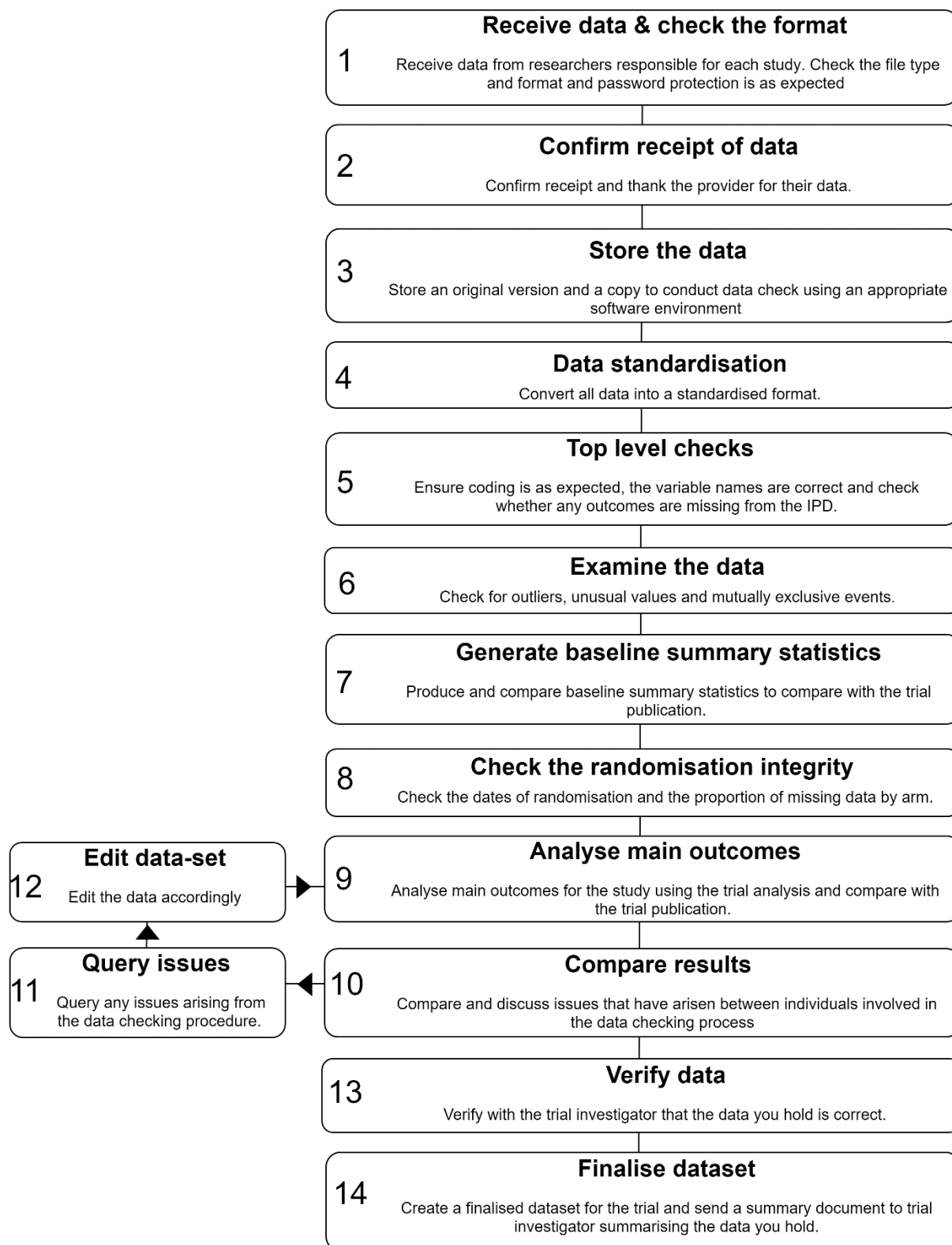


Figure 2-1 Stages of the individual participant data (IPD) checking process.

2.5 Baseline covariates and outcomes obtained from IPD

Table 2-1 Baseline covariates obtained from the IPD

IPD Study	Population	Treatments compared	Baseline covariate*																				
			PatID	Arm	DateRandom	AgeRand	Ethnicity	Weight	Height	Sex	Diagnosis	Duration	Chemo	Emetogenicity	ChemoBlock	ECOG	ConcomitantMed	PriorExposure	MotionSickHist	PriorCINV	BaseAnxiety	BaselineSleep	BaselineSleepQoL
Sharma et al. 2023	Child	1	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓			✓		✓				
Bakhshi et al. 2015	Child	2	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓			✓		✓				
Radhakrishnan et al. 2019	Child	2	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓		✓					
Kang et al. 2015	Child	2	✓	✓		✓	✓			✓	✓	✓		✓	✓								
Merck. Unpublished study	Child	2	✓	✓		✓	✓			✓	✓	✓		✓	✓								
Naik et al. 2020	Child	3	✓	✓		✓		✓	✓	✓	✓		✓	✓	✓	✓		✓		✓			
Moothedath et al 2022	Child	4	✓	✓		✓	✓	✓		✓		✓	✓	✓	✓			✓		✓			
Weinstein et al. 2016	Adult	2	✓	✓		✓	✓				✓	✓	✓					✓					
Rapoport et al. 2010	Adult	2	✓	✓		✓	✓																

Treatment comparison codes

- 1) Aprepitant + ondansetron + dexamethasone *vs* ondansetron + dexamethasone
- 2) Aprepitant + ondansetron + dexamethasone *vs* ondansetron + dexamethasone
- 3) Olanzapine + Aprepitant + ondansetron + dexamethasone *vs* Aprepitant + ondansetron + dexamethasone
- 4) Olanzapine + ondansetron + dexamethasone *vs* ondansetron + dexamethasone

*See appendix section 2.3 (data dictionary for individual participant data) for details of abbreviations for baseline covariates

Table 2-2 Outcomes of intended effects obtained from the IPD

IPD Study	Population	Treatments compared	Outcomes (intended effects) *																											
			AcuteComControl	AcuteParControl	AcuteNausea	AcuteNausSev	AcuteNausLength	AcuteVomit	AcuteVomSev	AcuteRescue	AcuteRescueType	DelayComControl	DelayParControl	DelayNausea	DelayNausSev	DelayNausLength	DelayVomit	DelayVomSev	DelayRescue	DelayRescueType	OverallComControl	OverallParControl	OverallNausea	OverallNausSev	OverallNausLength	OverallVomit	OverallVomSev	OverallRescue	OverallRescueType	
Sharma et al. 2023	Child	1	<					<	<			<				<	<			<					<	<	<	<		
Bakhshi et al. 2015	Child	2	<					<	<			<				<	<			<					<	<	<			
Radhakrishnan et al. 2019	Child	2	<	<	<	<		<	<			<	<	<		<	<			<	<	<	<		<	<	<	<		
Kang et al. 2015	Child	2	<					<	<	<		<				<	<	<		<					<	<	<			
Merck. Unpublished study	Child	2	<					<	<	<		<				<	<	<		<					<	<	<			
Naik et al. 2020	Child	3	<		<	<		<	<	<		<		<	<	<	<	<		<		<	<		<	<	<			
Moothedath et al 2022	Child	4	<	<				<	<			<	<			<	<			<	<				<	<	<	<		
Weinstein et al. 2016	Adult	2	<		<	<		<		<		<		<	<	<		<		<		<	<		<		<			
Rapoport et al. 2010	Adult	2	<		<	<		<		<		<		<	<	<		<		<		<	<		<		<			

Treatment comparison codes

- 1) Aprepitant + ondansetron + dexamethasone vs ondansetron + dexamethasone
- 2) Aprepitant + ondansetron + dexamethasone vs ondansetron + dexamethasone
- 3) Olanzapine + Aprepitant + ondansetron + dexamethasone vs Aprepitant + ondansetron + dexamethasone
- 4) Olanzapine + ondansetron + dexamethasone vs ondansetron + dexamethasone

*See appendix section 2.3 (data dictionary for individual participant data) for details of abbreviations for outcomes

Table 2-3 Outcomes related to quality of life obtained from the IPD

IPD Study	Population	Treatments compared	Outcomes (quality of life) *								
			QoL	IncreaseAppetite	DecreaseAppetite	IncreaseSleep	DecreaseSleep	IncreaseSleepQoL	DecreaseSleepQoL	MotionSick	Anxiety
Sharma et al. 2023	Child	1									
Bakhshi et al. 2015	Child	2			✓						
Radhakrishnan et al. 2019	Child	2			✓						
Kang et al. 2015	Child	2									
Merck. Unpublished study	Child	2									
Naik et al. 2020	Child	3		✓	✓						
Moothedath et al 2022	Child	4		✓	✓						✓
Weinstein et al. 2016	Adult	2									
Rapoport et al. 2010	Adult	2									

Treatment comparison codes

- 1) Aprepitant + ondansetron + dexamethasone *vs* ondansetron + dexamethasone
- 2) Aprepitant + ondansetron + dexamethasone *vs* ondansetron + dexamethasone
- 3) Olanzapine + Aprepitant + ondansetron + dexamethasone *vs* Aprepitant + ondansetron + dexamethasone
- 4) Olanzapine + ondansetron + dexamethasone *vs* ondansetron + dexamethasone

*See appendix section 2.3 (data dictionary for individual participant data) for details of abbreviations for outcomes

Table 2-4 Outcomes of unintended effects obtained from the IPD

IPD Study	Population	Treatments compared	Outcomes (unintended effects) *																									
			Anticipatory	Fluid	HospHyd	FoodIntake	NGTube	DisconTreat	Death	DrugRelAE	DrugRelSAE	Drowsy	DryMouth	WaterRet	Dizzy	BloodSug	Headache	Fatigue	Myalgia	AbPain	Gastritis	Diarrhoea	Constipation	Cough	Hiccups	Anaphylax	Anorexia	ExtraPhr
Sharma et al. 2023	Child	1														<	<		<			<	<	<		<		
Bakhshi et al. 2015	Child	2		✓		<										<			✓	✓	<	✓	✓	✓				
Radhakrishnan et al. 2019	Child	2														<			✓		<	✓	✓	✓				
Kang et al. 2015	Child	2																										
Merck. Unpublished study	Child	2																										
Naik et al. 2020	Child	3														<	✓	✓	✓	✓		✓	✓					
Moothedath et al 2022	Child	4						✓	✓				✓						✓			✓				✓		✓
Weinstein et al. 2016	Adult	2						✓																				
Rapoport et al. 2010	Adult	2						✓																				

Treatment comparison codes

- 5) Aprepitant + ondansetron + dexamethasone **vs** ondansetron + dexamethasone
- 6) Aprepitant + ondansetron + dexamethasone **vs** ondansetron + dexamethasone
- 7) Olanzapine + Aprepitant + ondansetron + dexamethasone **vs** Aprepitant + ondansetron + dexamethasone
- 8) Olanzapine + ondansetron + dexamethasone **vs** ondansetron + dexamethasone

*See appendix section 2.3 (data dictionary for individual participant data) for details of abbreviations for outcomes

Table 2-5 Outcomes of unintended effects obtained from the IPD continued

IPD Study	Population	Treatments compared	Outcomes (unintended effects continued) *												
			Sedation	Agitation	Pneumonia	FebNeut	Neutropenia	Anaemia	Thrombocyt	Mucositis	Fever	OtherAE	SAE	Exclusion	ReasonExcluded
Sharma et al. 2023	Child	1	✓		✓	✓	✓							✓	
Bakhshi et al. 2015	Child	2									✓			✓	
Radhakrishnan et al. 2019	Child	2				✓	✓		✓	✓	✓	✓	✓	✓	✓
Kang et al. 2015	Child	2													
Merck. Unpublished study	Child	2													
Naik et al. 2020	Child	3	✓			✓				✓				✓	
Moothedath et al 2022	Child	4	✓											✓	✓
Weinstein et al. 2016	Adult	2													
Rapoport et al. 2010	Adult	2													

Treatment comparison codes

- 1) Aprepitant + ondansetron + dexamethasone vs ondansetron + dexamethasone
- 2) Aprepitant + ondansetron + dexamethasone vs ondansetron + dexamethasone
- 3) Olanzapine + Aprepitant + ondansetron + dexamethasone vs Aprepitant + ondansetron + dexamethasone
- 4) Olanzapine + ondansetron + dexamethasone vs ondansetron + dexamethasone

*See appendix section 2.3 (data dictionary for individual participant data) for details of abbreviations for outcomes

2.6 Study characteristics of eligible clinical trials in children.

Table 2-6. Paediatric clinical trial included in the analyses of this research project.

Author and Year	Total N	Age range (years)	Reported cancer diagnoses	Emetogenicity of chemotherapy	Length of Chemotherapy Block	Prior chemotherapy exposure	Intervention (route of administration, dose and schedule Arm 1)	Intervention (route of administration, dose and schedule) Arm 2 and 3 (if applicable)
Sharma et al. 2020	78	5 to 18	Acute myeloid leukaemia	NR	3+7 regimens	chemotherapy naïve	Aprepitant (oral): Children 15–40kg: 80mg on days 1–3, children >40kg: 125mg on day 1, 80mg/kg on days 2-3. Ondansetron (IV): 0.15mg/kg (maximum of 8mg) every 8 hours on days 1-8	Ondansetron (IV): 0.15mg/kg (maximum of 8mg) every 8 hours on days 1-8
Bakshi et al. 2015	96	5 to 18	Hodgkin's lymphoma Osteosarcoma Ewing sarcoma Rhabdomyosarcoma Adenoid cystic carcinoma	HEC	Single-day and 3-day regimens	chemotherapy naïve	Aprepitant (oral): Children 15–40kg: 80mg on days 1–3, children >40kg: 125mg on day 1, 80mg/kg on days 2-3 Ondansetron (IV): 0.15mg/kg (maximum of 16mg) prior to chemotherapy + Dexamethasone (IV) 0.15 mg/kg prior to chemotherapy. Ondansetron (oral): 0.3 mg/kg + Dexamethasone(oral) 0.15 mg/kg every 8 hours until 48 hours after chemotherapy	Ondansetron (IV): 0.15mg/kg (maximum of 16mg) prior to chemotherapy + Dexamethasone (IV) 0.15 mg/kg prior to chemotherapy. Ondansetron (oral): 0.3 mg/kg + Dexamethasone(oral) 0.15 mg/kg every 8 hours until 48 hours after chemotherapy
Kang et al. 2015	307	0 to 17	Ewing's sarcoma Osteosarcoma Neuroblastoma Acute lymphocytic leukaemia Rhabdomyosarcoma Medulloblastoma Nephroblastoma	MEC and HEC	Most patients receiving chemotherapy for 3 days (range 1–7).	chemotherapy naïve and experienced	Aprepitant (oral): Children 6 months -12 years 3.0mg/kg (up to 125mg) on day 1, 2.0mg/kg (up to 80mg) on day 2-3. Children >12 years, 125mg on day 1, 80mg on day 2-3 + Ondansetron (oral): physicians' discretion median 0.18mg/kg (range 0.08-0.89) day 1 + Dexamethasone (IV) given	Ondansetron (oral): dose was at the physician's discretion on day 1 + Dexamethasone (IV) given at the physician's discretion in <50% patients

							at physician's discretion in <50% patients	
Gore et al. 2009	50	11 to 19	Most common bone sarcoma (remaining diagnoses NR)	NR	NR	chemotherapy naïve and experienced	Aprepitant (oral): 125mg on day 1, 80mg/kg on days 2-3 Ondansetron (IV): 0.15mg/kg, 3 times per day on days 1-2 Dexamethasone (oral): 8mg on day 1 and 4 mg on days 2-4	Ondansetron (IV): 0.15mg/kg, 3 times per day on days 1-2 Dexamethasone (oral): 16mg on day 1 and 8 mg on days 2-4
Malek et al. 2021	35	0 to 15	NR	MEC and HEC	NR	NR	Aprepitant (oral): Children 6 months -12 years 3.0mg/kg (up to 125mg) on day 1, 2.0mg/kg (up to 80mg) on day 2-3. Children >12 years, 125mg on day 1, 80mg on day 2-3 + Ondansetron (Route NR): 0.15 mg/kg then continued as prophylaxis on subsequent days of chemotherapy.	Ondansetron (Route NR): 0.15 mg/kg then continued as prophylaxis on subsequent days of chemotherapy.
Radhakrishnan et al. 2018	164	1 to 12	Acute lymphoblastic leukaemia Non-Hodgkin lymphoma Hodgkin Lymphoma Osteosarcoma Ewing sarcoma Wilms tumour Neuroblastoma Rhabdomyosarcoma	MEC and HEC	Single-day and 3-day regimens	chemotherapy naïve and experienced	Fosaprepitant (IV): 3 mg/kg on day 1 Ondansetron (IV): 0.15 mg/kg (max.16 mg) on day 1 Dexamethasone (IV): 0.075 mg/kg on day 1 then Ondansetron (oral): 0.3 mg/kg + Dexamethasone(oral) 0.075 mg/kg every 8 hours until 48 hours fosaprepitant then 0.15mg/kg until 48 hours after chemotherapy.	Ondansetron (IV): 0.15 mg/kg (max.16 mg) on day 1. Dexamethasone (IV): 0.075 mg/kg on day 1 then then Ondansetron (oral): 0.3 mg/kg + Dexamethasone(oral): 0.15mg/kg until 48 hours after chemotherapy.

Ruktrirong et al 2021	194	0 to 18	ALL AML HLH HL NHL LCH 7 Osteosarcoma Primary spinal cord germ cell tumour Extracranial germ cell tumour Rhabdomyosarcoma Fibrosarcoma	LEC, MEC and HEC	NR	chemotherapy naïve and experienced	Ondansetron (IV): 0.3mg/kg prior to chemotherapy (max dose 16mg)	Ondansetron (IV): 0.15mg/kg prior to chemotherapy (max dose 8mg) then subsequent doses every 8 hours until 24 hours after initial chemotherapy administration.
Sandoval et al 1999	31	0 to 18	Acute lymphoblastic leukaemia acute myeloblastic leukaemia; brain tumour; Ewing's sarcoma; hepatoblastoma; Hodgkin's disease; non- Hodgkin's lymphoma; neuroblastoma; rhabdomyosarcoma; Wilms' tumour.	MEC and HEC	Single- and 3-4- day regimens	chemotherapy naïve	Ondansetron (IV): 0.6mg/kg prior to chemotherapy (max dose 32mg)	Ondansetron (IV): 0.15mg/kg prior to chemotherapy (max dose 8mg) then 3 subsequent doses every 4 hours.
Chaudhary et al 2019	200	1 to 16	lymphoblastic leukaemia, Ewing's sarcoma, osteosarcoma, Hodgkin's lymphoma, non- Hodgkin's lymphoma, neuroblastoma	MEC and HEC	1-to-6-day regimens	chemotherapy naïve	Ondansetron (IV): 0.15mg/kg prior to chemotherapy (max dose 8mg), then subsequent doses every 8 hours for the period of chemotherapy. Dexamethasone (IV): 5 mg/kg/dose (max 8mg) every 12 hours after chemotherapy administration. Ondansetron (oral): 0.15mg/kg for 2 days + afterward the period of chemotherapy	Palonosetron (IV) 5µg/kg (max 0.25mg) prior to chemotherapy administration + additional dose at 72 hours if chemotherapy duration >3 days. Dexamethasone (IV): 5 mg/kg/dose (max 8mg) every 12 hours after chemotherapy administration.

White et al 2000	428	1 to 17	NR	MEC and HEC	NR	chemotherapy naïve and experienced	Ondansetron (oral): 8mg syrup prior to chemotherapy administration + Dexamethasone (oral): 2- 4mg prior to chemotherapy, then 6-8 hours after chemotherapy administration. Ondansetron (oral): 4mg 6- 8 hours after chemotherapy administration.	Ondansetron (IV): 5 mg/m2 prior to chemotherapy administration + Dexamethasone (oral): 2- 4mg prior to chemotherapy, then 6-8 hours after chemotherapy administration. Ondansetron (oral): 4mg 6- 8 hours after chemotherapy administration.
Brock et al 1996	187	1 to 16	NR	HEC	Multi-day regimens	chemotherapy naïve	Ondansetron (IV): 5 mg/m2 (maximum 8 mg) then two additional 5 mg/m2 dose at hours 8 and 16. Ondansetron (Oral): 4 mg for children < 1 m2 or 8 mg => 1 m2 3 times per day from 24 hours after chemotherapy to 3 - 5 days after last chemotherapy administration.	Ondansetron (IV): 10 mg/m2 (maximum 8 mg) then two additional 5 mg/m2 dose at hours 8 and 16. Ondansetron (Oral): 4 mg for children < 1 m2 or 8 mg => 1 m2 3 times per day from 24 hours after chemotherapy to 3 - 5 days after last chemotherapy administration.
Kovacs et al 2016	493	1 to 16	Acute lymphocytic leukaemia Nephroblastoma Rhabdomyosarcoma Neuroblastoma Medulloblastoma Acute leukaemia Ewing's sarcoma Hodgkin's disease Bone sarcoma Non-Hodgkin lymphoma Hodgkin's disease Acute myeloid leukaemia Ependymoma malignant Optic tract glioma T-cell type acute leukaemia	MEC and HEC	single to 6-day regimens	chemotherapy naïve and experienced	Ondansetron (IV): 3 × 150 µg/kg (max 32mg) prior to chemotherapy, then at hours 4 and 8 after chemotherapy administration	Arm 2: Palonosetron (IV) : 10 µg/kg (max 0.75 mg) prior to chemotherapy Arm 3: Palonosetron (IV): 20 µg/kg (max 1.5 mg) prior to chemotherapy

Li et al 2021	200	NR	Peripheral Osteosarcoma Medullary Osteosarcoma	MEC	Single and multiday regimens	NR	Palonosetron (IV): 10 µg/kg (max 0.75 mg) prior to chemotherapy	Granisetron (IV): 50 mg/kg prior to chemotherapy
Tan et al 2018	565	0–18	Neuroblastoma non-Hodgkin lymphoma Hodgkin's disease Hepatoblastoma Rhabdomyosarcoma Ewing's sarcoma Primitive neuroectodermal tumour Osteosarcoma	HEC	Single and multiday regimens	chemotherapy naïve and experienced	Ondansetron (IV): 150 µg/kg prior to chemotherapy, then every 8 hours on days of chemotherapy administration (up to max 32mg)	Arm 2: Palonosetron (IV): µg/kg (max 0.25 mg) prior to chemotherapy Arm 3: Palonosetron (IV): 10 µg/kg (max 0.5 mg) prior to chemotherapy
Siddique et al. 2011	60	4 to 11	Acute lymphoblastic leukaemia	Received only high-dose methotrexate	NR	NR	Ondansetron (oral): 4 mg before chemotherapy administration. Up to five additional doses given within 24 hours.	Granisetron (oral): 1mg before chemotherapy administration. Up to five additional doses given within 24 hours.
Dick et al 1995	30	2 to 15	NR	MEC	Multi-day regimens	NR	Ondansetron (IV): 3-8 mg/m ² before chemotherapy and at 12 hours after chemotherapy administration. Ondansetron (oral): 12 hourly at 36 hours for 3 days.	Metoclopramide (IV): 10 mg/m ² before chemotherapy administration, then every 6 hours for a minimum of 3 days. Dexamethasone (IV): 4mg/m ² before chemotherapy administration, then 2 mg/m ² every 6 hours for a minimum of 3 days. Procyclidine (IV): 2-5 mg was given with each

Naik et al 2020	240	5 to 18	Primitive Neuroectodermal Tumour Hodgkins Lymphoma Osteosarcoma Rhabdomyosarcoma Retinoblastoma Non-Hodgkins lymphoma Nasopharyngeal Carcinoma Germ cell tumour Soft Tissue Sarcoma	HEC	Single and multiday regimens (majority single day)	chemotherapy naïve	Olanzapine (oral): 0.14 mg/kg/dose (max. 10mg) during chemotherapy and for 3 days afterwards Aprepitant (oral): Children 15–40kg: 80mg on days 1–3, children >40kg: 125mg on day 1, 80mg/kg on days 2-3 Ondansetron (IV): 0.15mg/kg (maximum of 16mg) prior to chemotherapy + Dexamethasone (IV) 0.15 mg/kg prior to chemotherapy. Ondansetron (oral): 0.3 mg/kg + Dexamethasone(oral) 0.15 mg/kg every 8 hours during chemotherapy days until 48 hours after chemotherapy	Aprepitant (oral): Children 15–40kg: 80mg on days 1–3, children >40kg: 125mg on day 1, 80mg/kg on days 2-3 Ondansetron (IV): 0.15mg/kg (maximum of 16mg) prior to chemotherapy + Dexamethasone (IV) 0.15 mg/kg prior to chemotherapy. Ondansetron (oral): 0.3 mg/kg + Dexamethasone(oral) 0.15 mg/kg every 8 hours during chemotherapy days until 48 hours after chemotherapy
Moothedath et al. 2022	128	NR	Retinoblastoma Hodgkin lymphoma Ewing sarcoma Neuroblastoma Rhabdomyosarcoma Wilms tumour	HEC	Single- and two-day regimens	NR	Olanzapine (oral): 0.15 mg/kg/dose during chemotherapy and for 3 days afterwards. Ondansetron (IV): 0.15mg/kg prior to chemotherapy + Dexamethasone (IV) 0.15 mg/kg prior to chemotherapy. Ondansetron (oral): 0.15 mg/kg every 8 hours for a further 48 hours after the first chemotherapy administration.	Ondansetron (IV): 0.15mg/kg prior to chemotherapy + Dexamethasone (IV) 0.15 mg/kg prior to chemotherapy. Ondansetron (oral): 0.15 mg/kg every 8 hours for a further 48 hours after the first chemotherapy administration
Moshayedi et al 2021	40	NR	NR	MEC	Single to 3-day regimens	NR	Olanzapine (oral): 0.14 mg/kg/dose (max. 10mg) during chemotherapy and for 3 days afterwards. Ondansetron (IV or oral): 0.15mg/kg (maximum of 16mg) prior to chemotherapy + Dexamethasone (IV or oral) 2mg/dose for body surface area (BSA) ≤0.6m ² or 4mg/dose for BSA >0.6m ² prior to chemotherapy.	Ondansetron (IV or oral): 0.15mg/kg (maximum of 16mg) prior to chemotherapy + Dexamethasone (IV or oral) 2mg/dose for body surface area (BSA) ≤0.6m ² or 4mg/dose for BSA >0.6m ² prior to chemotherapy. Ondansetron (oral): 0.15 mg/kg every 8 hours for a

						Ondansetron (oral): 0.15 mg/kg every 8 hours for a further 24 hours after chemotherapy. Dexamethasone (oral) 2mg/dose for body surface area (BSA) ≤0.6m ² or 4mg/dose for BSA >0.6m ² every 12 hours until 24-hour chemotherapy.	further 24 hours after chemotherapy. Dexamethasone (oral) 2mg/dose for body surface area (BSA) ≤0.6m ² or 4mg/dose for BSA >0.6m ² every 12 hours until 24-hour chemotherapy.
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Table 2-7 Study characteristics of children's clinical trials eligible for inclusion in the review but not included in planned analyses .

Author and Year		Age range (years)	Reported cancer diagnoses	Emetogenicity of chemotherapy	Length of Chemotherapy Block	Prior chemotherapy exposure	Intervention (route of administration, dose and schedule Arm 1)	Intervention (route of administration, dose and schedule) Arm 2 and 3 (if applicable)
<u>Cross-over studies that did not use an analysis method that accounted for correlated data of patients between cycles, or report first cycle data separately.</u>								
Berrack et al. 2007	18	1–23	Low-grade glioma	MEC	Multiday	chemotherapy naïve and experienced (received interventions on alternating cycles of chemotherapy)	Granisetron (IV): 40 µg/kg 30 min before the start of chemotherapy.	Granisetron (IV): 10 µg/kg 30 min before the start of chemotherapy.
Cakir et al. 2012	16	2–21	Low-grade glioma	NR	Multiday	chemotherapy naïve and experienced (received interventions on alternating cycles of chemotherapy)	Granisetron (IV): 40 µg/kg 30 min before the start of chemotherapy.	Granisetron (IV): 10 µg/kg 30 min before the start of chemotherapy.

Alvarez et al. 1995	33	3-18	Osteosarcoma Brain tumours Rhabdomyosarcoma Neuroblastoma Peripheral neuroepithelioma	HEC	Single and multiday	chemotherapy naïve and experienced	Ondansetron (IV): 5mg/kg 30 min before the start of chemotherapy then two doses 4 h apart, given intravenously daily during the time the patient received chemotherapy (maximum 5 days). Dexamethasone (IV): 8mg/m ² 30 min before the start of chemotherapy, followed by 4 mg/m ² every 6 h or 8 mg/m ² every 4 h for two doses. Shown to be more effective than alternative intervention	Ondansetron (IV): 5mg/kg 30 min before the start of chemotherapy then two doses 4 h apart, given intravenously daily during the time the patient received chemotherapy (maximum 5 days).
Jaing et al. 2004	33	3-18	Acute lymphoblastic leukaemia (ALL)	MEC	NR	chemotherapy naïve and experienced	Granisetron (oral): (0.5 mg for patients weighing 25–50 kg or 1 mg for patients weighing ≥ 50 kg) 1 h before the administration of chemotherapy	Ondansetron (IV): (0.15 mg/kg administered 1 h prior before the administration the (oral) 4 h & 8hr after chemotherapy.
Komada et al. 1999	49	1-14	ALL	NR	Multiday	chemotherapy naïve and experienced	Granisetron (IV): 40 µg/kg immediately before the start of chemotherapy.	Granisetron (IV): 20 µg/kg immediately before the start of chemotherapy.
Patil et al. 2015	37	2-18	Hodgkin lymphoma Germ cell tumour, Neuroblastoma, Rhabdomyosarcoma, Osteosarcoma, Peripheral neuroectodermal tumour, Retinoblastoma, Synovial sarcoma, Desmoplastic small round cell tumour	MEC and HEC	Single and multiday	chemotherapy naïve and experienced (received interventions on alternating cycles of chemotherapy)	Palonosetron (IV): 5 µg/kg 30 minutes before chemotherapy on Day 1. Dexamethasone (IV): 10 mg/m ² 30 minutes before chemotherapy on all days of treatment	Ondansetron (IV): (5 mg/m ² before chemotherapy and every 8 hours thereafter on all days of chemotherapy. Dexamethasone (IV): 10 mg/m ² 30 minutes before chemotherapy on all days of treatment
Stiakaki et al. 1999	23	1-17	ALL Neuroblastoma Wilms' tumour Hodgkin lymphoma Ovarian germ cell	LEC, MEC and HEC	Single and multiday	NR	Tropisetron (IV) 0.2 mg/kg 30 min before chemotherapy administration (maximum dose, 5 mg)	Ondansetron (IV): (5 mg/m ² 30 mins before chemotherapy and 4 mg/m ² every 8 hours (maximum dose, 24 mg per 24 h)

			tumour Rhabdomyosarcoma				Shown to be more effective than alternative intervention	
<u>Studies reporting CIN V by the number of chemotherapy cycles or by the number of treatment days, as opposed to the number of patients</u>								
Koseoglu et al. 1998	15	NR	ALL Acute non-lymphoblastic leukaemia Hodgkin disease Non-Hodgkin lymphoma Neuroblastoma Ewing sarcoma	HEC	NR	chemotherapy naïve	Ondansetron (IV): 5 mg/m ² (max. 8mg) before chemotherapy then Ondansetron (oral): 4 mg/m ² per day twice a day for 5 days. Shown to be more effective than alternative intervention	Metoclopramide (IV): 1 mg/kg before chemotherapy administration then Metoclopramide(oral): 4 mg/m ² per day twice a day for 5 days. dimenhydrinate (oral): 5 mg/kg per day for 5 days.
Forni et al. 2000	90	6-40	NR	HEC (cisplatin–Adriamycin / high-dose ifosfamide)	Multi-day	chemotherapy naïve	Granisetron (IV): 2 mg/m ² , Dexamethasone (IV): 8 mg/m ² once-a-day.	<u>Arm 2:</u> Ondansetron (IV): 5.3 mg/m ² Dexamethasone (IV): 8 mg/m ² once-a-day. <u>Arm 3:</u> tropisetron (IV) 3.3 mg/m ² Dexamethasone (IV): 8 mg/m ² once-a-day.
Luisi et al. 2006	26	7-19	Osteosarcoma	NR	NR	NR	Granisetron (IV): 50 µg/kg single dose before the start of chemotherapy. Shown to be more effective than alternative intervention	Metoclopramide (IV): 2 mg/kg before the start of chemotherapy, plus an 8-hour infusion of 5 mg/kg of dimenhydrinate
Sepulveda-Vildosola et al. 2008	(50 courses)	NR	Low-grade astrocytoma High-grade astrocytoma Ependymoblastoma Ependymoma Glioblastoma multiforme Medulloblastoma Primary intracranial germ cell tumour Xanthoastrocytoma	HEC	NR	chemotherapy naïve and experienced	Palonosetron (IV): 0.25 mg prior to chemotherapy Shown to be more effective than alternative intervention	Ondansetron (IV): 8mg/m ² prior to chemotherapy then every 8 hours whilst receiving chemotherapy.

			Pinealoblastoma Osteosarcoma Ewing's sarcoma Histiocytoma Neuroblastoma Ovarian dysgerminoma PNET Hepatoblastoma Hepatic sarcoma Kidney sarcoma Wilm's tumour Rhabdomyosarcoma Retinoblastoma GIST Ganglioneuroma Non-Hodgkin lymphoma					
Studies not forming part of the connected networks for any outcome.								
Eghbali et al. 2023	120	5 to 18	acute lymphoblastic leukaemia, rhabdomyosarcoma, Wilms tumour, acute myeloid leukaemia, osteosarcoma hepatocellular carcinoma	HEC	NR	chemotherapy naïve and experienced	Aprepitant (oral): 125mg on day 1, 80mg/kg on days 2-3, Granisetron (IV): 3mg/m2 on day 1, Dexamethasone (oral): 0.1mg/kg on days 1 to 3.	Aprepitant (oral): 125mg on day 1, 80mg/kg, Granisetron (IV): 3mg/m2 on day 1, Dexamethasone (oral): 0.1mg/kg on days 1 to 3.
Tsuchida et al. 1999	23	1-13	Neuroblastoma Hepatoblastoma Osteosarcoma Retinoblastoma Ewings Sarcoma. Malignant teratoma Rhabdomyosarcoma Synovial sarcoma Hepatic sarcoma Lung cancer Clear cell sarcoma Angiosarcoma	HEC	NR	chemotherapy experienced	Granisetron (IV): 40 µg/kg immediately before the start of chemotherapy. Shown to be more effective than alternative intervention	Granisetron (IV): 20 µg/kg immediately before the start of chemotherapy.

References for ongoing studies

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2.7 Study characteristics of clinical trials in adults included in analyses.

Author and Year	N Participants	Age range (years)	Reported cancer diagnoses	Emetogenicity of chemotherapy	Length of Chemotherapy Block	Prior chemotherapy exposure	Intervention (route of administration, dose and schedule Arm 1)	Intervention (route of administration, dose and schedule) Arm 2 and 3 (if applicable)
<u>Clinical trials informing the network of treatments in children</u>								
Aapro et al 2006	667	NR range	Ovarian, Lung, Hodgkin's, Gastric, Breast	HEC	Single day	Naïve and experienced	Palonosetron (IV): 0.75mg day 1, dexamethasone (IV) 20 mg day 1	Arm 2: Palonosetron (IV): 0.25mg day 1, dexamethasone (IV) 20 mg day 1. Arm 3: Ondansetron (IV) 32mg day 1, dexamethasone (IV) 20 mg day 1
Aapro et al. 1993	284	NR range	NR	Cisplatin-based	Multi-day	Naïve	Granisetron (IV): 40 ug/kg/dose each day of chemotherapy treatment	Metoclopramide (IV) 3mg/kg day 1, followed by 4mg/kg day 1 & 2mg/kg days 3-5, dexamethasone (IV) 12mg each day of chemotherapy treatment
Chevallier et al 1994	281	17-82	NR	Cisplatin-based	Single day	Naïve	Granisetron (IV): 40 ug/kg/dose day 1	Metoclopramide (IV) 3mg/kg day 1, dexamethasone (IV) 12mg day 1
Dong et al 2010	89	NR	Non- small-cell lung cancer (Adenocarcinoma, Squamous carcinoma)	NR	NR	Naïve and experienced	Palonosetron (IV): 0.25mg day 1	Ondansetron (IV) 8 mg day 1-2
Du et al. 1997	189	NR range	Ovarian cancer	HEC and MEC	Single day	Naïve and experienced	Ondansetron (IV) 8mg day 1, (oral) 8mg x 2 days 2-3, Dexamethasone (IV) 20mg day 1	Metoclopramide (IV) 20mg day 1, followed by (oral) 20mg x3 days 2-3, Dexamethasone (IV) 20mg day 1
Fox-Geiman et al. 2001	96	NR range	Patients about to receive Stem Cell Transplantation	HEC	Multi-day	Naïve and experienced	Ondansetron (IV) 32 mg day 1, dexamethasone (IV) 10mg)	Arm 2: Ondansetron (oral) 8 mg day 1 until 1 day after chemotherapy, dexamethasone (IV) 10mg. Arm 3: Granisetron 1mg x 2 per day whilst on chemotherapy, dexamethasone (IV) 10mg.

Chui et al. 1994	56	NR range	Lymphoma, Leukaemia	MEC	Single and multi-day	Naïve	Ondansetron (IV) 8mg day 1, (oral) 8mg x 3 until day 5	Metoclopramide (IV) 10mg day 1 followed by (oral) 10mg x3 until day 5
Gebbia et al. 1994 (study 1)	182	25-76	Head and neck, Lung, Urinary bladder, Ovary, Stomach, Endometrium, Vulva, Breast, Testis, Sarcoma	HEC	Single day	Naïve	Ondansetron (IV) 16 mg day 1 and additional doses of 8mg x 2 if on fractionated chemotherapy	Granisetron (IV): 3 mg on day 1 and additional doses if on fractionated chemotherapy
Gebbia et al. 1994 (study 2)	164	24-78	Breast, Lung, Stomach, Non-Hodgkin lymphoma, Ovary Melanoma	MEC	NR	Naïve	Ondansetron (IV) 24 mg day 1 and additional doses of 8mg x 2 if on fractionated chemotherapy	Granisetron (IV): 3 mg on day 1 and additional doses if on fractionated chemotherapy
Ghosh & Dey 2010	1213	NR range	NR	HEC and MEC	NR	Naïve and experienced	Palonosetron (IV): 0.75mg day 1, dexamethasone (IV) 16 mg day 1, 4mg day 2-3	Arm 2: granisetron (IV) 3 mg day 1-2, dexamethasone (IV) 16 mg day 1, 4mg day 2-3. Arm 3: Ondansetron (IV) 8 mg day 1-2, dexamethasone (IV) 16 mg day 1, 4mg day 2-3
Gralla et al. 1998	1054	19-88	Respiratory, intrathoracic, genitourinary, head and neck	HEC	NR	Naïve	Ondansetron (IV) 2ml/ml (20ml multidose vials) day 1	Granisetron (oral): 1 mg x 2 day 1
Gralla et al. 2003	570	NR range	breast, lung, bladder, colon, rectal, small-cell lung, gastric	MEC	Single day	Naïve and experienced	Palonosetron (IV): 0.75mg day 1	Arm 2: Palonosetron (IV): 0.25mg day 1. Arm 3: Ondansetron (IV) 32mg on day 1,
Grunberg et al. 2011	2322	19-86	Lung, GI, Reproductive or genitourinary, Renal and urinary tract, Breast	Cisplatin-based	NR	Naïve	Fosaprepitant (IV) 150mg day 1, ondansetron (IV): 32mg day 1, dexamethasone (oral) 12mg day 1, 8mg days 2-4.	Aprepitant (oral): 125mg on day 1, 80mg on day 2 until 3 days after chemotherapy, ondansetron (IV): 32mg on day 1, dexamethasone (oral) 12mg day 1, 8mg days 2-4.
Hainsworth et al. 1991	307	NR range	Head and neck, Lung, Gastrointestinal, Genitourinary, Gynaecologic	Cisplatin-based	Single day	Naïve	Ondansetron (IV) 0.15 mg/kg before chemotherapy, then an additional 3 doses during day 1	Metoclopramide 2.0 mg/kg before chemotherapy, then an additional 5 doses during day 1
Herrington et al. 2000	65	20-91	Breast, Lymphoma, Multiple myeloma	MEC	NR	Naïve	Ondansetron (oral) 16mg + dexamethasone (oral) 12mg	granisetron (oral) 1mg + dexamethasone (oral) 12 mg
Hesketh et al. 2003	530	18-84	Respiratory, Urogenital	HEC	NR	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3,	Ondansetron (IV then oral): 32mg day 1, 8mg days 2-3.

							Ondansetron (IV): 32mg on day 1, Dexamethasone (oral): 12mg on day 1, 8mg days 2-4.	Dexamethasone (oral) 12mg day 1, 8mg days 2-4.
Huang et al 2013	240	31-73	Non-small cell lung, Colorectal, Gastric, Breast, Oesophageal, Head and neck, Ovarian	HEC and MEC	Single day	Naïve and experienced	Palonosetron (IV): 0.25mg day 1	Granisetron (IV): 3 mg day 1
Kassa et al. 1990	82	19-80	Breast, non-Hodgkins's lymphoma	NR	NR	Naïve	Ondansetron (IV) 8mg day 1, (oral) 8mg x 3 until day 5	Metoclopramide (IV) 60mg day 1, followed by (oral) 20mg x3 until day 5
Kim et al. 2017	494	23-85	Gastrointestinal, Lung, Gynaecologic	MEC	Single day	NR	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3 + Ondansetron (oral): 16mg on day 1, Dexamethasone (oral) 12mg on day 1.	Ondansetron (oral): 16mg day 1, Dexamethasone (oral) 12mg day 1.
Koralewski et al. 2001	76	24-79	Breast, stomach, Lymphoma, Lung	MEC	NR	Naïve	Ondansetron (oral) 8mg day 1 and 4mg day 1, 8 hours after chemotherapy, dexamethasone 8mg (IV) day 1.	Metoclopramide (IV) 40mg day 1 followed by (oral) 40mg at hours 4 and 8 after chemotherapy, dexamethasone 8mg (IV) day 1.
Levitt et al. 1993	165	NR range	Breast	NR	Single and multi-day	Naïve	Ondansetron (IV) 8mg day 1 & (oral) 8mg every 8 hours for 7 days.	Metoclopramide (IV) 10mg day 1, followed by 10mg every 8 hours for 7 days, dexamethasone (IV) 10mg day 1.
Martoni et al. 1996 (cycle one data)	124	32-77	NSCLC, Bladder, Ovary	Cisplatin-based	Single day	Naïve	Ondansetron (IV) 3x 8mg day 1, (oral) 8mg x 2 day 2.	Granisetron (IV) 3 mg day 1
Mattiuzzi et al. 2010	96	23-72	Acute myelogenous leukaemia	HEC	Single and multi-day	Naïve and experienced	Palonosetron (IV): 0.25mg day 1-5	Arm 2: Palonosetron (IV): 0.25mg days 1,3 & 5, Arm 3: Ondansetron (IV) 8 mg then 24 mg day 1 until 12 hours after chemotherapy
Morteza et al. 2021	160	NR range	Brain, breast, CRC, oesophagus, gastric, head and neck, mediastinum, pelvic.	MEC	NR	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3 + Ondansetron (IV): 8mg day 1, Dexamethasone (IV) 12mg day 1.	Ondansetron (IV): 8mg day 1, Dexamethasone (IV) 12mg day 1.
Navari et al. 1995	994	23-86	Lung cancer	Cisplatin-based	Single day	Naïve	Ondansetron 3 x 0.15mg/kg dose on day 1	Arm 2: Granisetron (IV): 10 µg/kg, Arm 3: Granisetron (IV): 40 µg/kg,

Noble et al. 1994 (first cycle data)	309	29-83	Head and neck, Lung, Ovary/cervix, Testis	NR	Multi-day	Naïve	Ondansetron (oral) 3x 8mg per day, for each day of chemotherapy	Granisetron (oral) 3 mg/day for each day of chemotherapy
Park et al. 1997	97	18-70	Head and neck, stomach oesophagus, colorectal, breast, gynaecological, soft tissue sarcoma, pancreas.	MEC	NR	Naïve	Ondansetron (IV) 3x 8mg day 1, (oral) 8mg every 12 hrs for each day of chemotherapy	Granisetron (IV) 3 mg day 1
Patel et al. 2020	136	NR	Glioma	NR	Multi-day	Naïve and experienced	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (oral): 8mg 1-5	Ondansetron (oral): 8mg days 1- 5
Poli-Bigelli et al. 2003	568	18-82	Respiratory, Urogenital, Eyes/ears/nose/throat	HEC	NR	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (IV): 32mg on day 1, Dexamethasone (oral): 12mg on day 1, 8mg on days 2-3.	Ondansetron (IV): 32mg day 1, Dexamethasone (oral) 20mg day 1, 8mg days 2-3.
Rapoport et al. 2010	848	NR range	Breast, Colon, Lung, Ovarian	MEC	NR	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3 , Ondansetron (oral): 8mg day 1-3, Dexamethasone 12mg day 1.	Ondansetron (oral): 8mg day 1- 3, Dexamethasone (oral) 20mg day 1.
Ruff et al. 1994	469	NR range	Gynaecological, Lung, Head and neck, Genito- urinary, Gastrointestinal, Bone/soft tissue	HEC and MEC	NR	Naïve	Ondansetron (IV) 8 mg day 1	Arm 2: Ondansetron (IV) 32 mg day 1, Arm 3: Granisetron (IV) 3mg day 1
Schmoll et al. 2006	489	20-82	Respiratory, Urogenital, Gastrointestinal, Eyes/ears/nose/throat	Cisplatin- based	Single and multi-day	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (IV): 32mg on day 1, Dexamethasone (oral): 12mg on day 1, 8mg on days 2-4.	Ondansetron (IV): 32mg day 1, Dexamethasone (oral) 20mg day 1, 8mg days 2-4.
Soukop et al. 1992	187	23-82	Breast	NR	NR	Naïve	Ondansetron (IV) 8mg day 1, (oral) 8mg x 3 until day 5, Dexamethasone (IV) 16mg day 1	Metoclopramide (IV) 60mg day 1, followed by (oral) 20mg x3 until day 5, Dexamethasone (IV) 16mg day 1
Spector et al. 1998	371	32-86	Lung, Gynaecological, Genitourinary,	HEC	Single day	Naïve	Ondansetron (oral) 24 mg day 1	Granisetron (IV) 10 µg/kg day 1

			Gastrointestinal, Head/neck					
Stiff et al 2013	181	19-79	Non-Hodgkin lymphoma, AML, Multiple myeloma, ALL, Hodgkin's lymphoma CML	HEC	Single and multi-day	Naïve and experienced	Aprepitant (oral): 125mg on day 1, 80mg on day 2 until 3 days after chemotherapy, Ondansetron (oral): 8mg x3 day 1-1 day after chemotherapy, Dexamethasone (IV) 7.5mg day 1-1 day after chemotherapy	Ondansetron (oral): 8mg x3 day 1-1 day after chemotherapy, Dexamethasone (IV) 10mg day 1-1 day after chemotherapy
Warr et al. 2005	866	NR range	Breast	MEC	NR	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3 , Ondansetron (oral): 8mg x2 day 1, Dexamethasone (oral) 12mg day 1.	Ondansetron (oral): 8mg x2 day 1, Dexamethasone (oral) 20mg day 1.
Weinstein et al. 2016	1150	NR range	Lung, Breast, Colorectal, Gynaecologic, Gastrointestinal, Head and neck	MEC	Single and multi-day	Naïve	Fosaprepitant (IV) 150mg day 1, ondansetron (oral): 8mg x2 day 1, dexamethasone (oral) 12mg day 1.	Ondansetron (oral): 8mg x2 day 1, dexamethasone (oral) 20mg day 1.
Yeo et al 2009	127	26-68	Breast	MEC	NR	Naïve	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (oral): 8mg x2 day 1, Dexamethasone (oral) 12mg day 1.	Ondansetron (oral): 8mg x2 day 1, Dexamethasone (oral) 20mg day 1.
Yu et al 2009	208	NR range	Non-small lung, Gastric, Breast, Oesophageal, Hepatocellular carcinoma, Head and neck	HEC	NR	Naïve and experienced	Palonosetron: (IV): 0.25mg day 1	Granisetron (IV): 3 mg day 1
<u>Clinical trial informing predictions of treatment effect in children</u>								
Ithimakin (2020)	141	24-79	Breast, Head and neck, Lung	HEC	NR	Naïve	Olanzapine (oral) 5mg days 1-4, aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (oral): 8mg day 1, Dexamethasone (IV) 12mg day 1, 8mg (oral) days 2-4.	Arm 2: Olanzapine (oral) 5mg days 1-4, aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (oral): 8mg day 1, Dexamethasone (IV) 12mg day 1, 8mg (oral) days 2- 4. Arm 3: Aprepitant (oral): 125mg on day 1, 80mg on day

								2-3, Ondansetron (oral): 8mg on day 1, Dexamethasone (IV) 12mg on day 1, 8mg (oral) on days 2-4.
Yeo (2020)	120	32-71	Breast	HEC	NR	Naïve	Olanzapine (oral) 10mg days 1-4, aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (oral): 8mg x 2 day 1, Dexamethasone (IV) 12mg day 1, 8mg (oral) days 2-3.	Aprepitant (oral): 125mg on day 1, 80mg on day 2-3, Ondansetron (oral): 8mg x 2 day 1, Dexamethasone (IV) 12mg day 1, 8mg (oral) days 2-3.
Tienchaiananda (2019)	39	27-67	Breast	HEC	NR	Naïve	Olanzapine (oral) 10mg days 1-4, Ondansetron (IV): 8mg day 1, Dexamethasone (IV) 20mg day 1, 10mg (oral) days 2-4.	Ondansetron (IV): 8mg day 1, Dexamethasone (IV) 20mg day 1, 10mg (oral) days 2-4.
Vimolchalao (2020) (first cycle data)	32	26-73	Breast, Head and neck, Lung	HEC	NR	Naïve	Olanzapine (oral) 10mg days 1-4, Ondansetron (IV): 8mg day 1, Dexamethasone (IV) 20mg day 1, 10mg (oral) days 2-4.	Ondansetron (IV): 8mg day 1, Dexamethasone (IV) 20mg day 1, 10mg (oral) days 2-4.

2.8 Dissemination

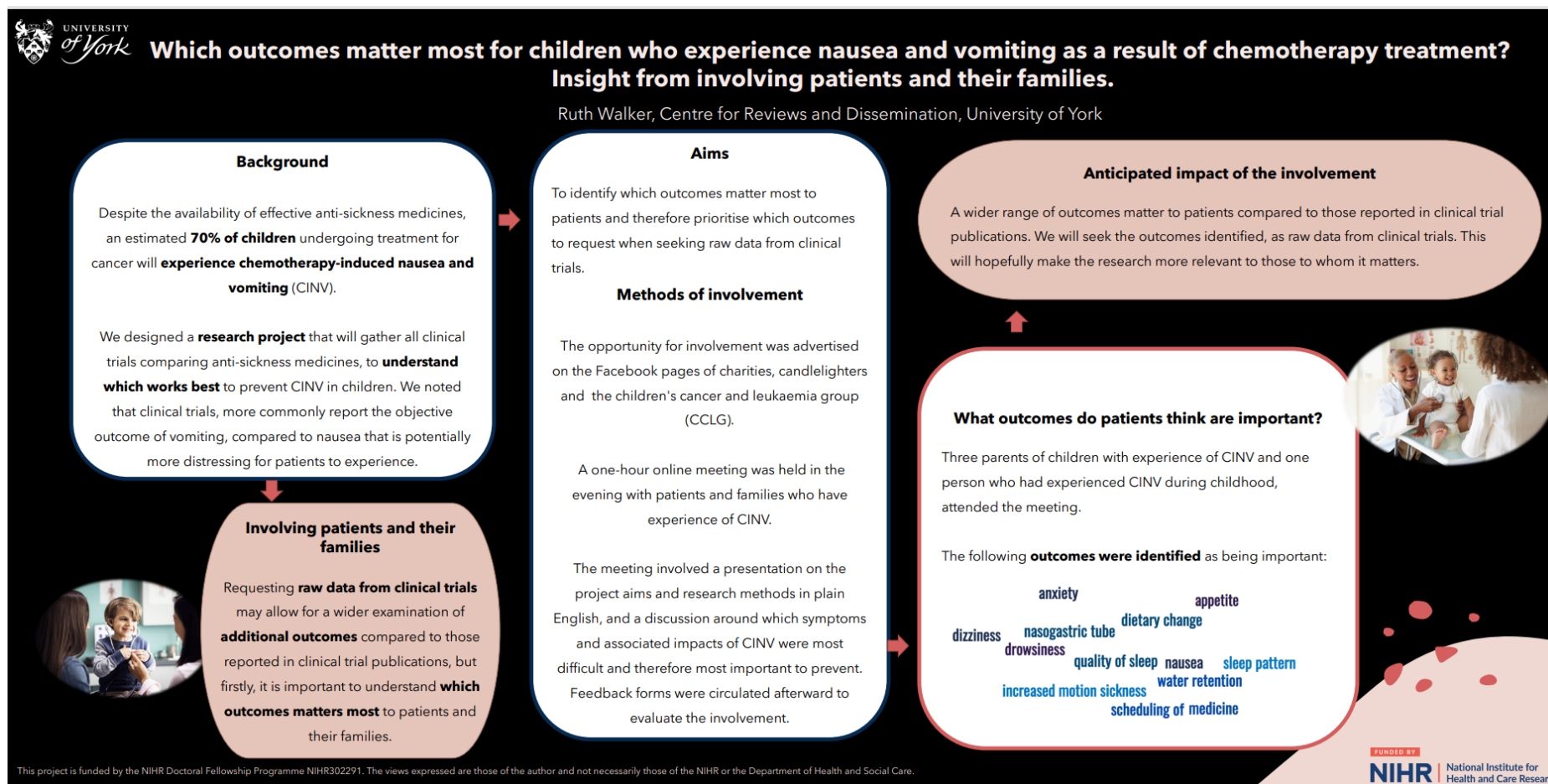


Figure 2-2 A poster reporting the methods and results of involving families in outcome prioritisation, which was presented at the Children's Cancer and Leukaemia Group (CCLG) conference in 2023.

3 Chapter 3 Appendix

3.1 BUGS code for NMA models

The code reported in this section has been acquired/ adapted from Dias et al. 2018 (Dias et al., 2018)

The following parameters were monitored across models:

d: treatment effect
dev: deviance
resdev: residual deviance
totresdev: total residual deviance
sd (for random effects models): standard deviation (between-study heterogeneity)
RR: relative risk (relative treatment effect)
lnRR: log relative risk
rk: rank
best: probability that treat k is best
DIC: deviance information criterion

3.1.1 Fixed effects model

```
# Binomial likelihood, log-Relative Risk
# Fixed effects model
model{
  # *** PROGRAM STARTS
  for(i in 1:ns){
    # LOOP THROUGH STUDIES
    mu[i] <- log(p[i,1])
    p[i,1] ~ dunif(0,1) # vague priors for all trial baselines
    for(k in 1:na[i]){
      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      # Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))
        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
    # model for linear predictor
    for(k in 2:na[i]){
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      delta[i,k] <- d[t[i,k]] - d[t[i,1]] # fixed effect model
    }
    # summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }
  totresdev <- sum(resdev[]) # Total Residual Deviance
  #
  d[1]<-0 # treatment effect is zero for reference treatment
  # vague priors for treatment effects
  for(k in 2:nt){ d[k] ~ dnorm(0,.0001) }
  # pairwise RRs for all possible pair-wise comparisons
  for(c in 1:(nt-1)){
    for(k in (c+1):nt){
      lnRR[c,k] <- d[k] - d[c]
      RR[c,k] <- exp(d[k] - d[c])
    }
  }
  # ranking on relative scale
  for(k in 1:nt){
    rk[k] <- nt+1-rank(d[,k]) # assumes events are "good"
    # rk[k] <- rank(d[,k]) # assumes events are "bad"
    best[k] <- equals(rk[k],1) # calculate probability that treat k is best
    # calculates probability that treat k is h-th best
    for(h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
  }
}
```

```
} # *** PROGRAM ENDS
```

3.1.2 Random effects model

```
# Binomial likelihood, log-Relative Risk
# Random effects model for multi-arm trials
model{
  # *** PROGRAM STARTS
  for(i in 1:ns){
    # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] <- log(p[i,1])
    p[i,1] ~ dunif(0,1) # vague priors for all trial baselines
    for (k in 1:na[i]) {
      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      # Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))
        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
    # summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {
      # LOOP THROUGH ARMS
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      # trial-specific LRR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      # mean of LRR distributions (with multi-arm trial correction)
      md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
      # precision of LRR distributions (with multi-arm trial correction)
      taud[i,k] <- tau * 2*(k-1)/k
      # adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
  toresdev <- sum(resdev[]) # Total Residual Deviance
  d[1] <- 0 # treatment effect is zero for reference treatment
  # vague priors for treatment effects
  for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
  sd ~ dunif(0,2) # vague prior for between-trial SD
  tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
  # pairwise RRs and LRRs for all possible pair-wise comparisons
  for (c in 1:(nt-1)) {
    for (k in (c+1):nt) {
      lnRR[c,k] <- d[k] - d[c]
      RR[c,k] <- exp(d[k] - d[c])
    }
  }
  # ranking on relative scale
  for (k in 1:nt) {
    rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
    # rk[k] <- rank(d[],k) # assumes events are "bad"
    best[k] <- equals(rk[k],1) # calculate probability that treat k is best
    # calculates probability that treat k is h-th best
    for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
  }
} # *** PROGRAM ENDS
```

3.1.3 Random effects model with an informative prior informing the between-study heterogeneity parameter.

The informative prior distribution has been acquired from Rhodes et al. 2016 (Rhodes et al., 2016)

```
# Binomial likelihood, log-Relative Risk
# Random effects model for multi-arm trials
model{
  # *** PROGRAM STARTS
  for(i in 1:ns){
    # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] <- log(p[i,1])
    p[i,1] ~ dunif(0,1) # vague priors for all trial baselines

# estimation of fixed 'typical' within-study variance

v[i] <- 1/r[i,2] + 1/r[i,1] - 1/n[i,2] - 1/n[i,1]
ws[i] <- 1/v[i]
wsq[i] <- ws[i]*ws[i]

    for (k in 1:na[i]) {
      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      # Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k]) - log(rhat[i,k])))
        + (n[i,k] - r[i,k]) * (log(n[i,k] - r[i,k]) - log(n[i,k] - rhat[i,k])))

    }
    # summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {
      # LOOP THROUGH ARMS
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      # trial-specific LRR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      # mean of LRR distributions (with multi-arm trial correction)
      md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
      # precision of LRR distributions (with multi-arm trial correction)
      taud[i,k] <- tau * 2*(k-1)/k
      # adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
  totesdev <- sum(resdev[]) # Total Residual Deviance
  d[1] <- 0 # treatment effect is zero for reference treatment
  # vague priors for treatment effects
  for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }

#sd ~ dunif(0,2) # vague prior for between-trial SD
#tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

W<-sum(ws[])
Wsq<- sum(wsq[])
ssq<- (W*(ns-1))/((W*W)-Wsq) # fixed 'typical' within-study variance
prior.prec <- 1/ var*var
logit.isq ~ dt(location_mu, prior.prec, df) # empirical prior for I2
```

```

sd.sq <-(ssq*isq)/(1-isq) # sqq - 'typical' within-study variance
isq <-exp(logit.isq)/(1+exp(logit.isq))
tau <- 1/sd.sq
sd <- sqrt(sd.sq)

# pairwise RRs and LRRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    lnRR[c,k] <- d[k] - d[c]
    RR[c,k] <- exp(d[k] - d[c])
  }
}
# ranking on relative scale
for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[,k])    # assumes events are "good"
  # rk[k] <- rank(d[,k])      # assumes events are "bad"
  best[k] <- equals(rk[k],1)  # calculate probability that treat k is best
  # calculates probability that treat k is h-th best
  for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}
# *** PROGRAM ENDS

```

3.2 Determining the structure of the networks

To determine the structure of the network for complete and partial response outcomes, a network diagram was produced, starting with variations in antiemetic regimens (i.e., variations of dose, schedule, and route of administration, and inclusion or exclusion of dexamethasone within the regimen) as separate nodes in the networks. This was done firstly for the most well-reported outcome, ‘complete response in the acute phase’.

As this resulted in a highly disconnected network structure (Figure 3-1) with twelve distinct satellites, the appropriateness of grouping different antiemetic emetic variations was then considered. Decisions about grouping antiemetic regimens were informed by clinical advice and by empirical results from clinical trials, and secondary analyses (systematic reviews and meta-analyses), where available. The need to connect the network to a certain extent, in order to produce a comparative analysis of the antiemetic agents, was also taken into consideration.

This was considered for all outcomes simultaneously, as the remaining complete and partial response outcomes were less well reported than the outcome of ‘complete response in the acute phase’, and every study that reported a remaining complete or partial response outcome also reported ‘complete response in the acute phase’. As such, their networks would be no better connected (but rather would be as connected, if not less well connected) than the network for the outcome ‘complete response in the acute phase’.



Figure 3-1 Network diagram for the outcome complete response in the acute phase with different doses, scheduling, and route of administration of antiemetic regimens included as separate interventions, including those given with or without dexamethasone. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

Grouping based on dosage of ondansetron.

Grouping regimens containing different doses of ondansetron was first considered, as variations of these antiemetics contributed to much of the disconnect within the initial network (Figure 1). Clinical advice was that different doses of ondansetron were not expected to produce different treatment effects. One study that compared different doses of ondansetron (5 mg/m² with 10 mg/m²) (Brock et al., 1996), supported this clinical experience, showing no difference in the efficacy of the doses in terms of controlling vomiting and nausea in both acute and delayed phases. Empirical comparison of the proportion of patients' complete response outcomes within treatment arms containing different doses of ondansetron was considered; however, these antiemetic regimens also differed in their scheduling and route of administration, so it is not possible to use these data to make any inference about the effect of ondansetron dose on complete response rates.

Considering this information and given that the network structure cannot be improved without the grouping of these antiemetic regimens, a decision was made to group antiemetic regimens with different doses of ondansetron within the network and report the range of doses identified in the clinical trials (Figure 3-2).



Figure 3-2 Network diagram for the outcome, complete response in the acute phase with antiemetic regimens containing different doses of ondansetron grouped. Dosing of other antiemetics, scheduling, and route of administration are maintained as separate interventions. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

Grouping based on dosage of dexamethasone.

As the network structure remained highly disconnected, with eleven distinct ‘satellites’ (figure 2), grouping of antiemetic regimens with different doses of dexamethasone was then considered. Clinical advice was that the effect of dexamethasone dose has been more ‘heavily debated’ within the clinical community and has also been considered more formally addressed in the literature. A systematic review assessing dexamethasone dosing for the prevention of acute chemotherapy-induced vomiting in paediatric patients (Patel et al., 2020), included eleven studies reporting dexamethasone doses ranging from 6mg/m² to 27 mg/m² and complete response rates ranged from 11%-90%. However, no formal quantitative synthesis or categorisation of data by dexamethasone dose was possible due to heterogeneity in populations and co-interventions (aprepitant, ondansetron and palonosetron). As these factors may produce differences in complete response rates, no conclusion can be drawn on the impact of dexamethasone dose.

A more focused secondary analysis pooled individual participant data from four clinical trials (735 patients) comparing regimens of Aprepitant/fosaprepitant, ondansetron and dexamethasone with regimens of ondansetron plus dexamethasone, to assess the factors associated with chemotherapy-induced vomiting control in paediatric patients (Dupuis et al., 2020). Complete response rates were summarised by dexamethasone dosing categorised as ‘low’ <12 mg/m²/day or 0.4 mg/kg/day, ‘high’ ≥12 mg/m²/day or 0.4 mg/kg/day or unknown and were comparable between categories, ranging from 30.0%-34.9% (Dupuis et al., 2020). This suggests complete response between different doses of dexamethasone could be similar; however, knowledge of the distribution of co-interventions between categories or a formal regression analysis controlling for these confounding factors would be needed to draw any firmer conclusion.

Due to this uncertainty, grouping of antiemetic regimens with dexamethasone based on categories of dexamethasone dosing proposed in Dupuis et al. 2020 (Dupuis et al., 2020), was considered within this project. However, differential reporting of dexamethasone dosing either by mg/kg/dose, mg/m²/dose or mg made this categorisation difficult. Conversion to a range of doses in mg may be achieved using baseline data on body weight or surface area. However, for trials where a maximum dose was not reported (Radhakrishnan et al., 2019), (Tan et al., 2018) and (Bakhshi et al., 2015)), the required baseline data were only available from one clinical trial (Radhakrishnan et al., 2019).

Taking this into consideration, a tentative decision was made to group antiemetic regimens that differ in their dosing of dexamethasone. The uncertainty surrounding the effect of dexamethasone dosing on complete response rates will be considered when interpreting the results, for example, if there is considerable heterogeneity in the estimates of complete response rate that is unaccounted for. However, as no antiemetic regimen differed only in the dosing of dexamethasone, this made no improvement to the network structure in Figure 3-2.

Grouping based on route of administration.

Further grouping of antiemetic regimens was then considered based on the route of administration. Clinical advice to the project was that the route of administration was not expected to greatly affect outcomes except when the patient cannot keep down oral medication. This could theoretically affect delayed phase outcomes, for example, if patients have poor acute phase control to the extent that there is insufficient time for oral medication to be absorbed, this may result in poorer control in the delayed phase. However, there is no evidence identified within this systematic review to support this. One clinical trial in the project addressed the effect of the route of administration in children (White et al., 2000), comparing oral and IV administration of ondansetron and found no significant difference for complete control outcomes between the two routes of administration. Considering this, along with the fact that the route of administration was responsible for much of the disconnect in the network, the decision was made to group antiemetic regimens that differ in the route they were administered (Figure 3).

Grouping based on scheduling.

Antiemetics were typically given as a single dose before chemotherapy administration (sometimes referred to as a loading dose) or multiple doses, one given before chemotherapy administration and subsequent doses given at regular intervals after the first dose, often until a given number of hours, often 12, 24 or 48 hours after chemotherapy administration ceased (see Appendix 2.6 for study characteristics).

Grouping of antiemetic regimens that used single-dose and multiple-dose schedules was considered. Clinical advice was that taking multiple doses of an antiemetic could potentially have a positive psychological impact on being and feeling sick, as taking more medication, more often, may help patients feel their symptoms are being better treated or controlled. Scheduling of antiemetic regimens was addressed by three clinical trials, one comparing multiple vs single dose aprepitant regimens (Eghbali et al., 2023) and two comparing single vs multiple dose ondansetron regimens (Ruktrirong et al., 2021, Sandoval et al., 1999). In all three trials, no significant differences were found in complete response outcomes/ emetic episodes. Due to this conflicting information, and since scheduling was not contributing highly to the remaining disconnect within the network, antiemetic regimens that differed in the scheduling of antiemetics were maintained as separate nodes in the network (Figure 3-3).

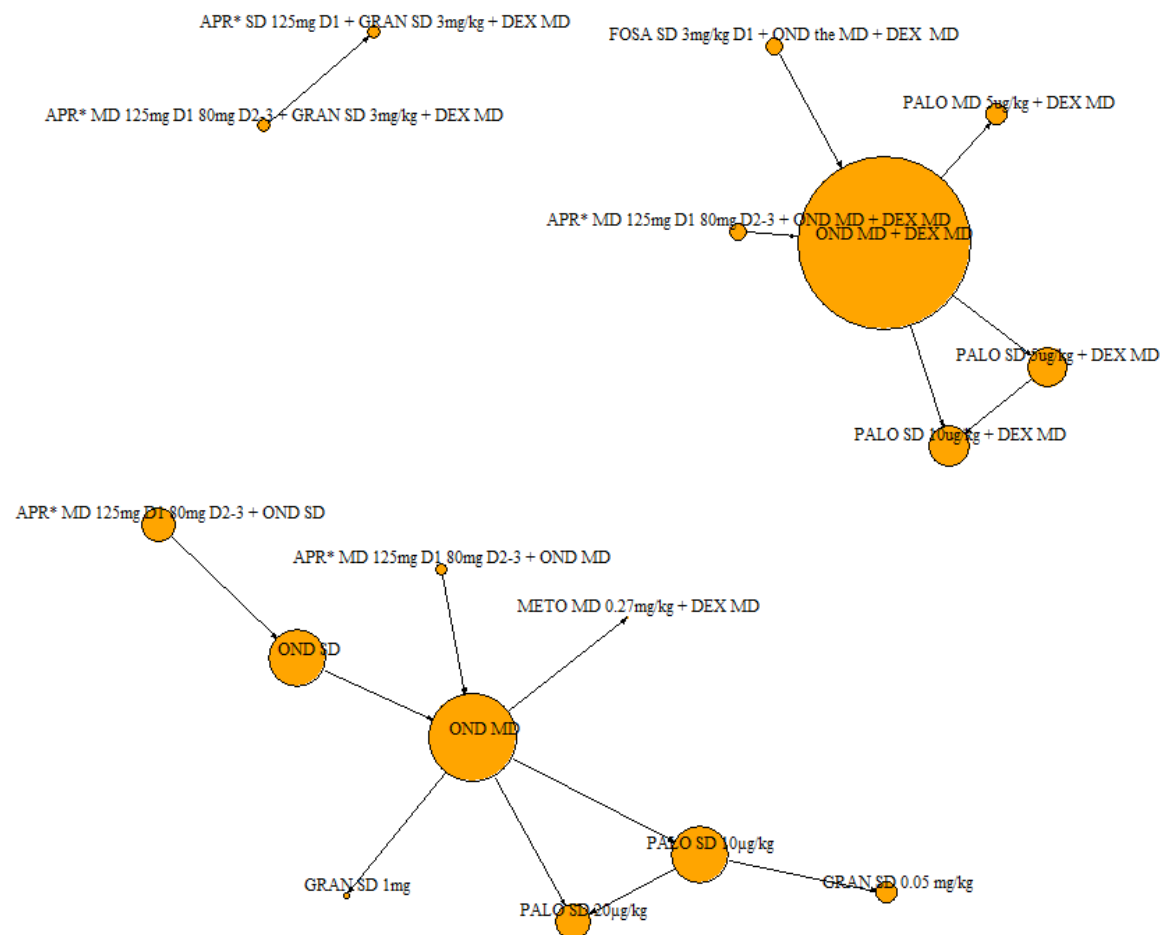


Figure 3-3 Network diagram for the outcome complete response in the acute phase with doses of ondansetron and dexamethasone, and route of administration for all antiemetics grouped, but scheduling of antiemetic regimens included as separate interventions . The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

Grouping based on whether regimens were given with or without dexamethasone.

Two distinct satellites remained (Figure 3-3), disconnected because the antiemetic regimens within each differ in whether they are given with or without dexamethasone (Figure 3-3). Some formal comparison of regimens with or without dexamethasone has been made for acute phase outcomes (Dupuis et al., 2020). Here, a multivariate generalised linear model was used to regress treatment-related factors of ‘acute phase duration’ and ‘antiemetic medication given’ against the outcome of complete control of vomiting in the acute phase. The results of the final model (Table 3-1) suggest that patients receiving ondansetron plus dexamethasone are less likely to achieve a complete response compared to those receiving ondansetron alone. The proportion of patients achieving a complete response with aprepitant plus ondansetron regimens with dexamethasone is also lower than that given the regimen without dexamethasone, although the relative risks are not estimated for these categories, as ondansetron alone was used as the reference treatment for all categories. Furthermore, the difference between ondansetron and aprepitant regimens is more for the regimens containing dexamethasone (~27%) compared to those not containing dexamethasone (~15%), potentially suggestive of effect modification (Dupuis et al., 2020).

Table 3-1 The proportion achieving complete control in the acute phase by antiemetic regimen and the relative risk for each category relative to ondansetron alone. Results from the final model of a multivariate generalised linear model performed by Dupuis et al. 2020 (Dupuis et al., 2020), including variables of antiemetic prophylaxis and acute phase duration.

	Proportion achieving complete vomiting control in the acute phase	RR (95% CI)	P value
Ondansetron (reference)	44.9%	-	-
Ondansetron + dexamethasone	20.9%	0.50 (0.34 to 0.72)	0.003
Aprepitant or fosaprepitant + Ondansetron	60.1%	1.028 (1.09 to 1.50)	0.0023
Aprepitant or fosaprepitant + Ondansetron + dexamethasone	47.3%	1.10 (0.88 to 1.39)	0.3894

For delayed phase outcomes, the difference in rates of complete vomiting control was not significant for regimens of ondansetron with dexamethasone compared to ondansetron without dexamethasone. For regimens aprepitant + ondansetron, the proportion achieving complete response was still higher without dexamethasone than with dexamethasone (Dupuis et al., 2020) (Table 3-2).

Table 3-2. The proportion achieving complete control in the delayed phase by the antiemetic regimen and the relative risk for each category relative to ondansetron alone. Results from the final model of a multivariate generalised linear model performed by Dupuis et al. 2020 (Dupuis et al., 2020), including variables of antiemetic prophylaxis and acute phase control.

	Proportion achieving complete vomiting control in the delayed phase	RR (95% CI)	P value
Ondansetron (reference)	49.6%	-	-
Ondansetron + dexamethasone	44.2%	1.24 (0.88 to 1.76)	0.2255
Aprepitant or fosaprepitant + Ondansetron	75.3%	1.32 (1.09 to 1.61)	0.0052
Aprepitant or fosaprepitant + Ondansetron + dexamethasone	49.1%	1.02 (0.76 to 1.37)	0.9118

Discussion with clinical advisors of the project indicated that differences in complete response rates between antiemetic regimens, with or without dexamethasone, may be attributable to the underlying risk of the study populations, as those receiving highly emetogenic chemotherapy are usually given antiemetic regimens with dexamethasone, and those receiving moderately emetogenic chemotherapy are given antiemetic regimens without dexamethasone. Clinical advisors explained that with increasing emetogenicity of chemotherapy, antiemetics are often given as ondansetron alone → ondansetron + dexamethasone → ondansetron + dexamethasone + aprepitant. It is theoretically possible, therefore, that it is the emetogenicity of chemotherapy that may be acting as an effect modifier, as well as being an underlying risk factor.

Investigation of the underlying populations within this dataset shows that whilst studies with patients receiving only HEC were given antiemetic regimens given with dexamethasone and studies with patients receiving only MEC were given antiemetic regimens given without dexamethasone, the majority of studies included mixed populations (Table 3-3).

Table 3-3. Emetogenicity of chemotherapy and whether dexamethasone was given as part of the antiemetic regimen, by clinical trial.

Study	Antiemetic regimens given with dexamethasone?	Emetogenicity of chemotherapy	Proportion HEC
Bakshi et al. 2015	yes	HEC	100
Gore et al. 2009	yes	HEC	100
Radhakrishnan et al. 2018	yes	Mostly HEC	70
Chaudhary et al 2019	yes	Mostly MEC	41
White et al 2000	yes	HEC and MEC (proportions not reported)	(Proportions not reported)
Tan et al 2018	yes	HEC	100
Siddique et al. 2011	no	NR	NR
Dick et al 1995	no	MEC	0
Sharma et al. 2020	no	MEC	0
Malek et al. 2021	no	HEC and MEC (proportions not reported)	(Proportions not reported)
Kang et al. 2015	Given at the physician's discretion (<50% patients received dexamethasone)	Mostly HEC	66% very highly emetogenic chemotherapy HEC % NR
Ruktrirong et al 2021	no	Mostly MEC	19.5
Sandoval et al 1999	no	Mostly MEC	38.7
Brock et al 1996	no	HEC	100
Kovacs et al 2016	Given at the physician's discretion (<50% patients received dexamethasone)	Mostly MEC	31.1%
Li et al 2021	no	MEC	0

Paw Cho Sing et al. 2019 (Paw Cho Sing et al., 2019) was used to determine the emetogenicity of chemotherapy, where this was not reported in the study publication. NR- not reported.

The option of separating clinical trials with patients receiving only HEC or only MEC was considered, but this would produce very limited network structures for each population. The majority of information on comparative treatment efficacy would still come from mixed populations, where treatment effect estimates are an average of those patients receiving HEC and MEC. The impact of the emetogenicity of chemotherapy received on treatment effect estimates would be better explored using patient-level data in stage two of the project.

Based on these considerations, it still may not be appropriate to group clinical trials giving antiemetic regimens with or without dexamethasone, as it remains uncertain whether dexamethasone or certain characteristics of patients within these studies giving dexamethasone are acting as an effect modifier. As such, the decision was made that the final network structure would keep clinical trials giving antiemetics with and without dexamethasone separate, and the Bayesian NMA would be run separately for the two main satellites in Figure 3-3. For comparison, and to assess the effect on heterogeneity of relative risk estimates, the network will also be conducted, grouping clinical trials giving antiemetics with or without dexamethasone, for complete response outcomes. Here, you may be expected to increase in heterogeneity of relative risk estimates in the network that groups clinical trials giving antiemetics with or without dexamethasone.

3.3 Summary data

Table 3-4. Number of patients experiencing the outcome, out of the total number of patients in each study, for the complete response outcomes (acute, delayed and overall phase)

Author and Year	Interventions Arm 1	Intervention Arm 2 (and 3 if applicable)	Complete response in acute phase N/ total		Complete response in delayed phase N/ total		Complete response in the overall phase N/ total	
			Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)
Sharma et al. 2020	Aprepitant + Ondansetron	Ondansetron	22/37	12/41	21/37	15/41	19/37	9/41
Malek et al. 2021	Aprepitant + ondansetron	Ondansetron	12/18	11/17	15/18	15/17	NR	NR
Bakshi et al. 2015	Aprepitant + Ondansetron + dexamethasone	Ondansetron + dexamethasone	24/52	5/44	17/52	13/44	11/52	4/44
Kang et al. 2015	Aprepitant + Ondansetron	Ondansetron	101/155	78/152	77/155	39/152	61/155	30/152
Gore et al. 2009	Aprepitant + Ondansetron + dexamethasone	Ondansetron + dexamethasone	17/32	7/18	10/32	1/18	8/32	1/18
Radhakrishnan et al. 2018	Fosaprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	70/82	49/82	64/82	42/82	57/82	34/82
Ruktrirong et al 2021	Single-dose Ondansetron	Divided dose Ondansetron	68/96	66/98	NR	NR/98	NR	NR
Sandoval et al, 1999	Single dose Ondansetron	Divided dose Ondansetron	12/16	9/15	16/16	15/15	NR	NR
Chaudhary et al, 2019	Ondansetron + dexamethasone	Palonosetron + dexamethasone	84/100	88/100	79/100	88/100	72/100	81/100
White et al 2000	Ondansetron + dexamethasone	Ondansetron + dexamethasone	168/216	172/212	NR	NR	NR	NR/212
Brock et al 1996	Ondansetron lower dose	Ondansetron higher dose	43/93	38/94	NR	NR	NR	NR
Kovacs et al 2016	Ondansetron	Arm 2: Palonosetron lower dose Arm 3: Palonosetron higher dose	95/162	90/166 (98/165)	46/162	48/166 (64/165)	39/162	39/166 (54/165)
Li et al 2021	Palonosetron	Granisetron	83/100	72/100	NR	NR	NR	NR

Tan et al 2018	Ondansetron	<u>Arm 2:</u> Palonosetron lower dose <u>Arm 3:</u> Palonosetron higher dose	121/194	125/185 (129/186)	62/194	72/185 (99/186)	41/194	66/185 (79/186)
Siddique et al. 2011	Ondansetron	Granisetron	21/30	27/30	18/30	12/30	NR	NR
Dick et al 1995	Ondansetron	Metoclopramide + dexamethasone	11/15	3/12	NR	NR	NR	NR

Table 3-5 Number of patients experiencing an event out of the total number of patients in each study, for partial response outcomes (acute, delayed and overall phase)

Author and Year	Interventions Arm 1	Intervention Arm 2 (and 3 if applicable)	Partial response in acute phase N/ total		Partial response in delayed phase N/ total		Partial response in the overall phase N/ total	
			Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)
Sharma et al. 2020	Aprepitant + Ondansetron	Ondansetron	9/15	18/29	15/16	24/26	15/16	24/26
Malek et al. 2021	Aprepitant + ondansetron	Ondansetron	NR	NR	NR	NR	NR	NR
Bakshi et al. 2015	Aprepitant + Ondansetron + dexamethasone	Ondansetron + dexamethasone	7/28	7/39	12/35	7/31	12/35	7/31
Kang et al. 2015	Aprepitant + Ondansetron	Ondansetron	27/54	36/74	26/78	33/121	NR	NR
Gore et al. 2009	Aprepitant + Ondansetron + dexamethasone	Ondansetron + dexamethasone	NR	NR	NR	NR	NR	NR
Radhakrishnan et al. 2018	Fosaprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	11/12	26/33	15/18	29/40	15/18	29/40
Ruktrirong et al 2021	Single-dose Ondansetron	Divided dose Ondansetron	NR	NR	NR	NR	NR	NR
Sandoval et al, 1999	Single-dose Ondansetron	Divided dose Ondansetron	NR	NR	NR	NR	NR	NR
Chaudhary et al, 2019	Ondansetron + dexamethasone	Palonosetron + dexamethasone	NR	NR	NR	NR	NR	NR
White et al. 2000	Ondansetron + dexamethasone	Ondansetron + dexamethasone	NR	NR	NR	NR	NR	NR
Brock et al. 1996	Ondansetron lower dose	Ondansetron higher dose	NR	NR	NR	NR	NR	NR

Kovacs et al 2016	Ondansetron	<u>Arm 2:</u> Palonosetron lower dose <u>Arm 3:</u> Palonosetron higher dose	NR	NR	NR	NR	NR	NR
Li et al 2021	Palonosetron	Granisetron	11/17	23/28	NR	NR	NR	NR
Tan et al 2018	Ondansetron	<u>Arm 2:</u> Palonosetron lower dose <u>Arm 3:</u> Palonosetron higher dose	NR	NR	NR	NR	NR	NR
Siddique et al. 2011	Ondansetron	Granisetron	9/9	3/3	NR	NR	NR	NR
Dick et al 1995	Ondansetron	Metoclopramide + dexamethasone	3/4	2/9	NR	NR	NR	NR

Table 3-6 Number of patients experiencing an event out of the total number of patients in each study, for outcomes of nausea (any phase) and decreased food intake (any phase)

Author and Year	Interventions Arm 1	Intervention Arm 2 (and 3 if applicable)	Nausea (any phase) N/ total		Decreased food intake/ appetite (any phase) N/ total	
			Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)
Sharma et al. 2020	Aprepitant + Ondansetron	Ondansetron	NR	NR	NR	NR
Malek et al. 2021	Aprepitant + ondansetron	Ondansetron	3/18	6/17	0/18	3/17
Bakshi et al. 2015	Aprepitant + Ondansetron + dexamethasone	Ondansetron + dexamethasone	NR	NR	16/52	20/44
Kang et al. 2015	Aprepitant + Ondansetron	Ondansetron	13/155	17/152	NR	NR
Gore et al. 2009	Aprepitant + Ondansetron + dexamethasone	Ondansetron + dexamethasone	7 /32.	4/18	NR	NR
Radhakrishnan et al. 2018	Fosaprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	NR	NR	NR	NR
Ruktrirong et al 2021	Single dose Ondansetron	Divided dose Ondansetron	NR	NR	5/96	10/98
Sandoval et al 1999	Single dose Ondansetron	Divided dose Ondansetron	1/16		0/16	1/15

Chaudhary et al 2019	Ondansetron + dexamethasone	Palonosetron + dexamethasone	NR	NR	NR	NR
White et al 2000	Ondansetron + dexamethasone	Ondansetron + dexamethasone	NR	NR	54/216	51/212
Brock et al 1996	Ondansetron lower dose	Ondansetron higher dose	39/93	36/94	NR	NR
Kovacs et al 2016	Ondansetron	<u>Arm 2:</u> Palonosetron lower dose <u>Arm 3:</u> Palonosetron higher dose	40/162	46/166 (56/165)	NR	NR
Li et al 2021	Palonosetron	Granisetron	NR	NR	NR	NR
Tan et al 2018	Ondansetron	<u>Arm 2:</u> Palonosetron lower dose <u>Arm 3:</u> Palonosetron higher dose	147/194	105/185 (109/186)	NR	NR
Siddique et al. 2011	Ondansetron	Granisetron	5/30	2/30	NR	NR
Dick et al 1995	Ondansetron	Metoclopramide + dexamethasone	NR	NR	NR	NR

3.4 Model fit statistics

Table 7: Model fit statistics for fixed effects, random effects, and random effects with an informative prior on the between-study heterogeneity parameter, of studies comparing antiemetic regimens for the prevention of outcomes of chemotherapy-induced nausea and vomiting in children.

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
Complete control in the acute phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects *	86.44	15.54	13	NA
		Random effects	86.51	13.88		0.542
		Random effects with informative prior	86.63	15.54		0.0197
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	128.9	22.29	21	NA
		Random effects	129.4	20.94		0.354
		Random effects with informative prior	128.5	21.99		0.032
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects *	215.6	40.12	34	NA
		Random effects	215.9	36.96		0.164
		Random effects with informative prior	215.4	39.51		0.0258
Partial control in the acute phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects*	21.38	4.016	4	NA
		Random effects	21.32	3.932		0.999
		Random effects with informative prior	21.14	4.037		0.0926
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	20.13	5.582	6	NA
		Random effects	20.8	5.558		1.003
		Random effects with informative prior	20.18	5.761		0.1302

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects *	39.85	9.045	10	NA
		Random effects	40.79	9.294		0.7734
		Random effects with informative prior	39.00	9.226		0.07713
Complete control in the delayed phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	83.22	14.95	11	NA
		Random effects	83.19	13.27		0.8327
		Random effects with informative prior*	72.46	13.5		0.03946
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	72.7	14.87	13	NA
		Random effects	71.49	12.94		0.7896
		Random effects with informative prior	72.54	14.56		0.05407
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects	157.7	33.64	24	NA
		Random effects	154.3	26.85		0.428
		Random effects with informative prior*	146.4	31.12		0.05539
Partial control in the delayed phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects*	21.81	3.912	4	NA
		Random effects	21.9	3.963		1.001
		Random effects with informative prior	22.06	4.033		0.0819
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	Insufficient data to run network			
		Random effects				
		Random effects with informative prior				

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects*	28.94	6.103	6	NA
		Random effects	29.42	5.853		0.03942
		Random effects with informative prior	29.07	6.158		0.757
Complete control in the overall phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects*	68.33	10.32	11	NA
		Random effects	68.97	10.5		0.858
		Random effects with informative prior	68.24	10.28		0.047
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	33.75	5.006	4	NA
		Random effects	33.74	5.002		1.001
		Random effects with informative prior	33.83	5.051		0.07088
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects	106.2	21.4	15	NA
		Random effects*	102.1	15.28		0.6664
		Random effects with informative prior	104.9	19.73		0.07086
Partial control in the overall phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects*	21.66	4.044	4	NA
		Random effects	21.64	4.024		0.9945
		Random effects with informative prior	21.57	4.01		0.1174
		Fixed effects*	Insufficient data to run network			
		Random effects				

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
	Studies comparing antiemetic regimens given without dexamethasone	Random effects with informative prior				
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects	35.46	9.643	6	NA
		Random effects*	32.66	5.959		1.089
		Random effects with informative prior	35.39	9.763		0.07288
Nausea (as defined in study)	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects*	33.2	5.017	5	NA
		Random effects	33.14	4.986		0.9967
		Random effects with informative prior	33.12	4.965		0.09971
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	74.2	12.4	13	NA
		Random effects	75.21	12.78		0.6172
		Random effects with informative prior	73.89	12.17		0.06713
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects*	105.5	17.55	18	NA
		Random effects	107.0	17.5		0.2558
		Random effects with informative prior	106.0	17.47		0.04884
Food intake	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	Insufficient data to form network		NA	NA
		Random effects				NA
		Random effects with informative prior				NA

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects	Insufficient data to form network		NA	NA
		Random effects				NA
		Random effects with informative prior				NA
	All studies included (antiemetic regimens given with or without dexamethasone grouped)	Fixed effects*	49.37	11.52	10	NA
		Random effects	50.57	11.95		0.4309
		Random effects with informative prior	49.99	11.78		0.0856

DIC: deviance information criterion, totresdev: Total residual deviance, SD: standard deviation.

3.5 Additional outcomes

The research in this chapter has been published in the Journal of Supportive Care in Cancer, Walker et al. 2024 (Walker et al., 2024), and is also available online as a pre-print version (Walker et al., 2023). The text in this chapter, particularly in the results section, therefore, aligns very closely and in some places will be identical to the wording used in the paper. The text in the methods and discussion sections has been expanded on, so it will contain additional detail and exploration.

N.B. Partial response outcomes were analysed using the number at risk (i.e., the total number of patients minus those who had a complete response) as the denominator.

3.5.1 Partial response in the acute phase

Five clinical trials informed the analyses for the outcome of nausea, two of which gave antiemetic regimens with dexamethasone (153 patients across four different antiemetic regimens) and three which gave them without (69 patients across four different antiemetic regimens) (Figure 3-4).

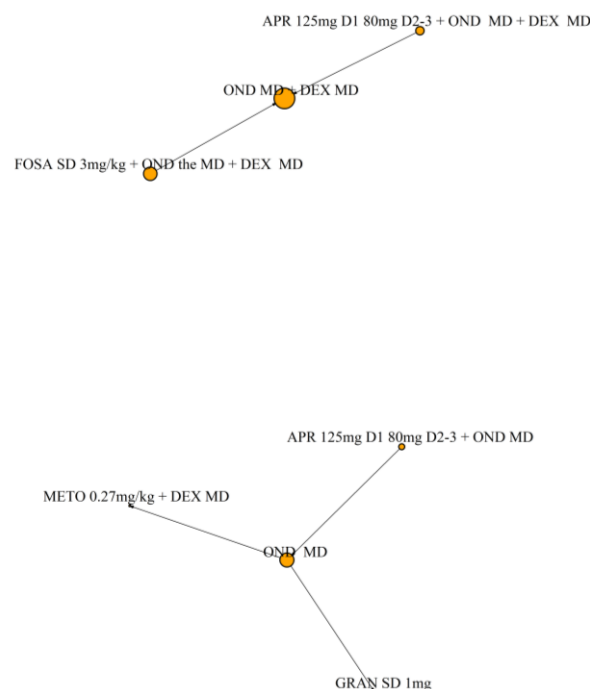


Figure 3-4. Network plot for the outcome partial response in the acute phase. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in Chapter 3 **Error! Reference source not found.**

For those not achieving a complete response in the acute phase, fosaprepitant 3mg/kg (single dose) + ondansetron (MD) + dexamethasone (MD) increased the chances of having a partial response compared to ondansetron (MD) + dexamethasone (MD). Of regimens given without dexamethasone, metoclopramide 0.27mg/kg decreased the chances of a partial response compared to ondansetron (MD). For other comparisons, there is a lack of evidence of a difference in efficacy (Figure 3-5).

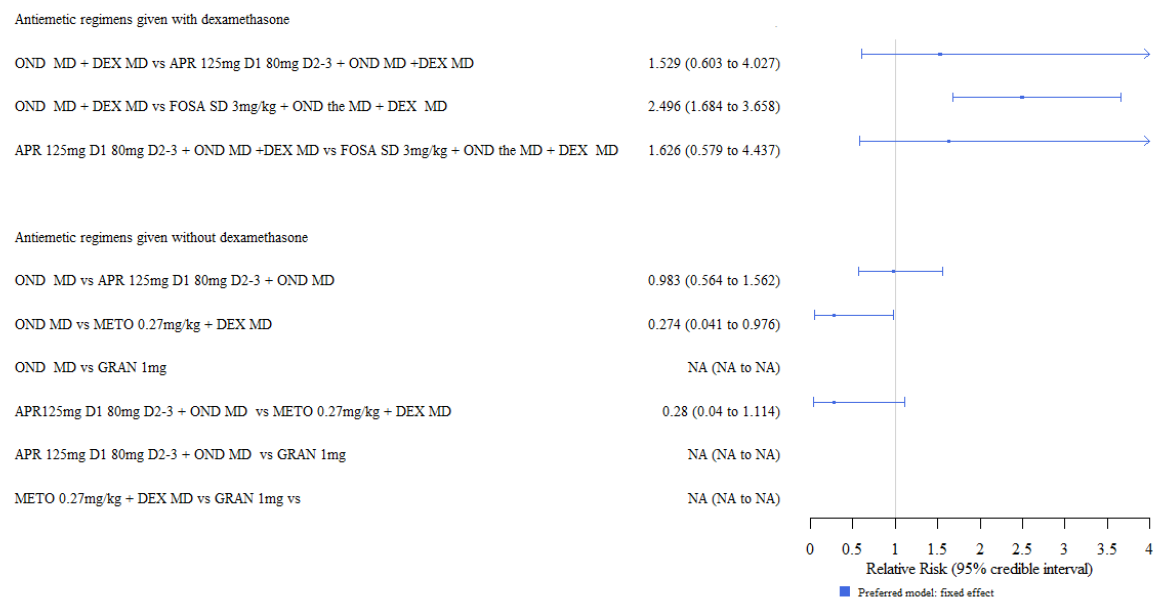


Figure 3-5. Partial response in the acute phase (0-24 hours after chemotherapy administration): **forest plot of relative effects** for each intervention. Values above one favour the second-named intervention. Values **above one** favour the second-named intervention. Where there are no results for certain models, the treatment effect for that comparison was not estimable (i.e., had a very wide credible interval). Abbreviations defined in Chapter 3

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3.5.2 Partial response in the delayed phase

Data were insufficient to run an NMA comparing antiemetic regimens given without dexamethasone. Two clinical trials informed the analyses of complete response in the delayed phase, both of which gave antiemetic regimens with dexamethasone (124 patients across three different antiemetic regimens (Figure 3-6).

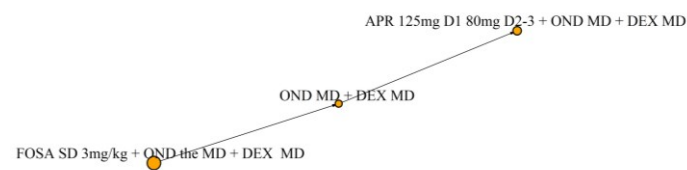


Figure 3-6. Network plot for the outcome partial response in the delayed phase. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Data were insufficient to run an NMA comparing antiemetic regimens given without dexamethasone. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

There was no evidence of difference between any of the three antiemetic regimens compared (Figure 3-7).

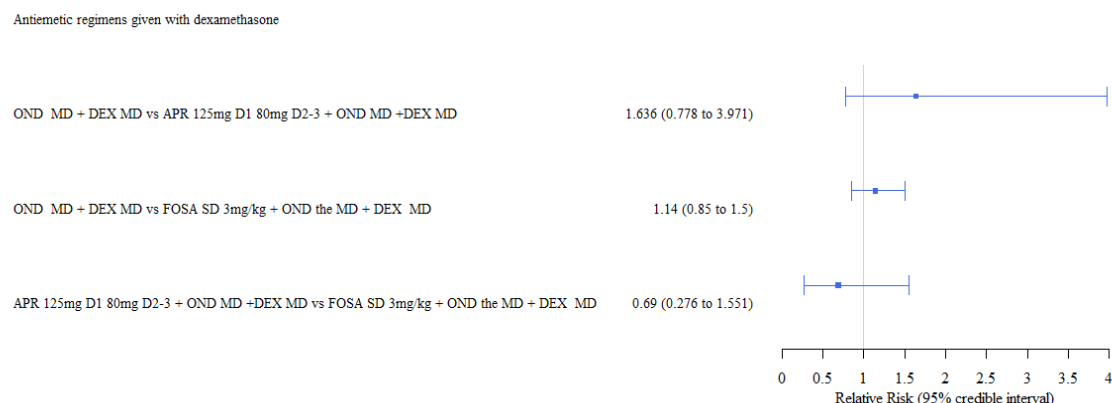


Figure 3-7 Partial response in the delayed phase (24 hours – 5-7 days after chemotherapy administration): **forest plot of relative effects** for each intervention. Preferred model: fixed effects. Values **above one** favour the second-named intervention. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

3.5.3 Partial response in the overall phase

Data were insufficient to run an NMA comparing antiemetic regimens given without dexamethasone. Two clinical trials informed the analyses of complete response in the delayed phase, both of which gave antiemetic regimens with dexamethasone (154 patients across three different antiemetic regimens (Figure 3-8).

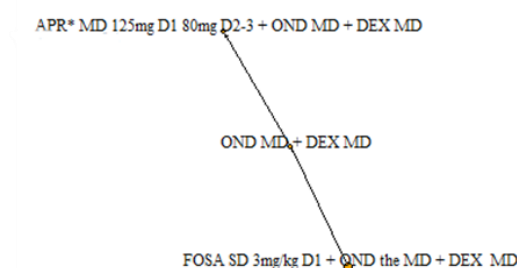


Figure 3-8 Network plot for the outcome partial response in the overall phase. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Data were insufficient to run an NMA comparing antiemetic regimens given without dexamethasone. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

For those not achieving a complete response in the acute phase, aprepitant 125mg (day 1) 80mg (day 2-3) + Ondansetron (MD) + dexamethasone (MD) increased the chances of having a partial response compared to ondansetron (MD) + dexamethasone (MD) and fosaprepitant 3mg/kg (single dose) + ondansetron (MD) + dexamethasone (MD) (Figure 3-9).

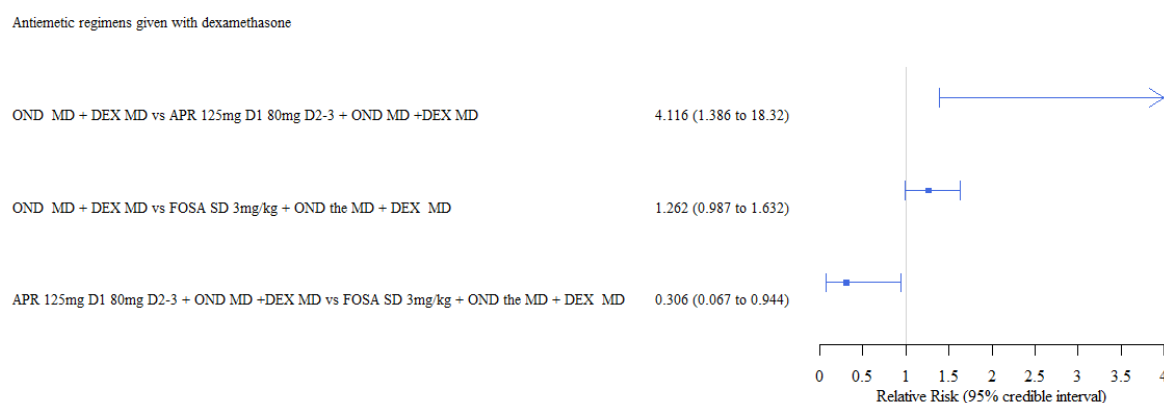


Figure 3-9 Partial response in the overall phase (0 hours- 5-7 days after chemotherapy administration): **forest plot of relative effects** for each intervention. Preferred model: fixed effect. Values **above one** favour the second-named intervention. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

3.5.4 Decreased food intake

Five clinical trials informed the analyses of decreased food intake, two of which gave antiemetic regimens with dexamethasone (524 patients across two different antiemetic regimens) (Figure 3-10), and three of which gave antiemetic emetic regimens without dexamethasone (260 patients across three different antiemetic regimens) (Figure 3-11).

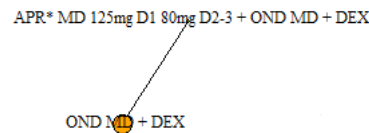


Figure 3-10 Food intake/ appetite (all phases) (Studies comparing antiemetic regimens given with dexamethasone): network diagram of interventions. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

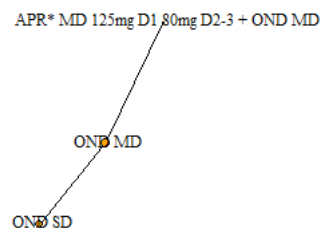


Figure 3-11. Food intake/ appetite (all phases) (Studies comparing antiemetic regimens given without dexamethasone): network diagram of interventions. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in Chapter 3 **Error! Reference source not found..**

No evidence of difference was observed for any antiemetic regimens (Figure 3-12)

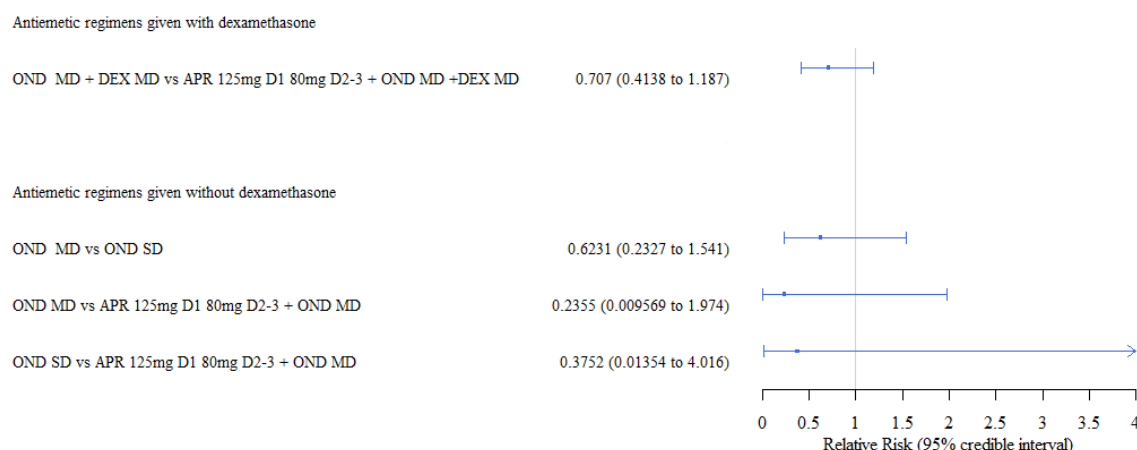


Figure 3-12 Food intake/ appetite (all phases): **forest plot of relative effects** for each intervention. Values of **less than one** favour the second-named intervention. Where there are no results for certain models, the treatment effect for that comparison was not estimable (i.e., had a very wide credible interval). Abbreviations defined in Chapter 3 **Error! Reference source not found..**

3.6 Sensitivity analyses

Grouping antiemetic regimens given with and without dexamethasone for complete response in the acute and delayed, made no discernible difference to conclusions drawn about the benefits of NK1 antagonists given with ondansetron, over and above 5-HT3 antagonists (Figure 3-13, Figure 3-14). However, in the delayed phase, comparison of fosaprepitant regimens with granisetron was possible, within these sensitivity analyses, and benefit was identified. For complete response in the acute and delayed phase, we also see a benefit of palonosetron 10ug/kg and 20ug/kg over ondansetron (Figure 3-13, Figure 3-14), not identified in the main analyses (Chapter 3, Figure 3-6). For complete response in the overall phase, there was additional uncertainty around treatment effect estimates, and many comparisons were inestimable, compared to in the main analyses (Figure 3-15).

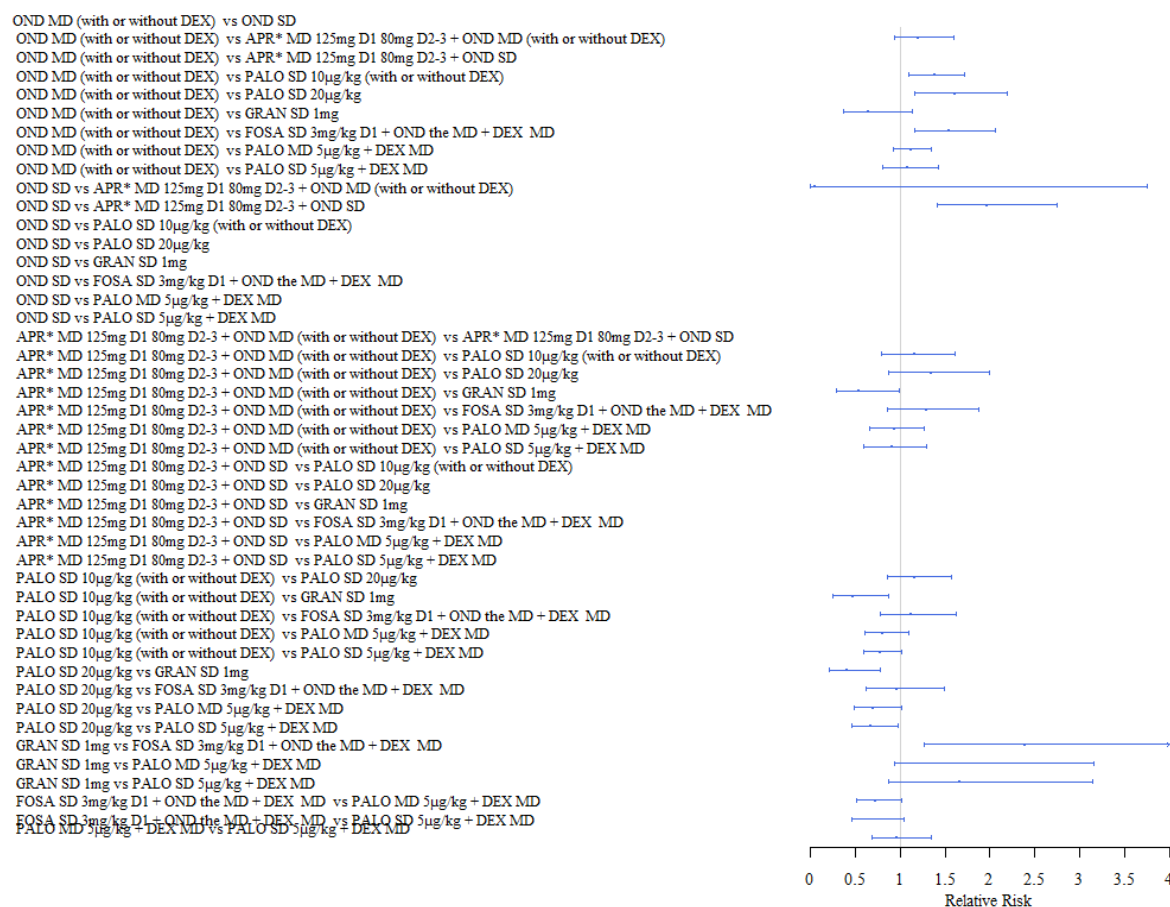


Figure 3-13 Forest plot: relative risks (95% credible interval) of antiemetic regimens (here regimens given with or without dexamethasone are grouped) for the outcome of complete response in the acute phase. Preferred models: random effect model with informative prior for the between-study heterogeneity parameter. Values above one favour the second-named intervention. Abbreviations defined in Chapter 3 **Error! Reference source not found.**

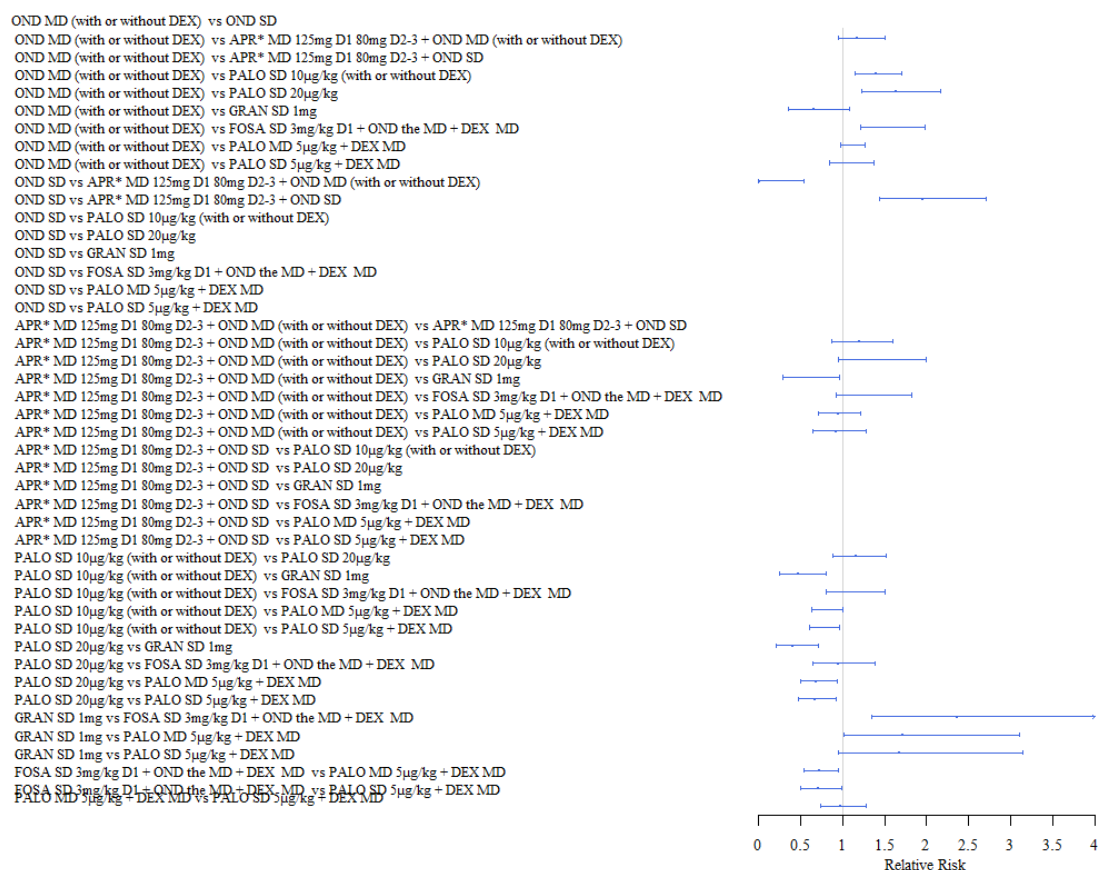


Figure 3-14 Forest plot: relative risks (95% credible interval) of antiemetic regimens (**here regimens given with or without dexamethasone are grouped**) for the outcome of complete response in the **delayed** phase. Preferred models: fixed effects. Values **above one** favour the second named intervention. Where there are no results for certain models, the treatment effect for that comparison was not estimable (i.e., had a very wide credible interval). Abbreviations defined in chapter 3 **Error! Reference source not found..**

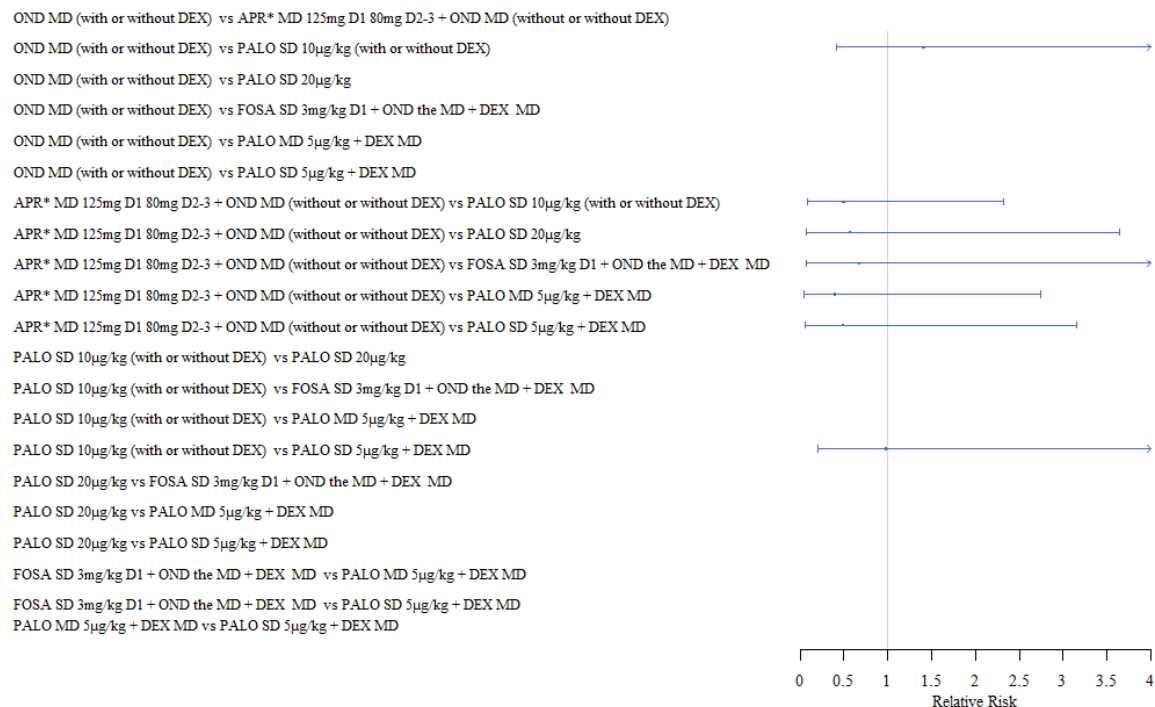


Figure 3-15 Forest plot: relative risks (95% credible interval) of antiemetic regimens (**here regimens given with or without dexamethasone are grouped**) for the outcome of complete response in the **overall** phase. Preferred models: random effects. Values **above one** favour the second-named intervention. Where there are no results for certain models, the treatment effect for that comparison was not estimable (i.e., had a very wide credible interval). Abbreviations defined in Chapter 3 **Error! Reference source not found.**

3.7 Children and family involvement activity

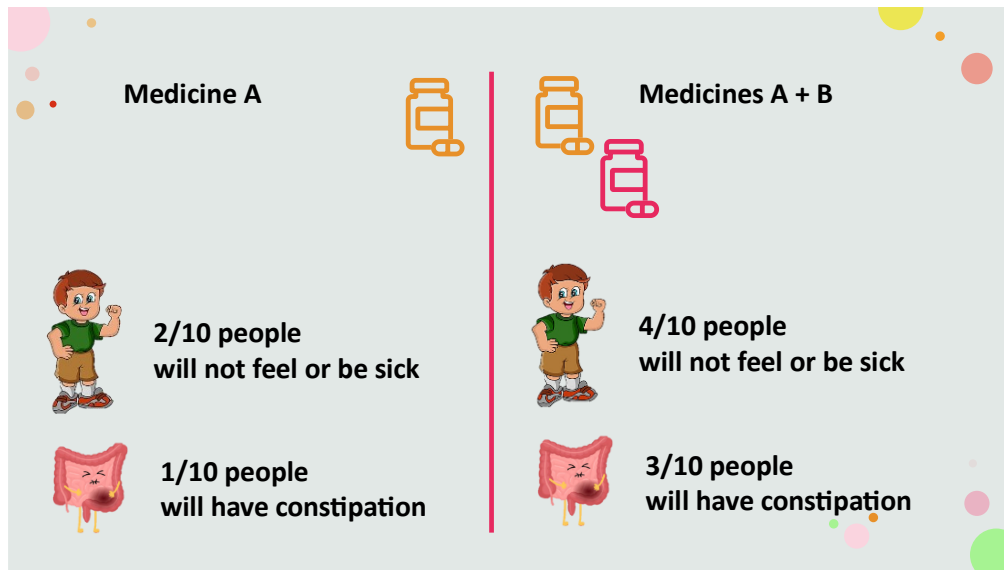


Figure 3-16 An activity (“trade-offs in practice”) designed to think about the trade-off of taking more medicines, having better outcomes, but being more likely to experience side-effects. Option B.

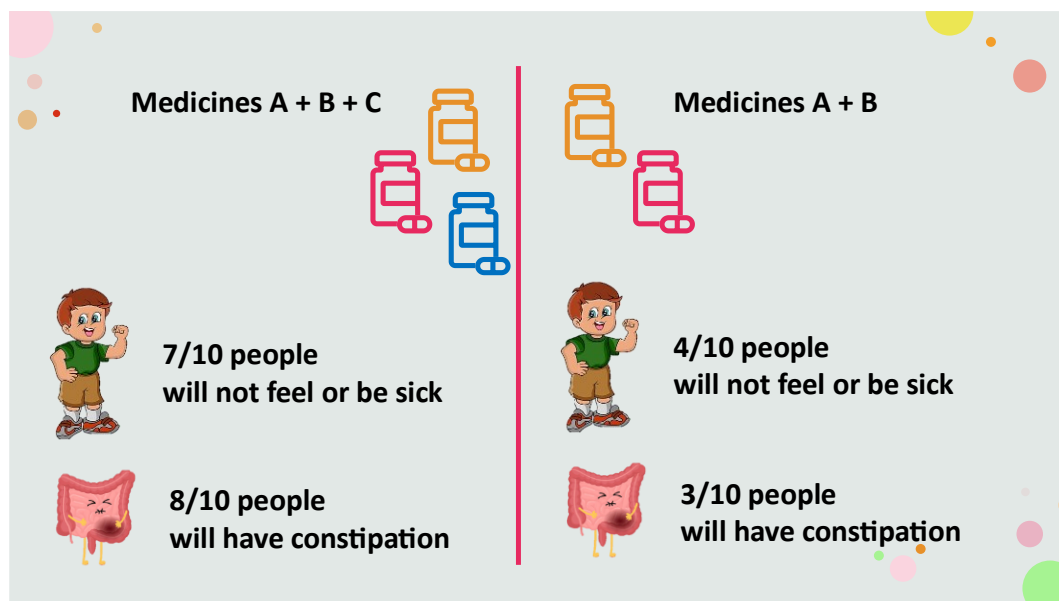


Figure 3-17 An activity (“trade-offs in practice”) designed to think about the trade-off of taking more medicines, having better outcomes, but being more likely to experience side-effects. Option C.

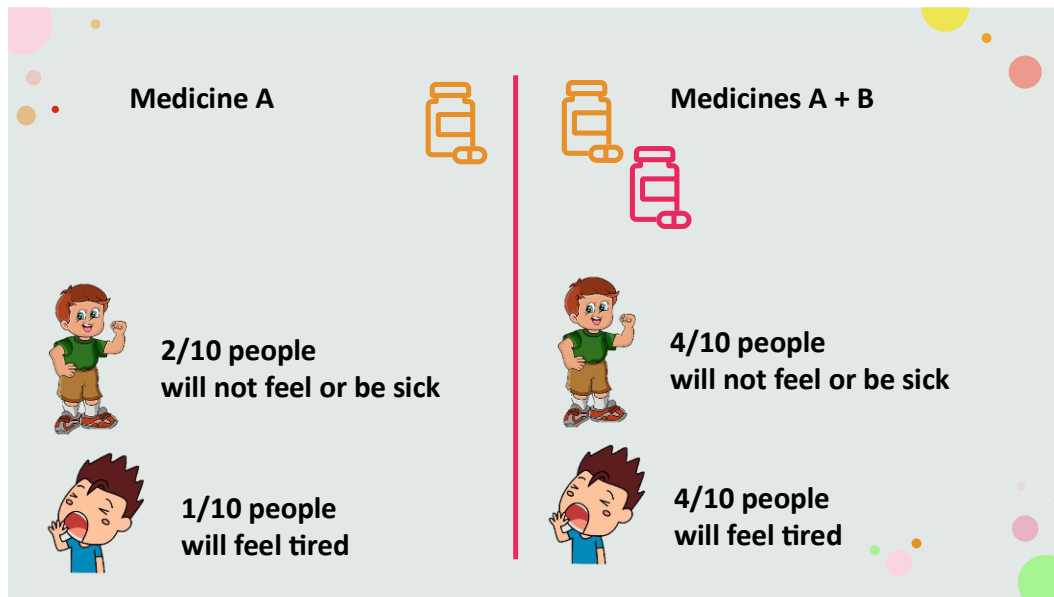


Figure 3-18 An activity (“trade-offs in practice”) designed to think about the trade-off of taking more medicines, having better outcomes, but being more likely to experience side-effects. Option D.

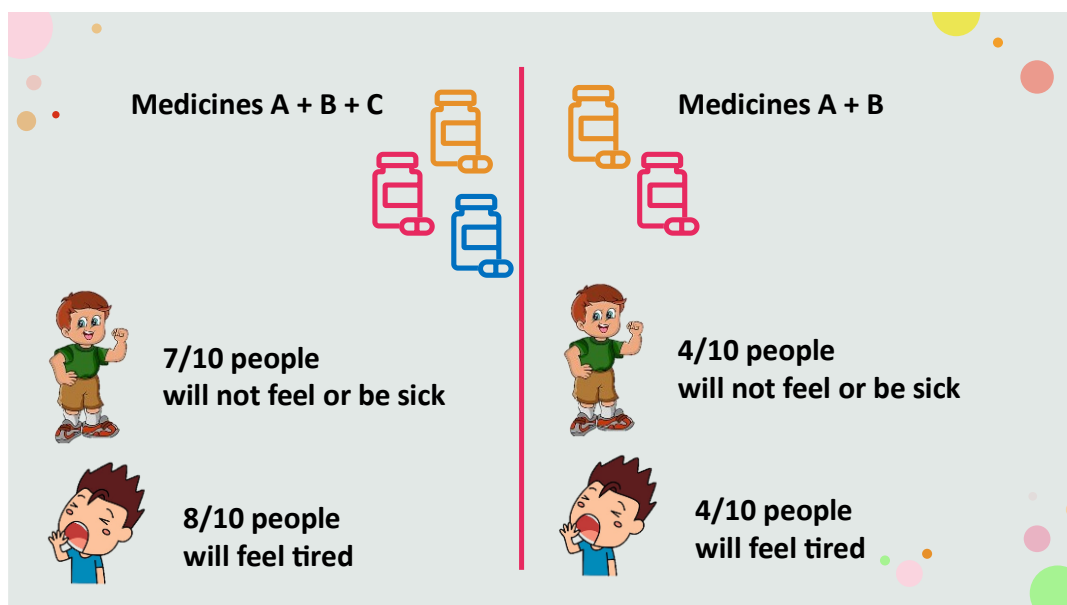


Figure 3-19 An activity (“trade-offs in practice”) designed to think about the trade-off of taking more medicines, having better outcomes, but being more likely to experience side-effects. Option D.

3.8 PRIMA NMA checklist

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	1
ABSTRACT			2
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	Introduction Section 3.1
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Research aims section 1.4 .
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Appendix section 1.3.6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	Inclusion and exclusion criteria 2.3.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Study identification section 2.3.1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix section 2.2

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Section 2.3.3 Screening methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Section 2.3.4 extraction of data
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Section 2.3.4 extraction of data
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation , and what characteristics were compiled and used to describe the evidence base to readers.	Determining the structure of the networks section 3.2.4
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 2.3.5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	Implementation section 3.2.3.1 – measures of effect
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • Handling of multi-arm trials; • Selection of variance structure; • Selection of prior distributions in Bayesian analyses; and • Assessment of model fit.	Implementation section 3.2.3.
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	NA no loops in the network to allow for evaluation
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Noted for side effect outcomes section 3.3.4
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • Alternative formulations of the treatment network; and • Use of alternative prior distributions for Bayesian analyses (if applicable).	Determining the network structure, section 3.2.4.

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Prisma flow diagram section 2.4.1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network. (chapter 3 results section 3.3)	
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network , gaps of evidence in the treatment network, and potential biases reflected by the network structure.	chapter 3 results section 3.3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2.5 Table of Study characteristics in children
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Risk of bias table –
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	Summary data are presented Appendix 3.3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	Reported forest plots chapter 3 results section 3.3
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA no loops in the networks
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Discussion of heterogeneity across studies and potential impact on results included in section 3.5.3.2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Section 3.5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Section 3.5

		Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 3.6
FUNDING Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Funded by an NIHR doctoral fellowship. NIHR302291

3.9 Poster designed for children and families

Preventing nausea and vomiting in children and young people undergoing chemotherapy.

Information for patients and families about on-going research.

Ruth Walker, Sofia Dias, Bob Phillips, University of York.

Background

Despite the availability of effective anti-sickness medicines, an estimated **70% of children undergoing treatment for cancer will experience** chemotherapy-induced **nausea and vomiting (CINV)**. Research into ways to prevent CINV is ongoing, with **clinical trials** testing new medicines by comparing them to those already in use.

The findings from existing clinical trials have also been combined using a technique called '**meta-analysis**'. This gives a better overview of how well one medicine works compared to another.

However, "meta-analysis" only combines findings for one treatment comparison, so **we don't know how well all anti-sickness medicines work compared to one-another.**

Methods

More recently we have combined the findings of clinical trials using a different statistical technique called a "**network-meta-analysis**", which allows you to compare more than two treatments at the same time.

We focused on clinical trials that compare anti-sickness medicines which are currently recommended for preventing CINV in children (and these tend to be the newer medicines). Patients and their families told us which outcomes were most important and we tried to focus on these.

By comparing each anti-sickness medicine with every other, we hoped to better understand **which works best to stop children and young people feeling sick from chemotherapy.**

What do patients think?

When we shared the results with patients and their families they told us:

- **Taking multiple tablets** each day was **difficult** when you felt sick.
- **Anti-sickness medicines** could **make side effects** of other treatments **worse**, particularly constipation.
- They might **modify** the number/ type of anti-sickness medicines they take to try and prevent side effects.
- Nausea and vomiting **before** chemotherapy and in the days **after** chemotherapy were important

Take aways

How well medicines prevent nausea and vomiting isn't the whole story, whilst taking multiple anti-sickness medicines might lead to less nausea and vomiting, it could lead to more (or make worse existing) side effects such as constipation and sleepiness, which are not trivial to patients. We will try to encourage those running clinical trials to **focus on the outcomes that matter most to patients**, and consider **testing combinations of fewer anti-sickness medicines** (including those given intravenously) to see if patients can safely reduce the number of tablets they take each day.

What are clinical trials?

Clinical trials are research studies that test new treatments. People are often randomly assigned to receive different treatments and then their outcomes are compared.

In clinical trials of anti-sickness medicines outcomes might be not feeling or being sick.

Results

We found 19 clinical trials of 3523 children.

Patients and families had told us **outcomes** including **nausea**, quality and quantity of **sleep**, **appetite**, need for a **feeding tube** and **side effects** (unintended effects) of anti-sickness medicines were **important**.

Clinical trials only consistently reported nausea, vomiting and need for additional (rescue) anti-sickness medication, on the day of chemotherapy (acute CINV) and in the days after (delayed CINV) so these were the outcomes we could focus on.

The following anti-sickness medicines/ combinations of medicines were compared, and are listed broadly in terms of how well they prevent nausea and vomiting.

1. Olanzapine (Zyprexa, Zentiva) + NK1 antagonist* + Ondansetron (Zofran)
1. NK1 antagonists* + Ondansetron
2. Palonosetron (Aloxi)
3. Ondansetron alone
4. Granisetron (Kytril, Sancuso)

*Like aprepitant and fosaprepitant (Emend, Ivamend)

The combinations of anti-sickness medicines, and those which contain newer medicines including NK1 antagonists and Olanzapine tend to better prevent nausea and vomiting, but may come along with more side effects.

These more effective combinations are currently recommended for children at high risk of CINV, i.e. those on chemotherapy regimens which are very likely to make you sick. However, more research is needed to know whether other children would also benefit from these anti-sickness medicines.

This project is funded by the NIHR Doctoral Fellowship Programme NIHR302291.
The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care

Figure 3-20. Poster designed to share with children and families, the research that is happening with this field, as well as their impact on the interpretation of the findings and recommendations for future research.

4 Chapter Four Appendix

4.1 BUGs code

This code will run a joint NMA for adults and children, allowing a proportional relationship for the treatment effect parameters (through the parameter 'lambda'), in the random effects model.

Information is also shared on the between-study heterogeneity parameter.

The code reported in this section has been acquired/ adapted from Dias et al. 2018 (Dias et al., 2018). Adaptations have been informed by work conducted by Nikolaidis 2020 (Nikolaidis, 2020).

4.1.1 Fixed effects model

```
# Binomial likelihood, log-Relative Risk
# Fixed effects model - 2 populations, functional relationship 'lambda'
model{
  # *** PROGRAM STARTS
  for(i in 1:ns){
    # LOOP THROUGH STUDIES
    mu[i] <- log(p[i,1])
    p[i,1] ~ dunif(0,1) # vague priors for all trial baselines
    for (k in 1:na[i]){
      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      # Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    } # close loop for the arms
    # The residual deviance for each study
    # summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  } # close loop for the studies
  # models for linear predictors-
  #
  # ADULTS LOOP
  for(i in 1:nsA){
    for (k in 2:na[i]){
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      delta[i,k] <- d[1,t[i,k]] - d[1,t[i,1]] # - this part edited for adults and children
    }
  }
  # CHILDRENS LOOP
  for(i in (nsA+1):(nsA+nsC)){
    for (k in 2:na[i]){
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      delta[i,k] <- d[2,t[i,k]] - d[2,t[i,1]] # - this part edited for adults and children
    }
  }
  totesdev <- sum(resdev[]) # Total Residual Deviance

  for (k in 2:nt){
    d[1,k] ~ dnorm(0,.0001) # vague prior for adult treatment effect
    d[2,k] <- d[1,k] + lambda[k] # FUNCTIONAL RELATIONSHIP for children
  }

  for (k in 2:4) {
    lambda[k] ~ dnorm(mu_lambda, tau_lambda) # prior for lambda
    explambda[k] <- exp(lambda[k])
  }

  mu_lambda ~ dnorm(0,0.001) # non-inf prior for sharing parameter
  tau_lambda <- pow(sd_lambda,-2) # between-trial precision = (1/between-trial variance)
  sd_lambda ~ dnorm(0, prec2)I(0,)
```

```

prec2 <- pow(0.5, -2)    # SD = 0.5

for (k in 5:6) {
  lambda[k] ~ dnorm(0,0.001)    # non-informative prior for sharing parameter
}

# estimate treatment effect of Olanzapine regimens from the mean of the lambda distribution

Child.pred_mean1 <- d[1,5] + mu_lambda
Child.pred_mean2 <- d[1,6] + mu_lambda

# Adapt using consistency equations

Child.pred_mean3 <- Child.pred_mean1 - d[2,2]

Pred1 <- exp(Child.pred_mean3)
Pred2 <- exp(Child.pred_mean2)

#estimate treatment effect of Olanzapine regimens taking into account the variance of the # lambda distribution

lambda_new ~ dnorm(mu_lambda, tau_lambda) # predictive interval

Child.pred_interval1 <- d[1,5] + lambda_new
Child.pred_interval2 <- d[1,6] + lambda_new

#Adapt using consistency equation d25= #d15- d12

Child.pred_interval3 <- Child.pred_interval1 - d[2,2]

Pred_interval1 <- exp(Child.pred_interval2)
Pred_interval2 <- exp(Child.pred_interval3)

for (j in 1:2){          # LOOP OVER POPULATIONS 1=adults; 2=children
  d[j,1] <- 0    # treatment effect is zero for reference treatment
  # pairwise RRs for all possible pair-wise comparisons
  for (c in 1:(nt-1)){
    for (k in (c+1):nt){
      lnRR[j,c,k] <- d[j,k] - d[j,c]
      RR[j,c,k] <- exp(d[j,k] - d[j,c])
    }
  }
  # ranking on relative scale
  for (k in 1:nt) {
    # rk[j,k] <- nt+1-rank(d[j, ],k) # assumes events are "good"
    rk[j,k] <- rank(d[j, ],k) # assumes events are "bad"
    best[j,k] <- equals(rk[j,k],1) #calculate probability that treat k is best
    # calculates probability that treat k is h-th best
    for (h in 1:nt){ prob[j,h,k] <- equals(rk[j,k],h) }
  }
}
# close loop over populations
}
# *** PROGRAM ENDS

```

N.B. Within the BUGs code, the between-trial precision *is used* ($1/\text{between-trial variance } \sigma^2$).

4.1.2 Random effects model

```
# Binomial likelihood, log-Relative Risk
# Random effects model for multi-arm trials, functional relationship 'lambda'
model{
  *** PROGRAM STARTS
  for(i in 1:ns){
    # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] <- log(p[i,1])
    p[i,1] ~ dunif(0,1) # vague priors for all trial baselines
    for (k in 1:na[i]) {
      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      #Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    } # CLOSE LOOP FOR ARMS
    # summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  } # CLOSE LOOP FOR STUDIES
  # models for linear predictors
  #
  # ADULTS LOOP
  for(i in 1:nsA){
    for (k in 2:na[i]) {
      # LOOP THROUGH ARMS
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      # trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      # mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <- d[1,t[i,k]] - d[1,t[i,1]] + sw[i,k]
      # precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau * 2*(k-1)/k
      # adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[1,t[i,k]] + d[1,t[i,1]])
      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    } # CLOSE LOOP FOR ARMS
  }
  # CHILDREN'S LOOP
  for(i in (nsA+1):(nsA+nsC)){
    for (k in 2:na[i]) {
      # LOOP THROUGH ARMS
      log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))
      # trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      # mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <- d[2,t[i,k]] - d[2,t[i,1]] + sw[i,k]
      # precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau * 2*(k-1)/k
      # adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[2,t[i,k]] + d[2,t[i,1]])
      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    } # CLOSE LOOP FOR ARMS
  }
  toresdev <- sum(resdev[]) # Total Residual Deviance
  sd ~ dunif(0,2) # vague prior for between-trial SD
  tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

  for (k in 2:nt){
    d[1,k] ~ dnorm(0,.0001) # vague prior for adult treatment effect
    d[2,k] <- d[1,k] + lambda[k] # FUNCTIONAL RELATIONSHIP for children
  }

  for (k in 2:4) {
```

```

lambda[k] ~ dnorm(mu_lambda, tau_lambda)      # Lambda distribution
explambda[k] <- exp(lambda[k])
}

mu_lambda ~ dnorm(0,0.001) # non-inf prior for sharing parameter
tau_lambda <- pow(sd_lambda,-2) # precision = (1/ variance)
sd_lambda ~ dnorm(0, prec2)I(0,)
prec2 <- pow(0.5, -2)      # SD = 0.5

for (k in 5:6) {
  lambda[k] ~ dnorm(0,0.001)      # non-inf prior for sharing parameter
}

# estimate treatment effect of Olanzapine regimens from the mean of the lambda distribution

Child.pred_mean1 <- d[1,5] + mu_lambda
Child.pred_mean2 <- d[1,6] + mu_lambda

# Adapt using consistency equations
Child.pred_mean3 <- Child.pred_mean1 - d[2,2]

Pred1 <- exp(Child.pred_mean3)
Pred2 <- exp(Child.pred_mean2)

#estimate treatment effect of Olanzapine regimens taking into account the variance of the #lamdba distribution

lambda_new ~ dnorm(mu_lambda, tau_lambda) # predictive interval

Child.pred_interval1 <- d[1,5] + lambda_new
Child.pred_interval2 <- d[1,6] + lambda_new
Child.pred_interval3 <- Child.pred_interval1 - d[2,2]

#Adapt using consistency equation d25= d15- d12

Pred_interval1 <- exp(Child.pred_interval3)
Pred_interval2 <- exp(Child.pred_interval2)

for (j in 1:2){      # LOOP OVER POPULATIONS 1=adults; 2=children
  d[j,1] <- 0      # treatment effect is zero for reference treatment
  # pairwise RRs for all possible pair-wise comparisons
  for (c in 1:(nt-1)){
    for (k in (c+1):nt){
      lnRR[j,c,k] <- d[j,k] - d[j,c]
      RR[j,c,k] <- exp(d[j,k] - d[j,c])
    }
  }
  # ranking on relative scale
  for (k in 1:nt) {
    # rk[j,k] <- nt+1-rank(d[j, ],k) # assumes events are "good"
    rk[j,k] <- rank(d[j, ],k) # assumes events are "bad"
    best[j,k] <- equals(rk[j,k],1) #calculate probability that treat k is best
    # calculates probability that treat k is h-th best
    for (h in 1:nt){ prob[j,h,k] <- equals(rk[j,k],h) }
  }
}      # close loop over populations
}      # *** PROGRAM ENDS

```

4.2 Summary data informing joint networks of child and adult data

Table 4-1 Adult clinical trial data informing the joint networks of child and adult data

Author and Year	Interventions Arm 1	Intervention Arm 2 (and 3 if applicable)	Complete response in the acute phase		Complete response in the delayed phase		Complete response in the overall phase	
			N/ total		N/ total		N/ total	
			Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)
Kim et al. 2017	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	234/244	244/250	176/244	173/250	174/244	171/250
Warr et al. 2005	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	329/438	293/428	238/438	208/428	221/438	178/428
Patel et al. 2020	Aprepitant + Ondansetron	Ondansetron	68/74	58/72	43/74	41/72	41/74	36/72
Rapoport et al. 2010	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	379/430	327/418	301/430	248/418	292/430	229/418
Poli-Bigelli et al. 2003	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	194/283	168/286	158/283	115/286	147/283	107/286
Schmoll et al. 2006	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	213/244	191/245	180/244	152/245	175/244	146/245
Yeo et al 2009	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	45/62	45/62	40/62	36/62	29/62	26/62
Stiff et al 2013	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	87/92	78/89	NR	NR	74/92	59/89
Hesketh et al. 2003	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	235/264	207.746/266	199/264	148/266	191.928/264	139.118/266

Herrstedt et al. 2005 (first cycle only)	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	NR	NR	NR	NR	219.964/433	180.2/424
Morteza et al. 2021	Aprepitant + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	77.08/82	74.62/82	80.36/82	75/82	80.36/82	74.62/82
Grunberg et al. 2011	Fosaprepitant + ondansetron + dexamethasone	Ondansetron + Dexamethasone	987/1147	1001/1175	824/1147	844/1175	797/1147	823/1175
Weinstein et al. 2016	Fosaprepitant + ondansetron + dexamethasone	Ondansetron + Dexamethasone	468/508	453/507	396/508	341/507	387/508	333/507
Aapro et al 2006	Palonosetron +dexamethasone	Arm 2: Palonosetron + dexamethasone, Arm 3 Ondansetron + dexamethasone.	146/223	132 (126)/ 223 (221)	107/146	101 (86)/ 233 (221)	94/146	91 (73)/ 223 (221)
Gralla et al. 2003	Palonosetron	Arm 2: Palonosetron Arm 3 Ondansetron	139/189	153(127)/189 (185)	122/189	140 (102)/ 189 (185)	111/189	131 (93)/ 189 (185)
Dong et al 2010	Palonosetron	Ondansetron	42/44	42/45	37/44	27/45	25/44	21/45
Mattiuzzi et al. 2010	Palonosetron	Arm 2: Palonosetron Arm 3 Ondansetron	NR	NR	NR	NR	15/48	17 (10)/ 48 (47)
Yu et al 2009	Palonosetron	Granisetron	86/104	75/104	62/104	55/104	NR	NR
Huang et al 2013	Palonosetron	Granisetron	56/117	49/119	59/117	36/119	43/117	32/119
Gebbia et al. 1994 (study 1)	Ondansetron	Granisetron	44/92	40/90	15/92	13/90	NR	NR
Gebbia et al. 1994 (study 2)	Ondansetron	Granisetron	54/82	54/82	35/82	42/82	NR	NR
Gralla et al. 1998 (without dex use)	Ondansetron	Granisetron	62/107	54/117	NR	NR	NR	NR
Navari et al. 1995	Ondansetron	Arm 2: Granisetron low dose Arm 3:	168/331	152 (155)/328 (328)	NR	NR	NR	NR

		Granisetron high dose						
Fox-Geiman et al. 2001	Ondansetron	Arm 2: Ondansetron, Arm 3: Granisetron.	NR	NR	NR	NR	17/34	16 (16)/ 34 (34)
Noble et al. 1994 (first cycle data)	Ondansetron	Arm 1 Ondansetron, Arm 2: Granisetron	163/183	161/176	NR	NR	68/183	69/176
Park et al. 1997	Ondansetron	Arm 1 Ondansetron, Arm 2: Granisetron	25/47	22/48	14/47	13/48	NR	NR
Martoni et al. 1996 (cycle one data)	Ondansetron	Arm 1 Ondansetron, Arm 2: Granisetron	43/58	50/66	NR	NR	NR	NR
Spector et al. 1998	Ondansetron	Arm 1 Ondansetron, Arm 2: Granisetron	106/184	95/187	NR	NR	NR	NR
Ruff et al. 1994	Ondansetron low dose	Arm 2: Ondansetron high dose Arm 3: Granisetron	97.35/165	83 (95)/163 (169)	NR	NR	NR	NR
Chevallier et al 1994	Granisetron	Metoclopramide + dexamethasone	100/143	93/138	NR	NR	51/143	65/138
Aapro et al. 1993	Granisetron	Metoclopramide + dexamethasone	125/143	95/141	NR	NR	66/143	61/141
Levitt et al. 1993	Ondansetron	Metoclopramide + dexamethasone	69/84	71/80	reported separately by days 2-5/	reported separately by days 2-5/	51/84	57/80
Koralewski et al. 2001	Ondansetron	Metoclopramide + dexamethasone	36/41	25/33	32/41	25/33	NR	NR

Table 4-2 Adult clinical trial data of olanzapine regimens, included in the joint network to facilitate predictions of treatment effects in children.

Author and Year	Interventions Arm 1	Intervention Arm 2 (and 3 if applicable)	Complete response in acute phase N/ total		Complete response in delayed phase N/ total		Complete response in the overall phase N/ total	
			Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)
Ithimakin et al. 2020	Olanzapine (low dose) + Aprepitant + Ondansetron + dexamethasone	Arm 2: Olanzapine (high dose) + Aprepitant + Ondansetron + dexamethasone Arm 3: Aprepitant + Ondansetron + dexamethasone	39/47	Arm 2: 38/ 46, Arm 3: 39/47	35/47	Arm 2: 35/ 46, Arm 3: 34/47	33/47	Arm 2: 30/ 46, Arm 3: 32/47
Yeo et al. 2020	Olanzapine + Aprepitant + Ondansetron + dexamethasone	Aprepitant + Ondansetron + dexamethasone	42/60	31/60	56/60	45/60	39/60	45/60
Tienchaiananda et al. 2019	Olanzapine + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	15/21	7/19	10/21	5/19	10/21	4/19
Vimolchalao et al 2020 (first cycle data)	Olanzapine + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	24/32	10/32	22/32	14/32	22/32	8/32

Table 4-3 Child clinical trial data of olanzapine regimens, used to determine the reliability of predicted treatment effects in children.

Author and Year	Interventions Arm 1	Intervention Arm 2 (and 3 if applicable)	Complete response in the acute phase N/ total		Complete response in the delayed phase N/ total		Complete response in the overall phase N/ total	
			Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)	Arm 1	Arm 2 (and 3)
Naik et al 2020	Olanzapine + Aprepitant +	Aprepitant + Ondansetron + dexamethasone	90/120	68/120	85/120	54/120	73/120	44/120

	Ondansetron + dexamethasone							
Moothedath et al. 2022	Olanzapine + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	38/63	35/65	46/63	31/65	30/63	22/65
Moshayediet al, 2021	Olanzapine + Ondansetron + Dexamethasone	Ondansetron + Dexamethasone	14/19	16/21	15/19	18/21	11/19	16/21

4.3 Table of preferred models

Table 4-4 Model fit statistics for Bayesian information sharing models used to assess improvements in the precision of treatment effect estimates in children (i.e. network excluding olanzapine regimens). Comparison of fixed effects, random effects, and random effects with an informative prior informing the between-study heterogeneity parameters.

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
Complete control in the acute phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	244	55.25	32	NA
		Random effects*	223	33.31		0.064
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effect	353	64.7	52	NA
		Random effects*	348	52.19		0.085
Complete control in the delayed phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	228	43.98	30	NA
		Random effects*	223	34.98		0.083
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects	111	23.13	16	NA
		Random effects *	106	16.27		0.487
Complete control in the overall phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	235	42.73	32	NA
		Random effects*	230	31.71		0.093
	Studies comparing antiemetic regimens given without dexamethasone	Fixed effects*	93	12.39	14	NA
		Random effects	95	13.09		0.348

Table 4-5 Model fit statistics for Bayesian information sharing models used to predict the effect of olanzapine regimens in children (including olanzapine regimens in adults). Comparison of fixed effects, random effects, and random effects with an informative prior informing the between-study heterogeneity parameters.

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
Complete control in the acute phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	290	69.7	41	NA
		Random effects*	274	42.84		0.061
Complete control in the delayed phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	275	51.08	37	NA
		Random effects*	270	40.39		0.078
Complete control in the overall phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	288	50.30	41	NA
		Random effects*	282	40.51		0.092

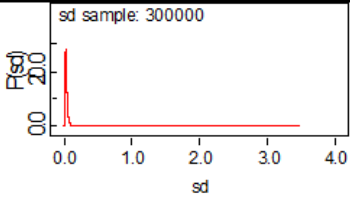
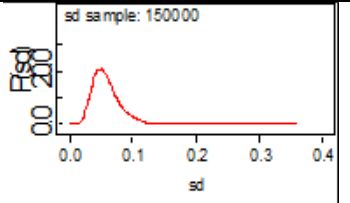
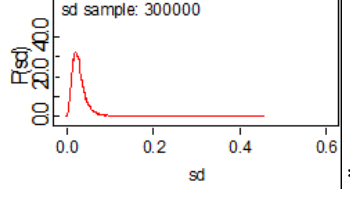
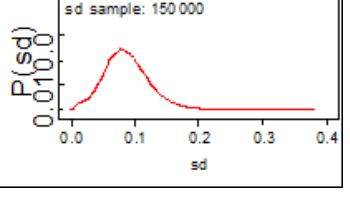
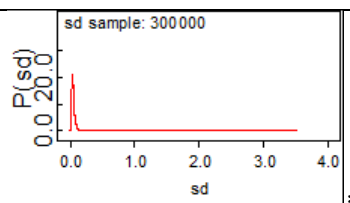
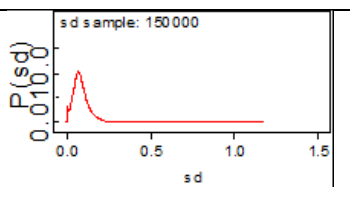
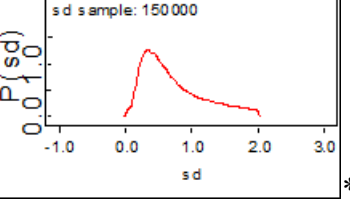
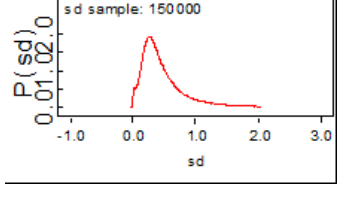
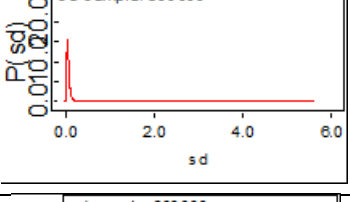
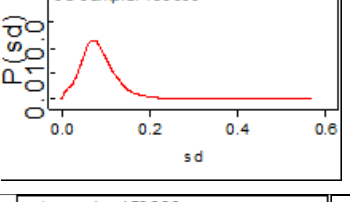
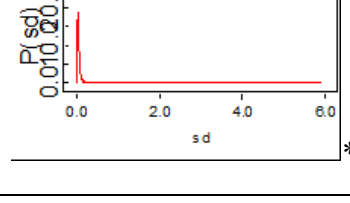
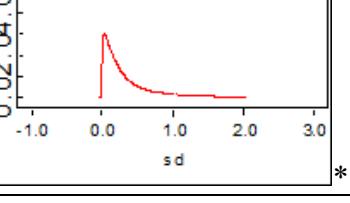
Table 4-6 Model fit statistics for Bayesian information sharing models used to predict the effect of olanzapine regimens in children (including olanzapine regimens in adults and children, for comparison with predictions). Comparison of fixed effects, random effects, and random effects with an informative prior informing the between-study heterogeneity parameters.

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
Complete control in the acute phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	326	70.70	47	NA
		Random effects*	309	43.44		0.065
Complete control in the delayed phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	315	61.7	43	NA
		Random effects*	308	40.85		0.083

<u>Outcome</u>	<u>Studies included in the network</u>	<u>Model</u> * indicates preferred model(s)	<u>DIC</u>	<u>totresdev</u>	<u>Number of data points</u>	<u>Between-study heterogeneity (SD)</u>
Complete control in the overall phase	Studies comparing antiemetic regimens given with dexamethasone	Fixed effects	327	70.56	47	NA
		Random effects*	321	41.07		0.093

4.4 Densities for the between-study heterogeneity parameter from random effects models of child data only vs child and adult data.

Table 4-7 Posterior distributions for the between-study heterogeneity parameter from the preferred random effects model of child-only data, and the random effects model of adult and child data.

Outcome	Antiemetic regimens given with dexamethasone?	Child only data <i>Random effects model</i>	Child and adult data <i>Random effects model</i>
Complete response in the acute phase	YES	 *	
	NO	 *	
Complete response in the delayed phase	YES	 *	
	NO	 **	
Complete response in the overall phase	YES	 *	
	NO	 *	 ***

*Preferred model: random effects with an informative prior for the between-study heterogeneity parameter

**Preferred model: random effects

***Preferred model: fixed effects

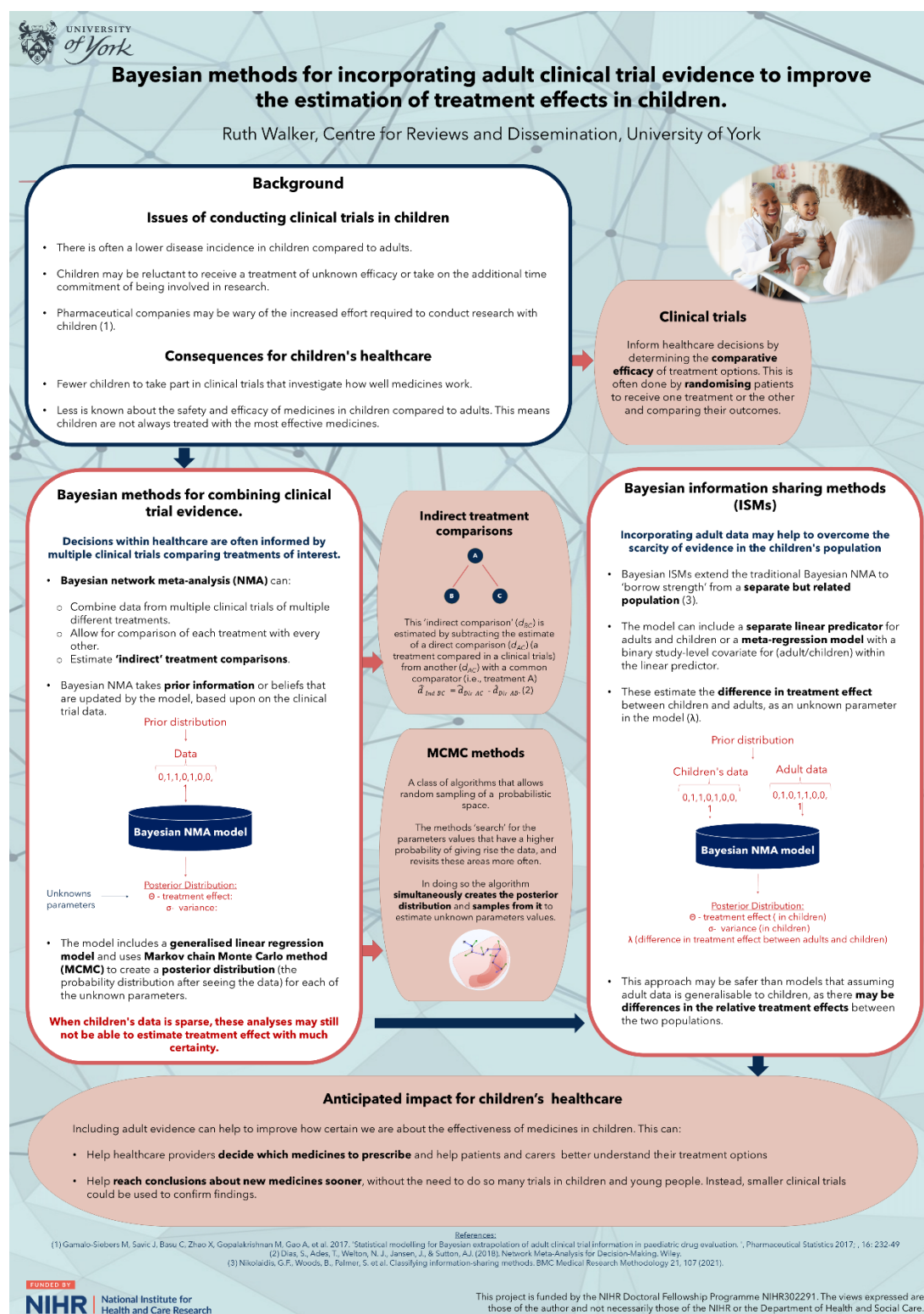


Figure 4-1 This poster was presented at the N8 Computationally Intensive Research national conference in Leeds in 2022. Summarising the rationale for using Bayesian information sharing models in the context of child health research.

Can Adult Evidence Improve Our Understanding Of Treatment Effect In Children?

Ruth Walker, Bob Philipps, Sofia Dias

University of York



Background

Data on treatment effect in children is often lacking compared to that in adults, in part, due to a lower disease incidence in children.

Incorporating adult evidence into evidence syntheses that inform child health policy, may be useful, as it may improve our understanding of how treatments work in children. However, this approach may also be risky as children may respond differently to treatments compared to adults.



Research aims

This concept was explored using data from randomised control trials (RCTs) evaluating anti-sickness medications in patients receiving chemotherapy.

The main aim was to determine whether the inclusion of adult evidence could improve the precision of treatment effect estimates in children and/or change conclusions about which treatment are most effective.



Methods

Firstly, a Bayesian network meta-analysis (NMA) comparing anti-sickness medicines recommended for use in children, was conducted using data from child RCTs only. These analyses were conducted using BUGS software.



Adult evidence was then incorporated into these analyses. The NMA model was modified to simultaneously combine child and adult data, whilst estimating differences in relative treatment effect between the two populations.



Models assuming all studies estimate the same effect (fixed-effect), were compared to models assuming study effects are exchangeable or similar (random effects).



Outcomes of 'complete response' i.e. no vomiting or use of rescue medication, were assessed in the acute (0-24hrs post chemotherapy) and delayed (24hrs-5 days post chemotherapy) phase.



The ability of the analyses to improve our understanding of how well treatments work in children was assessed.



Results

Sixteen studies were included in the analyses, four (1118 patients) in children and twelve (8034 patients) in adults. In the NMA's of child data, the fixed effects models mainly were preferred. Differences in relative treatment effect between the two populations meant when incorporating adult evidence into the NMA of child data, random effects models were mainly preferred.

On average, children gained greater relative benefit from anti-sickness medicines compared to adults (when medicines were compared to the reference treatment ondansetron), as shown in the example below for complete response in the acute phase (other outcomes showed similar results).

Including adult evidence introduced (in most cases), additional uncertainty into the analyses, making estimates of treatment effect in children, less precise. Even for outcomes where precision was improved, our understanding of which anti-sickness medicines work in children receiving chemotherapy has not changed.

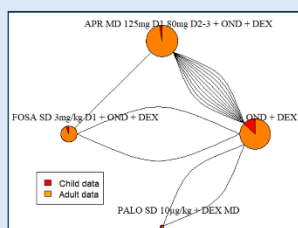


Figure 1. Network diagram for antiemetic regimens given with dexamethasone the outcome complete response in the acute phase. The circle size is proportional to the number of patients and the number of lines equals the number of clinical trials. All doses are indicative of dosing in children. (OND=ondansetron, APR=aprepitant, FOSA=fosaprepitant, PALO=palonosetron, DEX=dexamethasone, SD=single dose before chemotherapy, MD= multiple doses, both before and after chemotherapy).

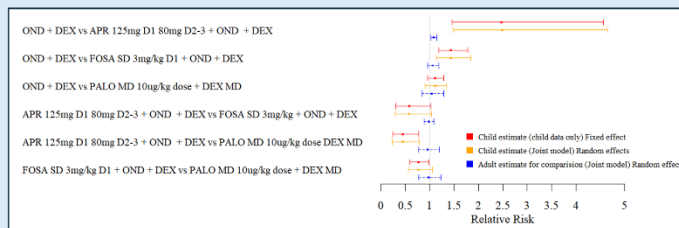


Figure 2. Forest plot: Relative risk (RR) (95% Credible Interval (CrI)) in children, estimated from child data only (red), and a joint model of child and adult data (blue). RR (95% CrI) in adults estimated from the joint model of child and adult data (blue) are shown for comparison. The outcome is complete response in the acute phase (0-24 hours after chemotherapy administration) (studies comparing antiemetic regimens given with dexamethasone). Values of above one favour the second named intervention. (OND= ondansetron, APR=aprepitant, FOSA=fosaprepitant, PALO=palonosetron, DEX=dexamethasone, SD=single dose before chemotherapy, MD= multiple doses, both before and after chemotherapy). N.B antiemetic regimens given with and without dexamethasone were analysed in separate networks due to differences in the emetogenicity of chemotherapy received by the underlying population.

Conclusion

Adult evidence should not be assumed generalisable to children, and methods of synthesising child and adult data should account for differences in treatment effect which may be present. For the inclusion of adult evidence to be beneficial, there may need to be sufficient similarities in treatment effect between the child and adult populations. It may therefore be advisable to compare relative treatment effects in primary studies, between child and adult populations, before deciding whether to include adult evidence in syntheses of child data.



This project has been conducted by Ruth Walker at the University of York and is funded by the NIHR Doctoral Fellowship Programme NIHR302291. The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

Figure 4-2 Study results presented at the Children's Cancer and Leukaemia Group (CCLG): The Children and Young People's Cancer Association conference in Birmingham 2024

5 Chapter Five Appendix

5.1 Multivariate Meta-analysis

5.1.1 R code for within-study correlations

This code has been informed by that provided in Riley et al. 2015 (Riley et al., 2015), as well as the material provided during the “**Statistical Methods for Meta-analysis of IPD**” course, delivered by Joie Ensor (lead), Richard Riley, Miriam Hattle & Katie Scandrett (University of Birmingham).

```
library(systemfit)
library(boot)
library(survival)
library(glmnet)
library(tidyverse)
library(broom)
library(fixest)
library(sandwich)
library(pscl)
library(MASS)
library(ordinal)

# Obtain the treatment effect (log Relative Risk) and its standard error for both outcomes (binary data)
summary(Outcome <- glm(outcome ~ factor(Arm), binomial(link="log"), data = name_of_study_IPD_file))#

# OR using a Poisson regression model, with robust errors was instead (Derived from Zou 2004 (Zou,
2004)).

summary(Outcome <- feglm(outcome ~ factor(Arm), family = poisson(link="log"), vcov = sandwich, data =
name_of_study_IPD_file))

# Obtain the treatment effect (log Rate Ratio) and its standard error for both outcomes (count data)

summary(Outcome <- glm.nb(outcome ~ factor(Arm), data = name_of_study_IPD_file))

# Obtain the treatment effect (log Odds Ratio) and its standard error for both outcomes (ordinal data)

model_polr <- polr(factor(outcome) ~ factor(Arm), data = name_of_study_IPD_file, Hess = TRUE)
```

replace 'outcome' with the name of the outcome variable in the raw IPD file, and 'Arm' with the name of the treatment variable.

Obtain the within-study correlation between the treatment effects for pairs of outcomes using the following function:

```
BOOTSTRAP <- function(data, indices){  
  name_of_study_IPD_file= data[indices, ]  
  
  reg1 <- glm(outcome_one ~ factor(Arm),family = poisson(link="log"),data = trial_1)  
  treat.coef.1 <- coef(summary(reg1))["factor(Arm)1", "Estimate"]  
  
  reg2 <- glm(outcome_two ~ factor(Arm),family = poisson(link="log"),data = trial_1)  
  treat.coef.2 <- coef(summary(reg2))["factor(Arm)1", "Estimate"]  
  
  regress.coeffs <- c(treat.coef.1, treat.coef.2)  
  
  return(regress.coeffs)  
}
```

Now produce the bootstrap sample using the above function

Set the seed for reproducibility.

```
set.seed(12345)
```

```
results <- boot(data = name_of_IPD_file, statistic = BOOTSTRAP, R = 2000)
```

(takes about 30 seconds)

```
print(results)
```

Calculate the correlation between the treatment effect estimates

```
corr1 <- cor(results$t[,1], results$t[,2], method = "pearson")
```

```
corr1
```

Repeat for different outcome pairs and use data to populate the table exemplified in Table 5-1 to Table 5-6.

5.1.2 Data used for the multivariate meta-analysis (main analysis)

Table 5-1 – Data for outcome 1) complete response, 2) vomiting, and 3) nausea in the **acute phase**

Study	Y1	Y2	Y3	V11	V12	V13	V22	V23	V33	SE1	SE2	SE3	Cor12	Cor13	Cor23
Bakshi	1.4178	-0.53031	0	0.198381	-0.02015	0.00E+00	0.021521	0.00E+00	1.00E+04	0.4454	0.146702	0.00E+00	-0.30832	0	0
Radhakrishnan	0.368945	-1.1578	-0.835	0.010153	-0.02399	-0.01445	0.121034	0.047291	0.213536	0.100762	0.3479	0.4621	-0.68431	-0.31036	0.294161
Kang	0.24517	-0.47755	0	0.009475	-0.0132	0.00E+00	0.023768	0.00E+00	1.00E+04	0.09734	0.15417	0.00E+00	-0.87986	0	0
Sharma	0.7088	-0.55659	0	0.077395	-0.04931	0.00E+00	0.049731	0.00E+00	1.00E+04	0.2782	0.223004	0.00E+00	-0.79482	0	0
Merck (unpublished)	0.048974	0	0	0.010525	0.00E+00	0.00E+00	1.00E+04	0.00E+00	1.00E+04	0.102591	0.00E+00	0.00E+00	0	0	0
Gore	0.441833	-0.38485	0	0.093952	-0.06452	0.00E+00	0.089832	0.00E+00	1.00E+04	0.306516	0.315653	0.00E+00	-0.66683	0	0

Y- Log relative risk, V-covariance, SE- standard error, Cor- within study correlation.

Table 5-2– Data for outcome 1) complete response, 2) vomiting, and 3) nausea in the **delayed phase**

Study	Y1	Y2	Y3	V11	V12	V13	V22	V23	V33	SE1	SE2	SE3	Cor12	Cor13	Cor23
Bakshi	0.1174	-0.05551	0	0.092477	-0.041958	0.00E+00	0.02038	0.00E+00	1.00E+04	0.3041	0.14276	0.00E+00	-0.96647	0	0
Radhakrishnan	0.433484	-0.8452	-0.393	0.014894	-0.023588	-0.01495	0.077173	0.020791	0.183784	0.12204	0.2778	0.4287	-0.69574	-0.28576	0.17458
Kang	0.667	-0.47587	0	0.025376	-0.01324	0.00E+00	0.010718	0.00E+00	1.00E+04	0.1593	0.10353	0.00E+00	-0.80258	0	0
Sharma	0.4391	-0.38285	0	0.06285	-0.0495	0.00E+00	0.049543	0.00E+00	1.00E+04	0.2507	0.222583	0.00E+00	-0.88712	0	0
Merck (unpublished)	-0.12717	0	0	0.028696	0.00E+00	0.00E+00	1.00E+04	0.00E+00	1.00E+04	0.1694	0.00E+00	0.00E+00	0	0	0
Gore	0.384674	-1.95606	0	0.027897	-0.09671	0.00E+00	0.745979	0.00E+00	1.00E+04	0.167023	0.863701	0.00E+00	-0.67038	0	0

Table 5-3 Data for outcome 1) complete response, 2) vomiting, and 3) nausea in the **overall phase**

Study	Y1	Y2	Y3	V11	V12	V13	V22	V23	V33	SE1	SE2	SE3	Cor12	Cor13	Cor23
Bakshi	0.8608	-0.15082	0	0.297679	-0.0158262	0.00E+00	0.008026	0.00E+00	1.00E+04	0.5456	0.089589	0.00E+00	-0.32378	0	0
Radhakrishnan	0.528961	-0.7056	-0.336	0.022414	-0.0159472	-0.037026	0.049863	0.02518	0.117649	0.149714	0.2233	0.343	-0.72103	-0.47702	0.328757
Kang	0.6964	-0.38948	0	0.036481	-0.013378	0.00E+00	0.007574	0.00E+00	1.00E+04	0.191	0.08703	0.00E+00	-0.80481	0	0
Sharma	0.8499	-0.47271	0	0.112292	-0.048935	0.00E+00	0.035388	0.00E+00	1.00E+04	0.3351	0.188117	0.00E+00	-0.77628	0	0
Merck (unpublished)	-0.1271	0	0	0.028696	0.00E+00	0.00E+00	1.00E+04	0.00E+00	1.00E+04	0.1694	0.00E+00	0.00E+00	0.00E+00	0	0
Gore	0.279314	-1.75539	0	0.023219	0.00E+00	0.00E+00	1.00E+04	0.00E+00	1.00E+04	0.152378	0.00E+00	0.00E+00	-0.52518	0	0

Y- Log relative risk, V-covariance, SE- standard error, Cor- within study correlation

5.1.3 Data used for multivariate meta-analysis (additional analysis with severity outcomes)

Table 5-4 Data for outcome 1) complete response, 2) nausea severity, and 3) vomiting severity in the **acute phase**

Study	Y1	Y2	Y3	V11	V12	V13	V22	V23	V33	SE1	SE2	SE3	Cor12	Cor13	Cor23
Bakshi	1.418	0.000	-0.696	0.198	0.000	-0.026	10000	0.000	0.031	0.445	0.000	0.176	0.000	-0.330	0.000
Venkat	0.369	-0.219	-1.684	0.010	-0.005	-0.031	0.01	0.018	0.266	0.101	0.101	0.515	-0.489	-0.591	0.346
Kang	0.245	0.000	-0.713	0.009	0.000	-0.015	10000	0.000	0.054	0.097	0.000	0.233	0.000	-0.645	0.000
Sharma	0.709	0.000	-0.475	0.077	0.000	-0.055	10000	0.000	0.068	0.278	0.000	0.261	0.000	-0.764	0.000
Merck	0.049	0.000	0.000	0.011	0.000	0.000	10000	0.000	10000	0.103	0.000	0.000	0.000	0.000	0.000
Gore	0.442	0.000	0.000	0.094	0.000	0.000	10000	0.000	10000	0.307	0.000	0.000	-0.489	-0.592	0.474

Table 5-5 Data for outcome 1) complete response, 2) nausea severity, and 3) vomiting severity in the **delayed phase**

Study	Y1	Y2	Y3	V11	V12	V13	V22	V23	V33	SE1	SE2	SE3	Cor12	Cor13	Cor23
Bakshi	0.117	0.000	-0.203	0.092	0.000	-0.049	10000	0.000	0.035	0.304	0.000	0.187	0.000	-0.859	0.000
Venket	0.433	-0.168	-1.662	0.015	-0.006	-0.028	0.024	0.020	0.235	0.122	0.154	0.485	-0.312	-0.470	0.263
Kang	0.667	0.000	-0.503	0.025	0.000	-0.014	10000	0.000	0.039	0.159	0.000	0.198	0.000	-0.432	0.000
Sharma	0.439	0.000	-0.465	0.063	0.000	-0.064	10000	0.000	0.092	0.251	0.000	0.304	0.000	-0.842	0.000
Merck	-0.127	0.000	0.000	0.029	0.000	0.000	10000	0.000	10000	0.169	0.000	0.000	0.000	0.000	0.000
Gore	0.385	0.000	0.000	0.028	0.000	0.000	10000	0.000	10000	0.167	0.000	0.000	0.000	-0.651	0.000

Table 5-6 Data for outcome 1) complete response, 2) nausea severity, and 3) vomiting severity in the **overall phase**

Study	Y1	Y2	Y3	V11	V12	V13	V22	V23	V33	SE1	SE2	SE3	Cor12	Cor13	Cor23
Bakshi	0.861	0.000	-0.243	0.298	0.000	-0.024	10000	0.000	0.031	0.546	0.000	0.176	0.000	-0.255	0.000
Venket	0.529	-0.478	-1.668	0.022	-0.015	-0.031	0.044	0.028	0.170	0.150	0.210	0.413	-0.482	-0.505	0.321
Kang	0.696	0.000	-0.552	0.036	0.000	-0.015	10000	0.000	0.033	0.191	0.000	0.183	0.000	-0.423	0.000
Sharma	0.850	0.000	-0.452	0.112	0.000	0.059	10000	0.000	0.058	0.335	0.000	0.242	0.000	0.726	0.000
Merck	-0.127	0.000	0.000	0.029	0.000	0.000	10000	0.000	10000	0.169	0.000	0.000	0.000	0.000	0.000
Gore	0.279	0.000	0.000	0.023	0.000	0.000	10000	0.000	10000	0.152	0.000	0.000	0.000	-0.114	0.000

5.1.4 R code for multivariate meta-analysis

Univariate meta-analysis using REML for comparison with multivariate results.

```
univ.y1.reml <- metagen(Y1, SE1, Study, data = MVMA,  
                        sm = "logRR", comb.random = FALSE )  
univ.y1.reml # View result
```

```
univ.y2.reml <- metagen(Y2, SE2, Study, data = MVMA,  
                        sm = "logRR", comb.random = FALSE )  
univ.y2.reml # View result
```

```
univ.y3.reml <- metagen(Y3, SE3, Study, data = MVMA,  
                        sm = "logRR", comb.random = FALSE )  
univ.y3.reml # View result
```

Producing the variance-covariance matrix for the MVMA

```
y <- as.matrix(MVMA[2:4])  
y # View result  
# and columns relating to the variances and covariances  
S <- as.matrix(MVMA[5:10])  
S # View result
```

Fitting the multivariate model using mvmeta

```
model.three.outcomes <- mvmeta(y, S, method="reml") # method = "fixed" for fixed effects model.  
print(summary(model.three.outcomes), digits=3)
```

Producing Odds Ratios and Confidence intervals

```
(ci <- confint(model.three.outcomes))  
# CIs assuming normality  
confint.default(model.three.outcomes)  
## odds ratios  
exp(coef(model.three.outcomes))  
## RR and CI  
exp(cbind(RR = coef(model.three.outcomes), ci))
```

5.1.5 Individual-level correlations

Table 5-7 reports the strength of the relationship between the binary variables of nausea, vomiting and complete response at the individual level. The negative correlation between nausea (a negative outcome) and complete response (a positive outcome) is greater than that between nausea and vomiting in both Radhakrishnan et al. 2019 and Naik et al. 2020. In Naik et al. 2020 stronger correlation is seen between nausea and vomiting outcomes.

Table 5-7 Correlations (phi coefficient estimates) between pairs of binary outcomes at the individual level estimated from Radhakrishnan et al. 2019 (Radhakrishnan et al., 2019) and Naik et al. 2020 (Naik et al., 2020).

	Nausea and complete response		Nausea and Vomiting	
Study	Radhakrishnan et al., 2019	Naik et al., 2020	Radhakrishnan et al., 2019	Naik et al., 2020
Acute phase	-0.615	-0.651	0.413	0.622
Delayed phase	-0.510	-0.647	0.175	0.628
Overall phase	-0.523	-0.723	0.237	0.697

Radhakrishnan et al. 2019: **Treatment comparison:** Fosaprepitant + ondansetron + dexamethasone vs ondansetron + dexamethasone.

Naik et al 2020: **Treatment comparison:** Olanzapine + aprepitant + ondansetron + dexamethasone vs aprepitant + ondansetron + dexamethasone.

As expected, in both studies, nausea and vomiting severity show a positive correlation (Figure 5-1).

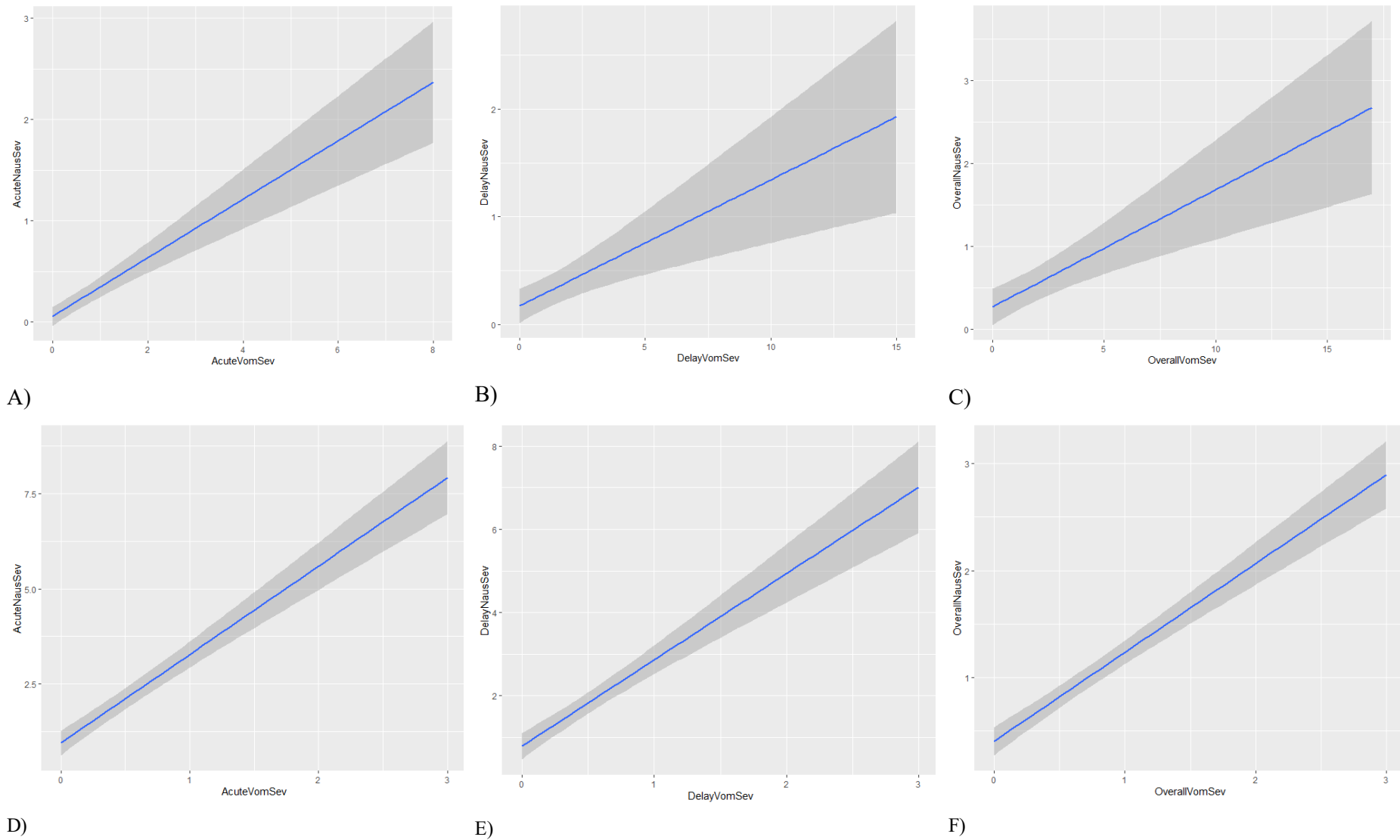


Figure 5-1 Relationship between pairs of continuous outcomes (nausea severity (Edmonton Symptom Assessment Scale (ESAS)) and vomiting severity (number of vomits) at the individual level estimated from Radhakrishnan et al. 2019 (Radhakrishnan et al., 2019) (panel A-C) and Naik et al. 2020 (Naik et al., 2020)(panel D-F).

5.1.6 Sensitivity analyses for main analyses

Table 5-8 Multivariate meta-analysis of outcomes, complete response, nausea and vomiting, **including IPD and aggregate data** and **excluding patients/ studies without dexamethasone** in the antiemetic regimen.

	Univariate analysis (Fixed effects) * RR (95%CI)	Confidence interval width	Multivariate analysis** (Fixed effects) RR (95%CI)	Confidence interval width	Multivariate analysis** (Random effects) RR (95%CI)	Confidence interval width	Between- study heterogeneity
Acute phase	0.433 (0.175 to 1.073)	0.898	0.550 (0.231 to 1.309)	1.078	0.51 (0.261 to 1.235)	0.974	0.001
Delayed phase	0.675 (0.291 to 1.564)	1.273	0.897 (0.397 to 2.029)	1.632	0.733 (0.319 to 1.687)	1.368	0.001
Overall phase	0.714 (0.365 to 1.399)	1.034	1.162 (0.678 to 1.994)	1.316	0.837(0.456 to 1.535)	1.079	0.004

Only those patients given dexamethasone were included in the analyses from the Kang et al 2015 and the Merck (unpublished) study, and no data from Sharma et al. 2020 were included.

*Including data on nausea only, the fixed effect model was used as the analyses were informed by one study. ** including data on complete response, vomiting and nausea. RR- relative risk

Table 5-9 Multivariate meta-analysis of outcomes, complete response, nausea and vomiting, including only IPD (**excluding aggregate data**) and **excluding patients/ studies without dexamethasone** in the antiemetic regimen.

	Univariate analysis (Fixed effects) * RR (95%CI)	Confidence interval width	Multivariate analysis** (Fixed effects) RR (95%CI)	Confidence interval width	Multivariate analysis** (Random effects) RR (95%CI)	Confidence interval width	Between- study heterogeneity
Acute phase	0.433 (0.175 to 1.073)	0.898	0.549 (0.231 to 1.307)	1.077	0.486 (0.203 to 1.163)	0.96	0.001
Delayed phase	0.675 (0.291 to 1.564)	1.273	0.869 (0.381 to 1.980)	1.599	0.713 (0.309 to 1.643)	1.334	0.001
Overall phase	0.714 (0.365 to 1.399)	1.034	0.952 (0.521 to 1.738)	1.217	0.832(0.441 to 1.570)	1.129	0.011

Only those patients given dexamethasone were included in the analyses from the Kang et al 2015 and the Merck (unpublished) study, and no data from Sharma et al. 2020 were included.

*Including data on nausea only, the fixed effect model was used as the analyses were informed by one study. ** including data on complete response, vomiting and nausea. RR- relative risk

Table 5-10 Multivariate meta-analysis of outcomes, complete response, nausea and vomiting, only IPD (**excluding aggregate data**) and **including patients/studies with or without dexamethasone** in the antiemetic regimen.

	Univariate analysis (Fixed effects) * RR (95%CI)	Confidence interval width	Multivariate analysis** (Fixed effects) RR (95%CI)	Confidence interval width	Multivariate analysis** (Random effects) RR (95%CI)	Confidence interval width	Between- study heterogeneity
Acute phase	0.433 (0.175 to 1.073)	0.898	0.581 (0.245 to 1.376)	1.131	0.550 (0.230 to 1.305)	1.075	0.001
Delayed phase	0.675 (0.291 to 1.564)	1.273	0.778 (0.344 to 1.764)	1.421	0.748 (0.325 to 1.721)	1.396	0
Overall phase	0.714 (0.365 to 1.399)	1.034	0.966 (0.561 to 1.663)	1.103	0.790 (0.415 to 1.504)	1.089	0.001

**Including data on nausea only, the fixed effect model was used as the analyses were informed by one study ** including data on complete response, vomiting and nausea. RR- relative risk*

5.2 Multivariate Network Meta-Analysis (MV-NMA)

5.2.1 Methods

A random effect multivariate NMA (methods derived from Achana et al. 2014 (Achana et al., 2014b)) was conducted in a Bayesian framework in OpenBUGS Version 3.2.3. The approach places a prior distribution on the within-study correlations, incorporating the mean within-study correlation for an outcome pair and a measure of uncertainty (Achana et al., 2014b) (in this case, the standard error). However, given the limited number of within-study correlation estimates available from the IPD, the uncertainty around the mean estimate was too large to allow for computation of the variance-covariance matrix. This is likely because the bounds of the prior distribution for the within-study correlation were too wide, resulting in a non-invertible/impossible matrix. Instead, an artificially small standard error was imputed (at 0.05, as this was as large as was possible to allow for the computation of the variance-covariance matrix). *An alternative approach was considered, which would assume that within-study correlation estimates were fixed for outcome pairs; however, this was thought to be implausible.*

IPD studies created a network of three treatments: (1) Ondansetron (with or without dexamethasone), (2) NK1 antagonists (aprepitant or fosaprepitant) + ondansetron (with or without dexamethasone), and (3) olanzapine + aprepitant + dexamethasone. As differences in relative treatment effect may exist between those receiving regimens with or without dexamethasone, analyses were conducted including only those patients who received dexamethasone and then compared with analyses including all patients (regardless of whether they received dexamethasone or not). If results were comparable, those analyses with all patients would make up the primary analysis.

The multivariate NMA allowed for the incorporation of aggregate data (AD) from studies for which no IPD is available (Achana et al., 2014b). This was possible provided the log treatment effect in each arm and the corresponding standard error for the outcome were available or calculable. AD from studies comparing those antiemetics present in the IPD network were incorporated into the main analyses. Sensitivity analyses excluding studies with AD only were conducted, and the results are reported in this appendix.

Incorporation of AD from clinical trials comparing regimens which were not present within this IPD network is also possible and was considered. However, this would require the assumption that their within-study correlations were the same or very similar to (the mean) for other treatment comparisons and given this would likely incorporate additional uncertainty into the model, it was not deemed appropriate.

As the code provided in Achana et al. 2014 (Achana et al., 2014a) is for a random-effect multivariate NMA, the results were compared to a random-effect univariate analysis, which, due to the lack of studies informing the analysis, included a prior distribution for I^2 to inform the between-study heterogeneity parameter (Rhodes et al., 2016) (see section 5.1.1 ‘R code and data for the univariate NMA’ section for further details). Results were compared informally to determine whether an improvement in precision was made with the multivariate analysis. The univariate analysis (as with the multivariate analysis) included studies reporting nausea in their IPD or AD in the acute, delayed and/or overall phase.

5.2.2 R code for within-study correlations/ arm level data

The same code is used to derive the within-study correlation estimates as is used in the MVMA (see section 5.1.1 ‘R code for within-study correlation’). However, to obtain the treatment effects and standard errors in each arm (as required for the MV-NMA code), modify the glm to include “-1” after “factor(Arm)”.

Obtain the treatment effect (log RR) and its standard error for both outcomes (in each treatment arm)

```
Outcome1 <- glm(outcome ~ factor(Arm)-1, binomial(link="log"), data = name_of_study_IPD_file)#
```

replace ‘outcome’ with the name of the outcome variable in the raw IPD file, and ‘Arm’ with the name of the treatment variable.

5.2.3 Data used for the MV-NMA

To run the MV-NMA using the code provided in Achana et al. 2014 (Achana et al., 2014b) in BUGS software, three data files are required. The first provides a list of data on the number of data point, studies and outcomes, along with the mean within-study correlation for outcome pairs, and the standard error (detailed below) and the number of arms in each study.

```
list(
```

```
  N1= X,      #no of datapoints
```

```
  N2= X,      # no of studies x no of outcomes (5 x 3=15)
```

```
  ns= X,      # no of studies
```

```
  no= X,      #no of outcomes
```

```
  nt.total =c(X, X, X),      # no of interventions for outcomes 1, 2 and 3
```

```
  mn.rhoW =c( X, X, X),      # mean of within-study correlations from IPD for each outcome
```

```
  # se.rhoW = c(0.05 , 0.05, 0.05), # se of within-study correlations from IPD for each outcome
```

```
  #se.rhoW needs to be small for it to run with the uniform prior distribution.
```

NA = c(2,2,2,2,2) # no. of arms in each study (five studies, each with two arms)

))

END

The within-study correlation estimates derived from the IPD (Table 5-11) and were used to inform the prior distribution in the main analysis for the MV-NMA (i.e. the mn.rhoW and se.rhoW values in data file one). However, as detailed in the methods section of the main thesis chapter, the standard error used to inform the variance-covariance matrix for the informative prior distribution was made artificially small (imputed as 0.05 for all outcome pairs). The data are derived from all patients (i.e. both those receiving and not receiving dexamethasone). The unpublished Merck study could not provide information on between-study correlation as nausea was not reported, and for the outcome of vomiting, there were an insufficient number of events to estimate a relative effect in the acute, delayed and overall phase.

Table 5-11. Within-study correlation estimates between outcome pairs in the acute, delayed and overall phase, derived from the IPD of clinical trials in children.

<u>Acute phase</u>			
	R12 (Complete response, vomit)	R13 (Complete response, nausea)	R23 (Vomit, Nausea)
Bakshi et al.	-0.3083237	x	x
Naik et al.	-0.8519577	-0.5771314	0.6317941
Kang et al.	-0.87986	x	x
Radhakrishnan et al	-0.6843064	-0.3103594	0.2941614
Sharma et al.	-0.7948215	x	x
Mean (mn.rhoW)	-0.70385386	-0.4437454	0.46297775
Standard error (se.rhoW)	0.104406473	0.133386	0.16881635
<u>Delayed phase</u>			
	R12 (Complete response, vomit)	R13 (Complete response, nausea)	R23 (Vomit, Nausea)
Bakshi et al.	-0.9664697	x	x
Naik et al.	-0.8312205	-0.5039884	0.5394396
Kang et al.	-0.8025795	x	x
Radhakrishnan et al	-0.6957413	-0.2857564	0.1745803
Sharma et al.	-0.88712	x	x
Mean (mn.rhoW)	-0.8366262	-0.3948724	0.35700995
Standard error (se.rhoW)	0.044969941	0.109116	0.18242965
<u>Overall phase</u>			
	R12 (Complete response, vomit)	R13 (Complete response, nausea)	R23 (Vomit, Nausea)
Bakshi et al.	-0.3237785	x	x
Naik et al.	-0.8519577	-0.6070872	0.6642133
Kang et al.	-0.804805	x	x
Radhakrishnan et al	-0.7210332	-0.4770154	0.3287573
Sharma et al.	-0.77628	x	x
Mean (mn.rhoW)	-0.69557088	-0.5420513	0.4964853
Standard error (se.rhoW)	0.095336456	0.0650359	0.167728

Data file two provides information on the treatment effect by arm, and the data input for the outcomes of complete response in the acute, delayed and overall phase are given below. Data from IPD are in black text, whilst data from aggregate data are in blue text. Here, studies are given a unique ID number, which needs to be in numerical form studyid[], arm[] is the arm number within the trial (not the numbering within the network), y[] is the treatment effect within that particular arm and se[] is the associated standard error (Table 5-12, Table 5-13, Table 5-14).

Table 5-12 Treatment effect by arm, and the data input for the outcomes of complete response in the **acute phase**

Study	studyid[]	study[]	arm[]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
Bakshi	11	1	1	-2.1518	-0.123614	NA	0.4204	0.055317	NA
Bakshi	11	1	2	-0.734	-0.653926	NA	0.1472	0.135873	NA
Naik	22	2	1	-0.53408	-0.9249	-0.72824	0.07801	0.1145	0.09611
Naik	22	2	2	-0.24512	-1.5669	-1.34373	0.04915	0.1816	0.15696
Radhakrishnan	33	3	1	-0.514899	-1.0394	-1.7677	0.090626	0.1493	0.2434
Radhakrishnan	33	3	2	-0.145954	-2.1972	-2.6027	0.044046	0.3143	0.3928
Kang	44	4	1	-0.65395	-0.76214	NA	0.07845	0.8729	NA
Kang	44	4	2	-0.40876	-1.2396	NA	0.05763	0.12708	NA
Gore	55	5	1	-0.944461	-0.587787	NA	0.119898	0.1216837	NA
Gore	55	5	2	-0.498991	-1.029619	NA	0.09617347	0.09515306	NA
Sharma	66	6	1	-1.2287	-0.346276	NA	0.2428	0.100462	NA
Sharma	66	6	2	-0.5199	-0.902868	NA	0.1357	0.199093	NA
Merck	77	7	1	-0.1941	NA	NA	0.0793	NA	NA
Merck	77	7	2	0.1451	NA	NA	0.0649	NA	NA

Table 5-13 Treatment effect by arm, and the data input for the outcomes of complete response in the **delayed phase**

Study	studyid[]	study[]	arm[]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
				(log Risk)	(log Risk)	(log Risk)			
Bakshi	11	1	1	-1.1963	-0.360003	NA	0.2317	0.100387	NA
Bakshi	11	1	2	-1.0788	-0.415515	NA	0.197	0.101504	NA
Naik	22	2	1	-0.76461	-0.6593	-0.64272	0.09949	0.0897	0.08816
Naik	22	2	2	-0.30228	-1.3437	-1.34373	0.0554	0.157	0.15696
Radhakrishnan	33	3	1	-0.66905	-0.9102	-1.9218	0.10777	0.1346	0.2667
Radhakrishnan	33	3	2	-0.23556	-1.7554	-2.315	0.057265	0.2431	0.3356
Kang	44	4	1	-1.34707	-0.3285	NA	0.13775	0.05092	NA
Kang	44	4	2	-0.68001	-0.80437	NA	0.08005	0.09015	NA
Gore	55	5	1	-2.89037	-2.890372	NA	0.06938776	0.06938776	NA
Gore	55	5	2	-1.02962	-0.934309	NA	0.09515306	0.09668367	NA
Sharma	66	6	1	-1.0055	-0.455476	NA	0.2056	0.118622	NA
Sharma	66	6	2	-0.5199	-0.902868	NA	0.1357	0.199093	NA
Merck	77	7	1	-0.348	NA	NA	0.111	NA	NA
Merck	77	7	2	0.475	NA	NA	0.128	NA	NA

Table 5-14 Treatment effect by arm, and the data input for the outcomes of complete response in the **overall phase**

Study	studyid[]	study[]	arm[]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
				(log RR)	(log RR)	(log RR)			
Bakshi	11	1	1	-2.3749	-0.097638	NA	0.4762	0.048839	NA
Bakshi	11	1	2	-1.5141	-0.248461	NA	0.2663	0.075107	NA
Naik	22	2	1	-0.9694	-0.50509	-0.46313	0.11876	0.07527	0.07126
Naik	22	2	2	-0.45447	-1.03136	-1.03136	0.07073	0.12527	0.12527
Radhakrishnan	33	3	1	-0.880359	-0.6931	-1.5735	0.13121	0.1104	0.2159
Radhakrishnan	33	3	2	-0.351398	-1.3987	-1.9095	0.072098	0.194	0.2664
Kang	44	4	1	-1.60944	-0.23995	NA	0.1633	0.04252	NA
Kang	44	4	2	-0.91301	-0.62943	NA	0.9907	0.07594	NA
Gore	55	5	1	-2.89037	-2.89037	-1.79175	0.0693877	0.0693877	0.101020
Gore	55	5	2	-1.25276	-1.13498	-0.84729	0.0905612	0.0931122	0.1
Sharma	66	6	1	-1.5163	-0.247836	NA	0.2945	0.082824	NA
Sharma	66	6	2	-0.6665	-0.720546	NA	0.16	0.168903	NA
Merck	77	7	1	-0.348	NA	NA	0.11	NA	NA
Merck	77	7	2	-0.475	NA	NA	0.128	NA	NA

Finally, the third data file provides information on the treatment numbering for each arm within the network, the presence of each outcome within the clinical trial and the number of arms in each clinical trial. Again, data from IPD are in black text, whilst that from aggregate data are in blue text. Here, there is one row per outcome, the studyid1[] allows data files two and three to be linked, t[,] indicates the treatment numbering in the network, o[] equals the outcome number out[] if this outcome is reported in the clinical trial, otherwise it equals 0, and na[] is the number of arms (Table 5-15, Table 5-16, Table 5-17).

Table 5-15 Treatment numbering for each arm within the network, the presence of each outcome within the clinical trial and the number of arms in each clinical trial for **acute phase** outcomes.

Study	studyid1[]	s[]	t[,1]	t[,2]	t[,3]	o[]	out[]	na[]
Bakshi	11	1	1	2	NA	1	1	2
Bakshi	11	1	1	2	NA	2	2	2
Bakshi	11	1	1	2	NA	0	3	2
Naik	22	2	2	3	NA	1	1	2
Naik	22	2	2	3	NA	2	2	2
Naik	22	2	2	3	NA	3	3	2
Radhakrishnan	33	3	1	2	NA	1	1	2
Radhakrishnan	33	3	1	2	NA	2	2	2
Radhakrishnan	33	3	1	2	NA	3	3	2
Kang	44	4	1	2	NA	1	1	2
Kang	44	4	1	2	NA	2	2	2
Kang	44	4	1	2	NA	0	3	2
Gore	55	5	1	2	NA	1	1	2
Gore	55	5	1	2	NA	2	2	2
Gore	55	5	1	2	NA	0	3	2
Sharma	66	6	1	2	NA	1	1	2
Sharma	66	6	1	2	NA	2	2	2
Sharma	66	6	1	2	NA	0	3	2
Merck	77	7	1	2	NA	1	1	2
Merck	77	7	1	2	NA	0	2	2
Merck	77	7	1	2	NA	0	3	2

Table 5-16 Treatment numbering for each arm within the network, the presence of each outcome within the clinical trial and the number of arms in each clinical trial for **delayed phase** outcomes.

Study	studyid1[]	s[]	t[,1]	t[,2]	t[,3]	o[]	out[]	na[]
Bakshi	11	1	1	2	NA	1	1	2
Bakshi	11	1	1	2	NA	2	2	2
Bakshi	11	1	1	2	NA	0	3	2
Naik	22	2	2	3	NA	1	1	2
Naik	22	2	2	3	NA	2	2	2
Naik	22	2	2	3	NA	3	3	2
Radhakrishnan	33	3	1	2	NA	1	1	2
Radhakrishnan	33	3	1	2	NA	2	2	2
Radhakrishnan	33	3	1	2	NA	3	3	2
Kang	44	4	1	2	NA	1	1	2
Kang	44	4	1	2	NA	2	2	2
Kang	44	4	1	2	NA	0	3	2
Gore	55	5	1	2	NA	1	1	2
Gore	55	5	1	2	NA	2	2	2
Gore	55	5	1	2	NA	0	3	2
Sharma	66	6	1	2	NA	1	1	2
Sharma	66	6	1	2	NA	2	2	2
Sharma	66	6	1	2	NA	0	3	2
Merck	77	7	1	2	NA	1	1	2
Merck	77	7	1	2	NA	0	2	2
Merck	77	7	1	2	NA	0	3	2

Table 5-17 Treatment numbering for each arm within the network, the presence of each outcome within the clinical trial and the number of arms in each clinical trial for **overall phase** outcomes.

studyid1[]	studyid1[]	s[]	t[,1]	t[,2]	t[,3]	o[]	out[]	na[]
Bakshi	11	1	1	2	NA	1	1	2
Bakshi	11	1	1	2	NA	2	2	2
Bakshi	11	1	1	2	NA	0	3	2
Naik	22	2	2	3	NA	1	1	2
Naik	22	2	2	3	NA	2	2	2
Naik	22	2	2	3	NA	3	3	2
Radhakrishnan	33	3	1	2	NA	1	1	2
Radhakrishnan	33	3	1	2	NA	2	2	2
Radhakrishnan	33	3	1	2	NA	3	3	2
Kang	44	4	1	2	NA	1	1	2
Kang	44	4	1	2	NA	2	2	2
Kang	44	4	1	2	NA	0	3	2
Gore	55	5	1	2	NA	1	1	2
Gore	55	5	1	2	NA	2	2	2
Gore	55	5	1	2	NA	3	3	2
Sharma	66	6	1	2	NA	1	1	2
Sharma	66	6	1	2	NA	2	2	2
Sharma	66	6	1	2	NA	0	3	2
Merck	77	7	1	2	NA	1	1	2
Merck	77	7	1	2	NA	0	2	2
Merck	77	7	1	2	NA	0	3	2

5.2.4 R code for MV-NMA

This MV-NMA model code is taken from Achana et al. 2014 (Achana F, 2014) and applied in OpenBuGs Version 3.2.3.

```
model{

  # i = data point (one for each arm of each study),

  # arm = study arm

  # s = study

  # m = outcome


#Likelihood for arm level data

#=====

for(i in 1:N1){

  tmp1[i] <- studyid[i]

  y[i,1:3] ~ dnmnorm(mean.y[study[i],arm[i],1:3],omega[i,,])      # multivariate likelihood

  omega[i,1:3,1:3] <- inverse(cov.mat[i,,])      # within-study precision matrix

  #define elements of within-study covariance matrix

  cov.mat[i,1,1] <- pow(se[i,1],2)

  cov.mat[i,2,2] <- pow(se[i,2],2)

  cov.mat[i,3,3] <- pow(se[i,3],2)

  cov.mat[i,1,2] <- se[i,1]*se[i,2]*cor[i,1]

  cov.mat[i,1,3] <- se[i,1]*se[i,3]*cor[i,2]

  cov.mat[i,2,3] <- se[i,2]*se[i,3]*cor[i,3]

  cov.mat[i,2,1] <- cov.mat[i,1,2]

  cov.mat[i,3,1] <- cov.mat[i,1,3]

  cov.mat[i,3,2] <- cov.mat[i,2,3]


  for(m in 1:no){

    se[i,m] ~ dnorm(0, prec.se[m])T      # input missing standard errors

# in OpenBUGS truncation is indexed with T( , ) not I

    unif.a[i,m] <- mn.rhoW[m] - (sqrt(12)*se.rhoW[m]/2)      # parameter a of uniform distribution

    unif.b[i,m] <- mn.rhoW[m] +(sqrt(12)*se.rhoW[m]/2)      # parameter b of uniform distribution

    cor[i,m] ~ dunif(unif.a[i,m], unif.b[i,m]) # within-study correlation model

  }

}
```

```

}
for(j in 1:ns){
  for(k in 1:NA[j]) {
    for(m in 1:no){
      mean.y[j,k,m] <- mu[j,m] + delta[j,k,m]      # define study-specific treatment effects
    }
  }
}

```

#Random effects between-study model

```

#=====

```

```

for(j in 1:ns) {
  for(m in 1:no) {
    delta[j,1,m] <-0      # delta in control arm to zero for all outcomes
    w[j,1,m] <-0          # multi-arm adjustment in control group set to zero
  }

  for(k in 2:NA[j]){
    delta[j,k,1:no] ~ dmnorm(md[j,k,1:no],precBK[j,k,1:no,1:no])  #random effects model

    for(m in 1:no){
      for(mm in 1:no) {
        precBK[j,k,m,mm] <- prec[m,mm]*2*(k-1)/k      # between-study precision matrix
      }
    }
  }
}

```

#Consistency relations between basic parameters

```

#=====

```

```

for(i in 1:N2) {
  tmp2[i] <- studyid1[i]      # temp variable to identify study id, not used

  for(k in 2:na[i]) {
    md[s[i],k,out[i]] <- (d[out[i],t[i,k]] - d[out[i],t[i,1]])*equals(o[i],out[i]) + sw[s[i],k,out[i]]
    w[s[i],k,out[i]] <- (delta[s[i],k,out[i]] - (d[out[i],t[i,k]] - d[out[i],t[i,1]]))*equals(o[i],out[i])
  }
}

```

```

      sw[s[i],k,out[i]] <- sum(w[s[i],1:k-1,out[i]])/(k-1)
    }
  }

```

```

#Constraints

```

```

# Effect in usual care arm is set to zero

```

```

d[1,1] <- 0

```

```

d[2,1] <- 0

```

```

d[3,1] <- 0

```

```

#Prior distributions and parameters to estimate

```

```

prec[1:no,1:no] <- inverse(sigma[,])

```

```

sd.se~ dunif(0, 2)

```

```

for(m in 1:no) {

```

```

  prec.se[m] <- pow(sd.se,-2)

```

```

  sigma[m,m] <- pow(sd[m],2)

```

```

  sd[m] ~ dunif(0, 2)

```

```

  for(j in 1:ns){

```

```

    mu[j, m] ~ dnorm(0,0.001)

```

```

  }

```

```

  for(k in 2: nt.total[m]){

```

```

    or[m,k] <- exp(d[m,k])

```

```

    d[m,k] ~ dnorm(0,0.001)

```

```

  }

```

```

}

```

```

# consistency equations:

```

```

Outcome1_23<- d[1,3] - d[1,2]

```

```

RR1_23 <- exp(Outcome1_23)

```

```

Outcome2_23 <- d[2,3] - d[2,2]

```

```

RR2_23 <- exp(Outcome2_23)

```

```

Outcome3_23 <- d[3,3] - d[3,2]
RR3_23 <- exp(Outcome3_23)

#spherical parameterization (Wei and Higgins 2013)
pi <- 3.1415
for(i in 1:2) {
  for(j in (i+1):no) {
    sigma[i,j] <- rho[i,j]*sd[i]*sd[j]
    sigma[j,i] <- sigma[i,j]
    g[j,i] <- 0
    a[i,j] ~ dunif(0, pi)
    rho[i,j] <- inprod(g[,i], g[,j])
  }
}

g[1,1] <- 1
g[1,2] <- cos(a[1,2])
g[2,2] <- sin(a[1,2])
g[1,3] <- cos(a[1,3])
g[2,3] <- sin(a[1,3])*cos(a[2,3])
g[3,3] <- sin(a[1,3])*sin(a[2,3])
}

```

5.2.5 R code and data for the univariate NMA used for comparison

This is a random effects model for multi-arm trials with a binomial likelihood for log-relative risks applied in OpenBuGs Version 3.2.3. It includes an informative prior distribution for I^2 to inform the between-study heterogeneity parameter. This informative prior was derived from work conducted by Rhodes et al. 2016 (Rhodes et al., 2016) who re-analysed meta-analyses with binary outcomes from the Cochrane Database of Systematic Reviews to obtain predictive distributions for inconsistency, measured by the I^2 statistic, for different types of outcomes (all-cause mortality, semi-objective and subjective). A predictive distribution for semi-objective outcomes (from clinical trials with <50 participants) was used as an informative prior for I^2 within the Bayesian NMA comparing antiemetic regimens in children, for both complete and partial response outcomes. The between-study heterogeneity standard deviation was then calculated from the simulated values of I^2 .

```
model{                                     # *** PROGRAM STARTS

for(i in 1:ns){                           # LOOP THROUGH STUDIES

  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm

  delta[i,1] <- 0 # treatment effect is zero for control arm

  mu[i] <- log(p[i,1])

  p[i,1] ~ dunif(0,1) # vague priors for all trial baselines

# estimation of fixed 'typical' within-study variance

  v[i] <- 1/r[i,2] + 1/r[i,1] - 1/n[i,2] - 1/n[i,1]
  ws[i] <- 1/v[i]
  wsq[i] <- ws[i]*ws[i]

  for (k in 1:na[i]) {                   # LOOP THROUGH ARMS

    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

    # Deviance contribution

    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

  }

# summed residual deviance contribution for this trial

  resdev[i] <- sum(dev[i,1:na[i]])
```

```

for (k in 2:na[i]) {      # LOOP THROUGH ARMS

  log(p[i,k]) <- mu[i] + min(delta[i,k], -log(p[i,1]))

  # trial-specific LRR distributions

  delta[i,k] ~ dnorm(md[i,k],taud[i,k])

  # mean of LRR distributions (with multi-arm trial correction)

  md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]

  # precision of LRR distributions (with multi-arm trial correction)

  taud[i,k] <- tau *2*(k-1)/k

  # adjustment for multi-arm RCTs

  w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])

  # cumulative adjustment for multi-arm trials

  sw[i,k] <- sum(w[i,1:k-1])/(k-1)

}

}

totresdev <- sum(resdev[])      # Total Residual Deviance

d[1] <- 0      # treatment effect is zero for reference treatment

# vague priors for treatment effects

for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }


#sd ~ dunif(0,2)      # vague prior for between-trial SD

#tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)


W<-sum(ws[])

Wsqsq<- sum(wsqs[])

ssq<- (W*(ns-1))/((W*W)-Wsqsq) # fixed 'typical' within-study variance

prior.prec <- 1/ var*var

logit.isq ~ dt(location_mu, prior.prec, df) # empirical prior for I2


sd.sq <- (ssq*isq)/(1-isq) # sqq - 'typical' within-study variance

isq <- exp(logit.isq)/(1+exp(logit.isq))

tau <- 1/sd.sq

sd <- sqrt(sd.sq)


# pairwise RRs and LRRs for all possible pair-wise comparisons

for (c in 1:(nt-1)) {

```

```

for (k in (c+1):nt) {
  lnRR[c,k] <- d[k] - d[c]
  RR[c,k] <- exp(d[k] - d[c])
}
}

# ranking on relative scale

for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[,k])    # assumes events are "good"
  # rk[k] <- rank(d[,k])      # assumes events are "bad"

  best[k] <- equals(rk[k],1)  # calculate probability that treat k is best
  # calculates probability that treat k is h-th best

  for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}
}                                     # *** PROGRAM ENDS

```

```
list(ns=2, nt=3, location_mu = -3.20 , df = 5, var= 1.63)
```

t[,1]	r[,1]	n[,1]	t[,2]	r[,2]	n[,2]	t[,3]	r[,3]	n[,3]	na[]	#	Study
2	56	116	3	30	115	NA	NA	NA	2	#	Naik
1	14	82	2	15	82	NA	NA	NA	2	#	Venkat

END

```
list(ns=2, nt=3, location_mu = -3.20 , df = 5, var= 1.63)
```

Delayed

t[,1]	r[,1]	n[,1]	t[,2]	r[,2]	n[,2]	t[,3]	r[,3]	n[,3]	na[]	#	Study
2	61	116	3	30	115	NA	NA	NA	2	#	Naik
1	12	82	2	17	82	NA	NA	NA	2	#	Venkat

END

```
list(ns=2, nt=3, location_mu = -3.20 , df = 5, var= 1.63)
```

Overall

t[,1]	r[,1]	n[,1]	t[,2]	r[,2]	n[,2]	t[,3]	r[,3]	n[,3]	na[]	#	Study
2	73	116	3	41	115	NA	NA	NA	2	#	Naik
1	17	82	2	21	82	NA	NA	NA	2	#	Venkat
1	14	17	2	15	27	NA	NA	NA	2	#	Gore

END

5.2.6 Results of the multivariate NMA

5.2.6.1 Correlation at the individual level between nausea and vomiting outcomes

The multivariate NMA was informed by the within-study correlation estimates for nausea and vomiting outcomes studies derived from Radhakrishnan et al. 2019 (Radhakrishnan et al., 2019) and Naik et al. 2020 (Naik et al., 2020) (Table 5-18), as these were the only studies which provided nausea outcomes within their IPD.

Table 5-18. Within-study correlation in treatment effect estimates between outcome pairs estimated from Naik et al. 2020 (Naik et al., 2020)

	Within-study correlation between outcome pairs	
	Nausea and Complete response	Nausea and Vomiting
Acute phase	-0.577	0.632
Delayed phase	-0.504	0.539
Overall phase	-0.607	0.664

Treatment comparison: Olanzapine + aprepitant + ondansetron + dexamethasone VS aprepitant ondansetron + dexamethasone

Analyses including both IPD and AD, as well as patients/ studies including or excluding dexamethasone from the antiemetic regimens, were chosen as the main analyses, as the results were comparable with the sensitivity analyses (Table 5-20, Table 5-21, Table 5-22). For all outcomes, the multivariate analyses introduced significant amounts of uncertainty and produced results dissimilar and largely more imprecise than the random effects univariate analyses (with an informative prior informing the between-study heterogeneity parameter). The multivariate analysis also failed to detect the benefit of adding olanzapine to aprepitant, ondansetron and dexamethasone for nausea prevention in the acute, delayed and overall phase (as identified by the univariate analysis) (Table 5-19).

5.2.6.2 Results of the MV-NMA for the binary outcome of nausea

Table 5-19 Analysis including IPD and aggregate data, and including patients/ studies without dexamethasone in the antiemetic regimen.

Phase	Treatment comparison*	Random effects Univariate analysis** RR (95%CrI)	Confidence interval width	Between-study heterogeneity	Random effects Multivariate analysis*** RR (95%CrI)	Confidence interval width	Between-study heterogeneity
Acute phase	1	0.994 (0.491 to 1.975)	1.48	0.0546	0.553 (0.0459 to 6.324)	6.28	1.003
	2	0.529 (0.233 to 1.18)	0.95		0.299 (0.009 to 9.066)	9.06	
	3	0.533 (0.357 to 0.789)	0.43		0.541 (0.044 to 6.869)	6.83	
Delayed phase	1	1.339 (0.698 to 2.598)	1.90	0.0556	0.759 (0.0769 to 7.171)	7.09	1.947
	2	0.653 (0.303 to 1.42)	1.12		0.378 (0.0146 to 9.764)	9.75	
	3	0.491 (0.326 to 0.716)	0.39		0.506 (0.0383 to 5.668)	5.63	
Overall phase	1	1.177 (0.668 to 2.154)	1.49	0.0459	1.046 (0.227 to 4.567)	4.34	0.9264
	2	0.657 (0.341 to 1.303)	0.96		0.625 (0.033 to 8.665)	8.63	
	3	0.561 (0.405 to 0.761)	0.36		0.573 (0.0537 to 5.911)	5.86	

*Treatment comparison codes: 1) ondansetron + dexamethasone vs aprepitant + ondansetron + dexamethasone,

2) ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone

3) aprepitant + ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone.

Including data on nausea only, * including data on complete response, vomiting and nausea

RR- relative risk

5.2.6.3 Sensitivity analyses

Table 5-20 Analysis **including IPD and aggregate data** and **excluding patients/ studies without dexamethasone** in the antiemetic regimen.

Phase	Treatment comparison*	Random effects univariate analysis** RR (95%CrI)	Confidence interval width	Between-study heterogeneity	Random effects Multivariate analysis** RR (95%CrI)	Confidence interval width	Between-study heterogeneity
Acute phase	1	0.994 (0.491 to 1.975)	1.48	0.0546	0.534 (0.056 to 5.026)	4.97	0.9861
	2	0.529 (0.233 to 1.18)	0.95		0.290 (0.010 to 8.785)	8.78	
	3	0.533 (0.357 to 0.789)	0.43		0.543 (0.045 to 6.791)	6.75	
Delayed phase	1	1.339 (0.698 to 2.598)	1.90	0.0556	0.762 (0.091 to 6.504)	6.41	0.9714
	2	0.653 (0.303 to 1.42)	1.12		0.381 (0.014 to 9.65)	9.64	
	3	0.491 (0.326 to 0.716)	0.39		0.494 (0.042 to 5.641)	5.60	
Overall phase	1	1.177 (0.668 to 2.154)	1.49	0.0459	1.111 (0.224 to 4.607)	4.38	0.9468
	2	0.657 (0.341 to 1.303)	0.96		0.646 (0.039 to 8.174)	8.14	
	3	0.561 (0.405 to 0.761)	0.36		0.559 (0.058 to 5.682)	5.62	

*Treatment comparison codes: 1) ondansetron + dexamethasone vs aprepitant + ondansetron + dexamethasone,

2) ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone

3) aprepitant + ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone.

Including data on nausea only- fixed effect model preferred in all analyses, * including data on complete response, vomiting and nausea. Only those patients given dexamethasone were included in the analyses from Kang et al 2015 and the Merck (unpublished) study, and no data from Sharma et al. 2020 were included.

RR- relative risk

Table 5-21 Analysis of IPD only (excluding aggregate data) and including patients/studies with or without dexamethasone in the antiemetic regimen.

Phase	Treatment comparison*	Random effects univariate analysis** RR (95%CrI)	Confidence interval width	Between-study heterogeneity	Random effects Multivariate analysis** RR (95%CrI)	Confidence interval width	Between-study heterogeneity
Acute phase	1	0.994 (0.491 to 1.975)	1.48	0.0546	0.519 (0.049 to 5.287)	5.24	0.9308
	2	0.529 (0.233 to 1.18)	0.95		0.280 (0.008 to 8.229)	8.22	
	3	0.533 (0.357 to 0.789)	0.43		0.541 (0.040 to 6.59)	6.55	
Delayed phase	1	1.339 (0.698 to 2.598)	1.90	0.0556	0.741 (0.056 to 8.969)	8.91	1.026
	2	0.653 (0.303 to 1.42)	1.12		0.363 (0.010 to 13.12)	13.11	
	3	0.491 (0.326 to 0.716)	0.39		0.496 (0.040 to 6.363)	6.32	
Overall phase	1	1.177 (0.664 to 2.162)	1.49	0.0459	0.814 (0.099 to 6.73)	6.63	0.9913
	2	0.657 (0.341 to 1.314)	0.97		0.463 (0.019 to 11.49)	11.47	
	3	0.561 (0.405 to 0.761)	0.35		0.572 (0.049 to 6.975)	6.93	

*Treatment comparison codes: 1) ondansetron + dexamethasone vs aprepitant + ondansetron + dexamethasone,

2) ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone

3) aprepitant + ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone.

Including data on nausea only, * including data on complete response, vomiting and nausea.

RR- relative risk

Table 5-22 Analysis of IPD only (excluding aggregate data) and excluding patients/ studies without dexamethasone in the antiemetic regimen.

Phase	Treatment comparison*	Random effects univariate analysis** RR (95% CrI)	Confidence interval width	Between-study heterogeneity	Random effects Multivariate analysis** RR (95%CrI)	Confidence interval width	Between-study heterogeneity
Acute phase	1	0.994 (0.491 to 1.975)	1.48	0.0546	0.569 (0.0521 to 5.61)	5.56	1.005
	2	0.529 (0.233 to 1.18)	0.95		0.306 (0.011 to 9.43)	9.42	
	3	0.533 (0.357 to 0.789)	0.43		0.541 (0.044 to 7.11)	7.07	
Delayed phase	1	1.339 (0.698 to 2.598)	1.90	0.0556	0.808 (0.076 to 9.123)	9.05	0.9628
	2	0.653 (0.303 to 1.42)	1.12		0.395 (0.013 to 13.08)	13.07	
	3	0.491 (0.326 to 0.716)	0.39		0.495 (0.042 to 6.305)	6.26	
Overall phase	1	1.177 (0.664 to 2.162)	1.49	0.0459	0.793 (0.082 to 7.363)	7.28	0.9879
	2	0.657 (0.341 to 1.314)	0.97		0.449 (0.0148 to 13.1)	13.09	
	3	0.561 (0.405 to 0.761)	0.35		0.567 (0.050 to 6.902)	6.85	

*Treatment comparison codes: 1) ondansetron + dexamethasone vs aprepitant + ondansetron + dexamethasone,

2) ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone

3) aprepitant + ondansetron + dexamethasone vs olanzapine + aprepitant + ondansetron + dexamethasone.

Including data on nausea only- fixed effect model preferred in all analyses, * including data on complete response, vomiting and nausea. Only those patients given dexamethasone were included in the analyses from Kang et al 2015 and the Merck (unpublished) study, and no data was included from Sharma et al. 2020 were included.

RR- relative risk

6 Chapter Six Appendix

6.1 Data used for MLNMR

6.1.1 IPD format

IPD was read into R in a wide format, i.e. one row per participant

Table 6-1. An example of the IPD format required to conduct an ML-NMR with the multinma package in R.

Study	PatID	Arm	Treatment	Sex	AgeRand	Weight	Diagnosis	ChemoBlock	Emetogenicity	Dex	AcuteComControl	DelayComControl	OverallComControl

6.1.2 Aggregate data

Child population

Table 6-2. Aggregate data informing the sensitivity analyses conducted in the child population.

Study	Treatment	Arm	AcuteComControl	DelayComControl	OverallComControl	Total_N	AgeRand_mean	Age_sd	Sex
Moshayedi et al. 2021	1	Ondansetron	16	18	16	21	8.5	2.5	47.5
Moshayedi et al. 2021	3	Olanzapine + Ondansetron	14	15	11	19	10	1.5	18.7
Tan et al. 2018	1	Ondansetron	121	62	41	194	5.11	4.81	52.9
Tan et al. 2018	5	Palonosetron 5ug	124	72	66	181	5.07	4.13	51.4
Tan et al. 2012	6	Palonosetron 10ug	129	99	79	186	4.97	4.38	51.4
Gore et al. 2009	1	Ondansetron	7	1	1	18	15	1.91	25
Gore et al. 2009	2	NK1 antagonist	17	10	8	32	15	1.73	33
Kovacs et al. 2016	1	Ondansetron	95	46	39	162	8.18	5.17	40
Kovacs et al. 2016	6	Palonosetron 10ug	90	48	39	166	8.07	4.81	47
Kovacs et al. 2016	7	Palonosetron 20ug	98	64	54	165	8.39	4.91	54
Li et al. 2022	6	Palonosetron 10ug	83	NR	NR	100	10.2	2.8	32
Li et al. 2022	8	GRAN SD 0.05 mg/kg	72	NR	NR	100	10.2	1.9	36

Adult population

Table 6-3 Aggregate data informing the sensitivity analyses conducted in the adult population.

Study	Treatment	Arm	AcuteComControl	DelayComControl	OverallComControl	Total_N	AgeRand_mean	Age_sd	Sex
Kim et al. 2017	1	Ondansetron	238	173	171	250	60.9	11.5	44.9
Kim et al. 2017	2	NK1 antagonist	227	176	174	244	59.7	11.4	45.6
Warr et al. 2005	1	Ondansetron	293	208	178	428	52.1	10.9	100
Warr et al. 2005	2	NK1 antagonist	329	238	221	438	53.1	10.7	99.5
Poli-Bigelli et al. 2003	1	Ondansetron	180	123	114	286	53	14	49
Poli-Bigelli et al. 2004	2	NK1 antagonist	216	176	163	283	54	13	48
Schmoll et al. 2006	1	Ondansetron	191	152	146	245	58	11	35
Schmoll et al. 2006	2	NK1 antagonist	213	180	175	244	59	11	39
Hesketh et al. 2003	1	Ondansetron	203	145	136	266	58	12	38
Hesketh et al. 2003	2	NK1 antagonist	231	196	189	264	59	12	37
Morteza et al. 2021	1	Ondansetron	73	73	73	82	56.22	10.27	50
Morteza et al. 2021	2	NK1 antagonist	78	78	78	82	53.32	13.73	50
Grunberg et al. 2011	2	NK1 antagonist	1001	844	823	1175	55.9	12	36.3
Grunberg et al. 2011	2	NK1 antagonist	987	824	797	1147	55.2	11.9	37.1

6.2 Code for MLNMR

The R code for the main analysis (i.e. the IPD network meta-regression is detailed below. The extension of this code needed to implement the IPD network meta-regression, inclusive of aggregate data, is freely available at https://dmphillippo.github.io/multinma/articles/example_plaque_psoriasis.html and is informed by work conducted by Phillippo et al. 2020 (Phillippo et al., 2020).

```
library(cli)

library(multinma)

library(dplyr)    # dplyr and tidyr for data manipulation
library(tidyr)

library(ggplot2)  # ggplot2 for plotting covariate distributions
library(rstantools)
library(readxl)

options(mc.cores = parallel::detectCores())

setwd("~/Data")

IPD <- read.csv("IPD.csv")

## Variables need to be set as numeric to be understood by STAN.

nma_ipd <- IPD %>%

  mutate(                                     # Variable transformations

    Age = as.numeric(Age),                    # edit with covariates as needed

    Sex = as.numeric(Sex),

    Weight = as.numeric(Weight),

    ChemoBlock = as.numeric(ChemoBlock),
```

```

Diagnosis= as.numeric(Diagnosis),

AcuteComControl= as.numeric(AcuteComControl),    # edit with outcomes as needed

# Set treatment classes- delete if not using class model

trtclass = case_when(Arm == 2 ~ "NK1 antagonist",
                     Arm == 1 ~ "5HT3 antagonist",
                     Arm == 3 ~ "OLZ + OND",
                     Arm == 4 ~ "OLZ + APR + OND"),

# Check complete cases for covariates and outcomes of interest

complete = complete.cases(AgeRand, Sex, ChemoBlock, Diagnosis, AcuteComControl)
)

# check for missing values in the IPD.

sum(!nma_ipd$complete)

mean(!nma_ipd$complete)

#Exclude these missing values from analyses

nma_ipd <- filter(nma_ipd, complete)

#Set up the networks, setting the IPD with set_ipd(),

Network_IPD <- set_ipd(nma_ipd,
                       study = Study,
                       trt = Treatment,
                       r = AcuteComControl,
                       trt_class = trtclass,
                       trt_ref = "Ondansetron"

```

)

Network_IPD

ML-NMR models###

##specify weakly-informative $N(0,102)$ priors on each parameter.

summary(normal(scale = 10)) # check the range of parameter values implied by this prior distributions

##The regression models are specified with regression = $\sim(\text{covariate} + \text{covariate})^*.\text{trt}$,

The outputs will include the prognostic effects of each covariate as well as interactions with treatment.

Fixed effects model

FE_Model<- nma(Network_IPD,

trt_effects = "fixed", # fixed effect model

link = "logit", ## link function

likelihood = "bernoulli",

regression = $\sim(\text{Age} + \text{Sex})^*.\text{trt}$, # edit with covariates

class_interactions = "common",

prior_intercept = normal(scale = 10),

prior_trt = normal(scale = 10), # vague prior for treatment effect

prior_reg = normal(scale = 10),

init_r = 0.1, # initial values

QR = TRUE)

output <- print(FE_Model)

```
# Random effects model
```

```
RE_Model <- nma(Network_IPD,  
  
  trt_effects = "random", # random effect model  
  
  link = "logit",  
  
  likelihood = "bernoulli", ## link function  
  
  regression = ~(AgeRand + Sex )*.trt, ,      # edit with covariates  
  
  # class_interactions = "common",  
  
  prior_intercept = normal(scale = 10), # vague prior for treatment effect  
  
  prior_trt = normal(scale = 10),  
  
  prior_reg = normal(scale = 10),  
  
  prior_het = half_normal(scale = 2.5),  
  
  init_r = 0.1,  
  
  QR = TRUE)  
  
output <- print(RE_Model)
```

```
# convergence checks
```

```
library(rstan)  
  
stan_trace(as.stanfit(FE_Model), pars = c("d", "beta"))  
  
stan_trace(as.stanfit(RE_Model), pars = c("d", "beta"))
```

6.3 Table of outcomes reported by each study providing IPD

Table 6-4 Outcomes included within the IPD for each clinical trial- indicative of which trials contributed to each analysis. Columns in blue indicate the additional outcomes included in the appendix that were not reported in the main text of this chapter.

Study	Complete response in acute phase	Complete response in delayed phase	Complete response in overall phase	Rescue Medication in acute phase	Rescue Medication in delayed phase	Rescue Medication in overall phase	Nausea in Acute Phase	Nausea in delayed phase	Nausea in overall phase	Severe Nausea acute phase	Severe Nausea delayed phase	Severe Nausea overall phase
Children's clinical trials												
Kang et al. 2015	✓	✓	✓	✓	✓	✓						
Merck (unpublished)	✓	✓	✓	✓	✓	✓						
Radhakrishnan et al. 2019	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓
Bakshi et al. 2015	✓	✓	✓			✓						
Sharma et al. 2020	✓	✓	✓			✓						
Naik et al. 2020	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Moothedath et al. 2022	✓	✓	✓			✓						
Adult's clinical trials												
Weinstein et al. 2016	✓	✓	✓	Analyses with adult data were only planned for complete response outcomes.								
Rapoport et al. 2010	✓	✓	✓									

6.4 Results of interaction analyses by outcome for the child population

In chapter six of this thesis, prognostic factors and effect modifiers have been considered across outcomes. However, here in the appendix (for transparency), the results of the IPD meta-regression for each outcome are reported in turn, including the network structure for the analysis, the forest plot, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect, and a bullet point summary of the prognostic factors and effect modifiers identified. Finally (for complete response outcomes), the network plot and forest plot for the sensitivity analyses, including aggregate data, are reported (as no additional information was gained from these sensitivity analyses, they were not conducted for the remaining outcomes).

6.4.1 Complete response in the acute phase

The final IPD meta-regression model for outcome complete response in the acute phase included covariates of age, diagnosis and length of chemotherapy block. Here, the fixed effects model was preferred (DIC: fixed effects 1181 vs random effects 1182).

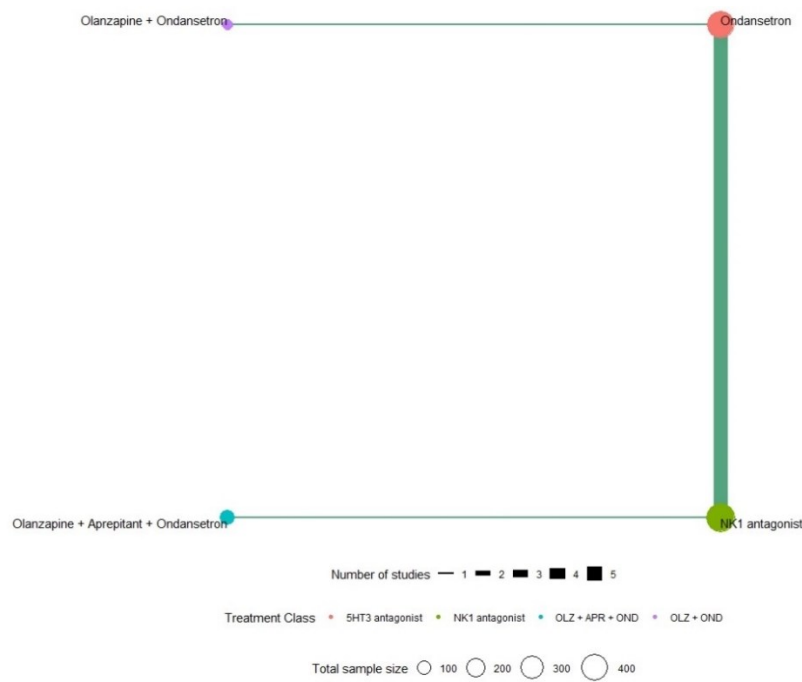


Figure 6-1. Network plot for the IPD network meta-regression for the outcome of **complete response in the acute phase**.

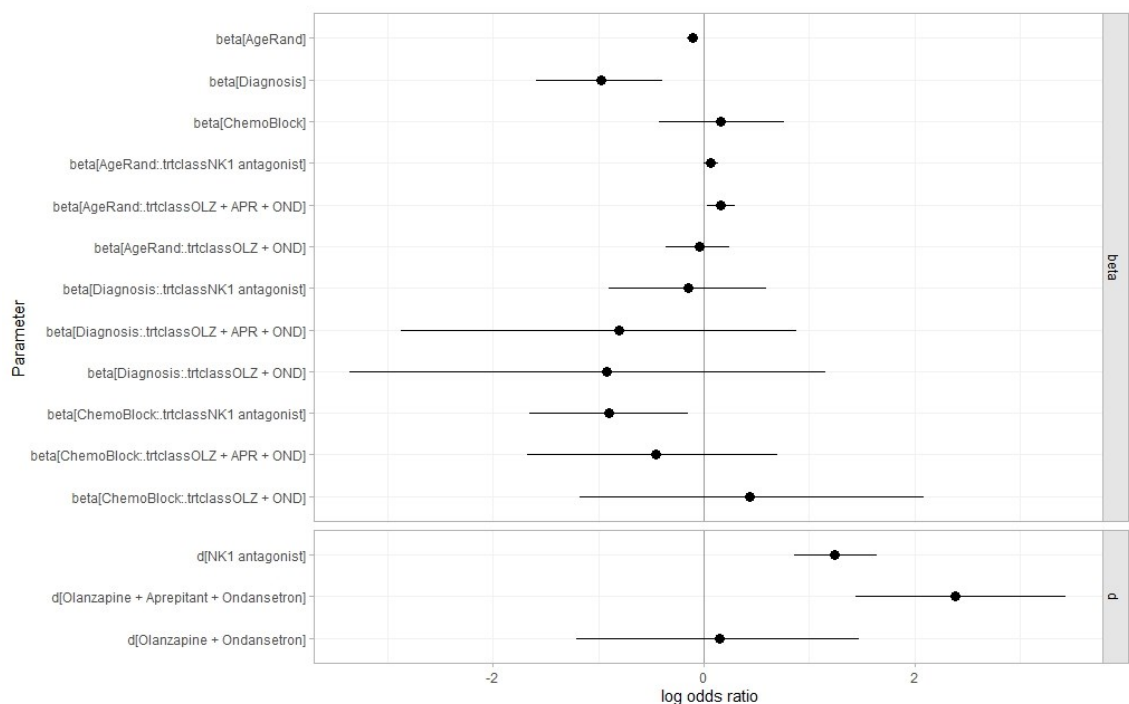


Figure 6-2 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **complete response in the acute phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.1.1 IPD meta-regression - Prognostic factors

- Those with a solid tumour diagnosis have a ~63% lower odds of achieving a complete response in the acute phase compared to those with a diagnosis of blood cancer (OR 0.375 (0.208 to 0.684)).
- For every one-year increase in age, the odds of achieving a complete response in the acute phase reduces by ~10% OR 0.905 (0.861 to 0.923).

6.4.1.2 IPD meta-regression - Interactions with treatment effect

- When on a multi-day chemotherapy regimen, the relative treatment effects of NK1 antagonist + ondansetron compared to ondansetron, reduces by ~59 % compared to when on a single day regimen (OR 0.407 (0.194 to 0.852)). N.B. Adding NK1 antagonists to ondansetron is still beneficial for both patients on single and multi-day regimens, when other covariates are held at their mean value.
- A one unit increase in age translates into a ~9% increase in the relative effect of treatment effects of NK1 antagonist + ondansetron compared to ondansetron (OR 1.09 (1.04 to 1.13)) and a ~22% increase in the relative effect of treatment effects of Olanzapine + aprepitant + ondansetron compared to ondansetron (OR 1.22 (1.02 to 1.34)). Suggesting that older children derive greater relative benefit from additional antiemetics. N.B. When predicting these relative treatment effects for ages 5, 10 and 15, a benefit is seen for each age.

6.4.1.3 Sensitivity analyses- IPD meta-regression including aggregate data

The final IPD meta-regression model, inclusive of aggregate data, included the covariate of age. Here, the fixed effects model was preferred (DIC: fixed effects 1239 vs random effects 1236). As with the main analyses, increasing age is associated with an increased risk of CINV in the acute phase, and age modifies (increases) the treatment effect of both NK1 antagonist + ondansetron and olanzapine + aprepitant + ondansetron (relative to ondansetron alone).

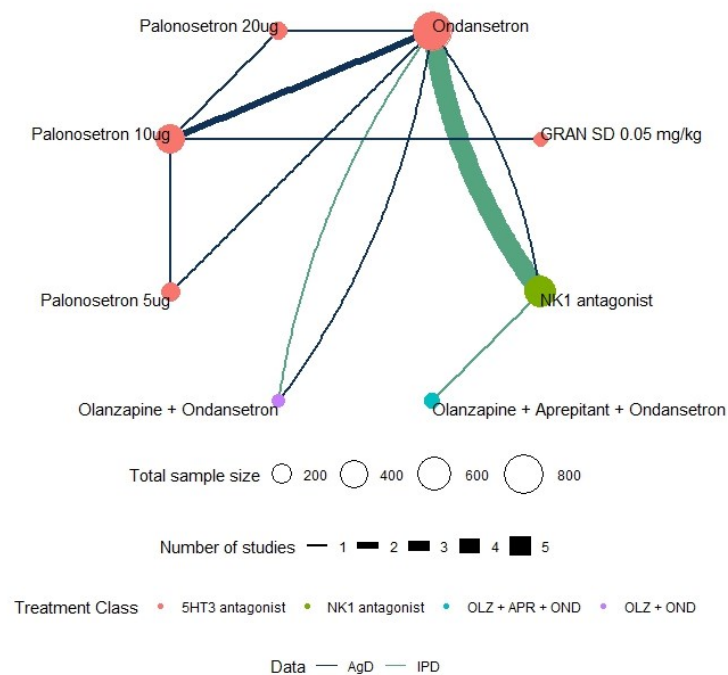


Figure 6-3 Network plot for the IPD network meta-regression, inclusive of aggregate data, for the outcome of **complete response in the acute phase**.

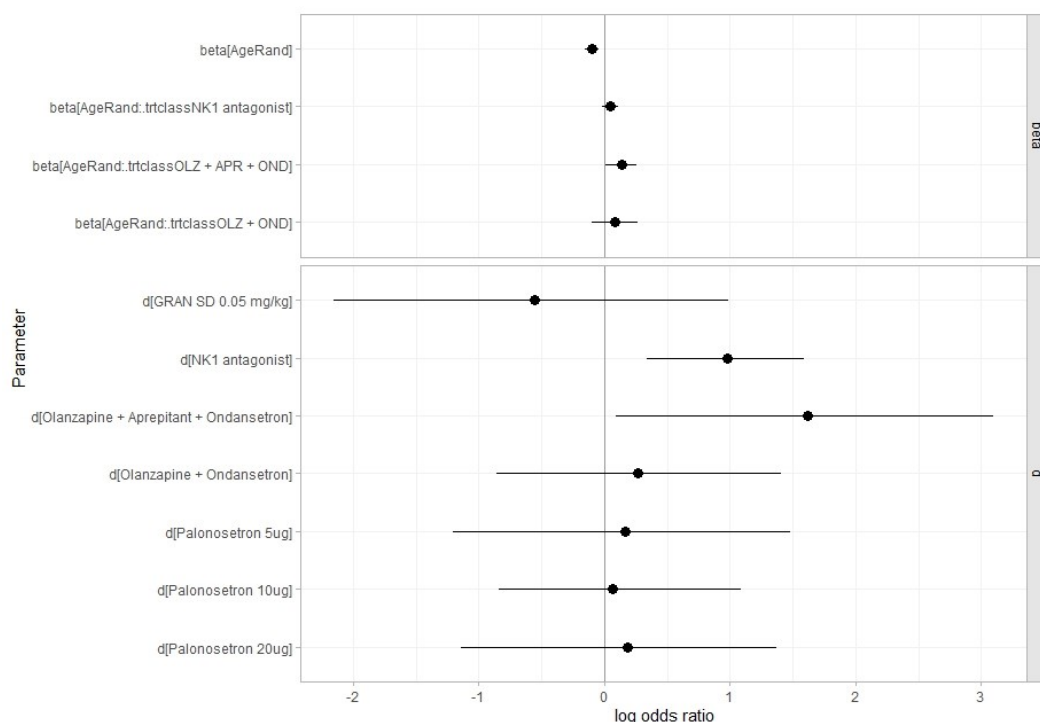


Figure 6-4 Forest plot for the IPD network meta-regression inclusive of aggregate data (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **complete response in the acute phase**. OLZ- olanzapine, APR-

aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand' - is a continuous covariate for age at randomisation.

6.4.2 Complete response in the delayed phase

The final IPD meta-regression model for outcome complete response in the delayed phase included age, sex, diagnosis and length of chemotherapy block. Here, the random effects model was preferred (DIC: fixed effects 1195 vs random effects 1182).

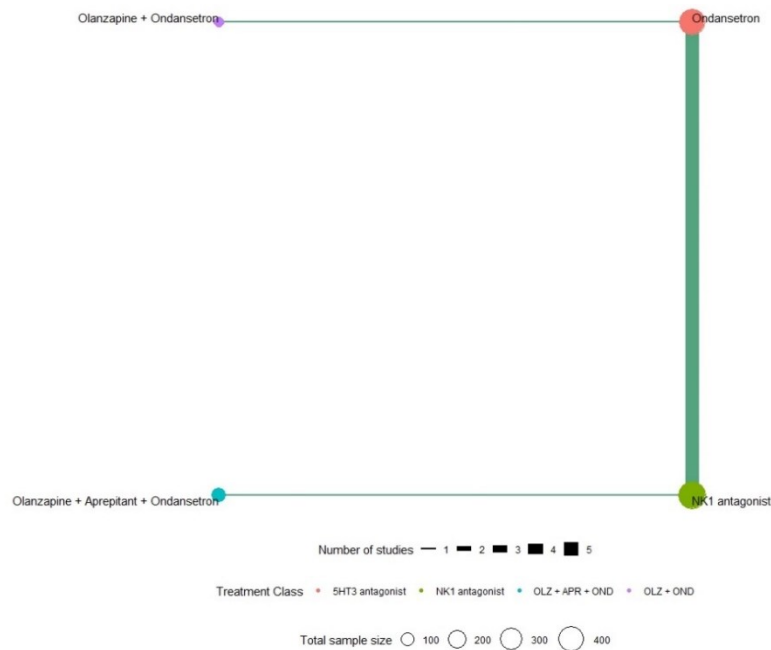


Figure 6-5 Network plot for the IPD network meta-regression for the outcome of **complete response in the delayed phase**.

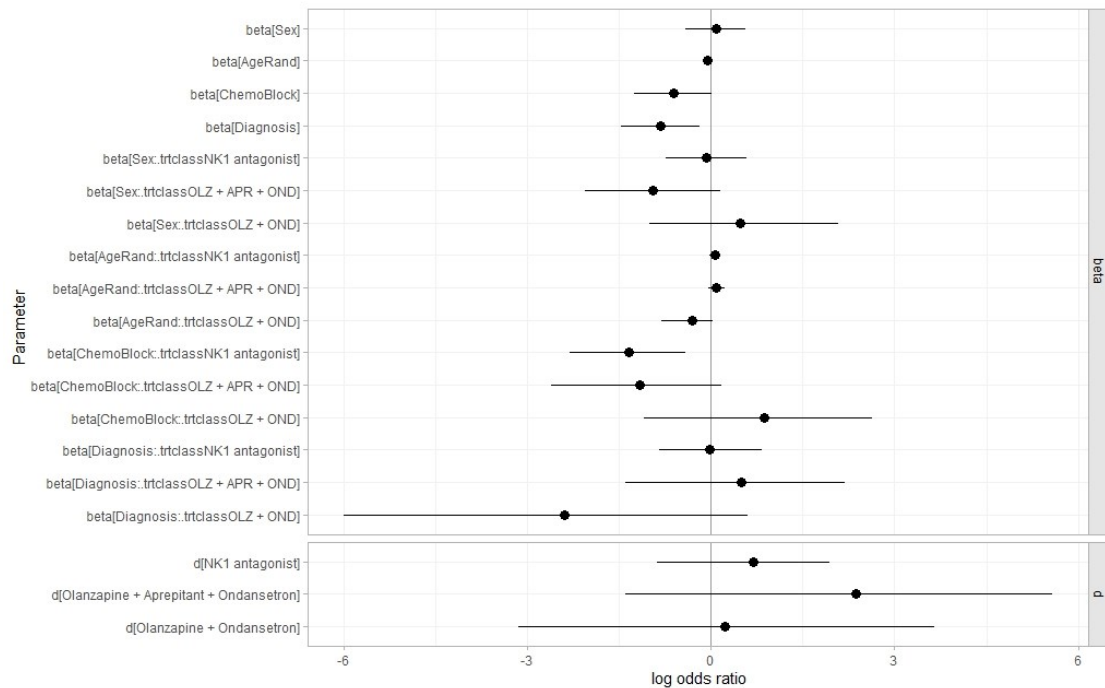


Figure 6-6 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **complete response in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Sex' a binary covariate 0-male, 1-female, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.2.1 IPD meta-regression - Prognostic factors

- Those with a solid tumour diagnosis have a ~54% lower odds of achieving a complete response in the delayed phase compared to those with a diagnosis of blood cancer (OR 0.4554 (0.229 to 0.835)).
- For every one-year increase in age, the odds of achieving a complete response in the delayed phase reduce by ~6% (OR 0.941 (0.923 to 1.00))

6.4.2.2 IPD meta-regression - Interactions with treatment effect

- When on a multi-day chemotherapy regimen, the relative treatment effects of NK1 antagonist + ondansetron compared to ondansetron are reduced by ~74 % compared to when on a single

day regimen (OR 0.262 (0.101 to 0.657)). N.B. Here, there is no evidence of benefit of adding NK1 antagonists to ondansetron for patients on multi-day chemotherapy regimens, when other covariates are held at their mean value, and for those on single-day regimens, the 95% CR just crosses the line of no effect but is tending in the direction of benefit.

6.4.2.3 Sensitivity analyses- IPD meta-regression including aggregate data

The final IPD meta-regression model, inclusive of aggregate data, included the covariates of age and sex. Here, the random effects model was preferred (DIC: fixed effects 1301 vs random effects 1288). As with the main analyses, increasing age is associated with an increased risk of CINV in the delayed phase.

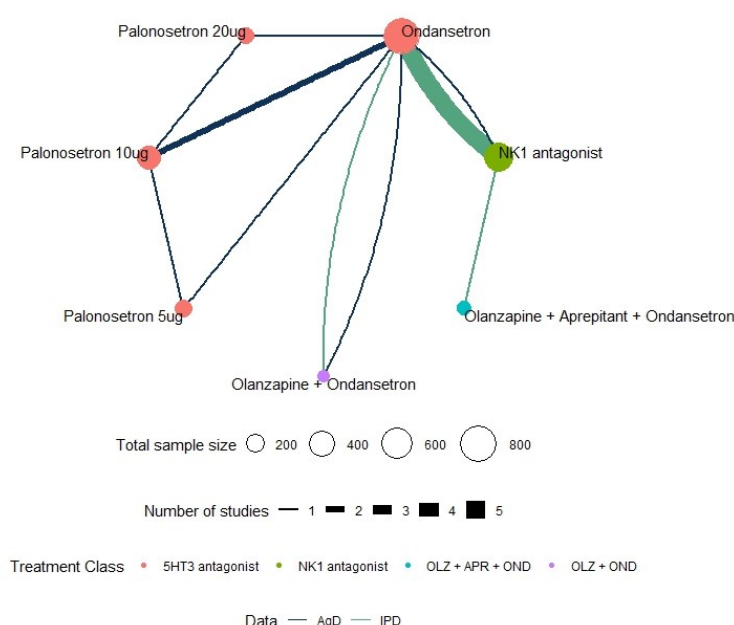


Figure 6-7 Network plot for the IPD network meta-regression, inclusive of aggregate data, for the outcome of **complete response in the delayed phase.**

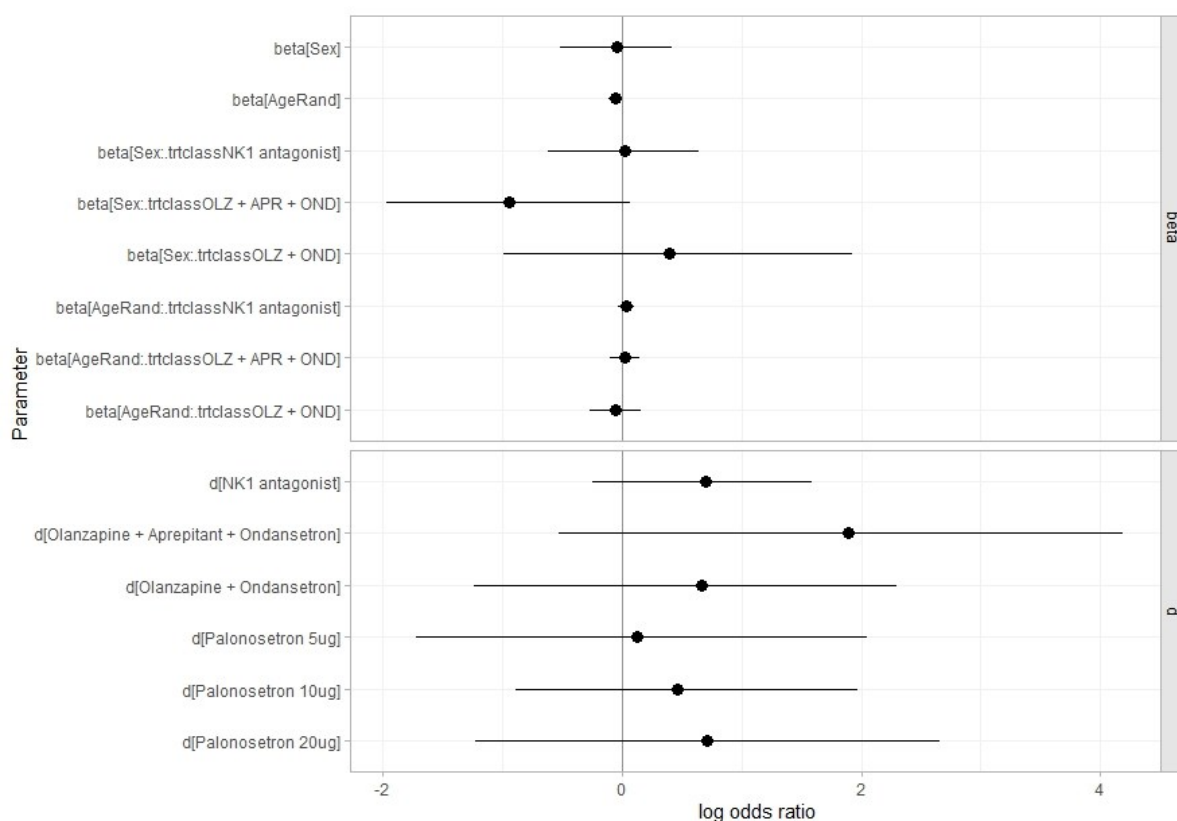


Figure 6-8 Forest plot for the IPD network meta-regression inclusive of aggregate data (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **complete response in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation and 'Sex' is a binary covariate 0-male, 1-female.

6.4.3 Complete response in the overall phase

The final IPD meta-regression model for outcome complete response in the overall phase included age, diagnosis and length of chemotherapy block. Here, the random effects model was preferred (DIC: fixed effects 1168 vs random effects 1155).

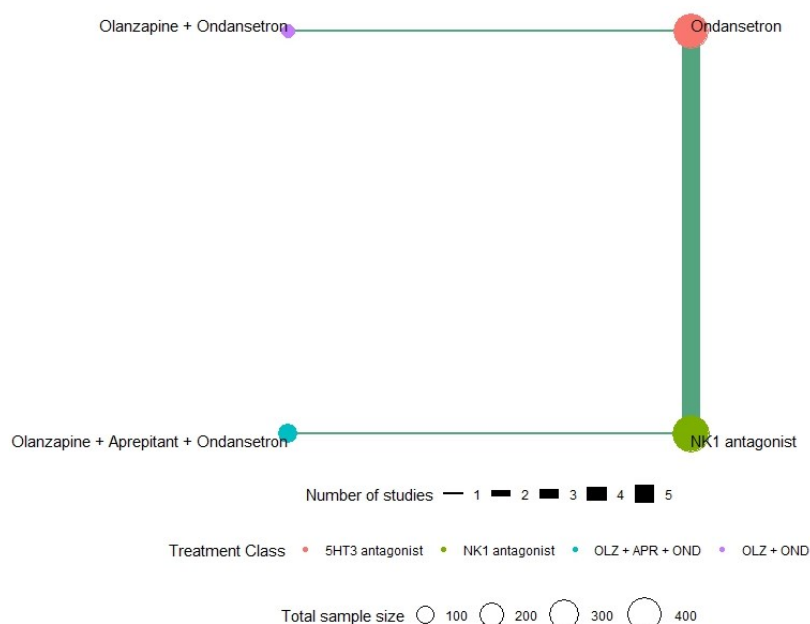


Figure 6-9 Network plot for the IPD network meta-regression for the outcome of **complete response in the overall phase**.

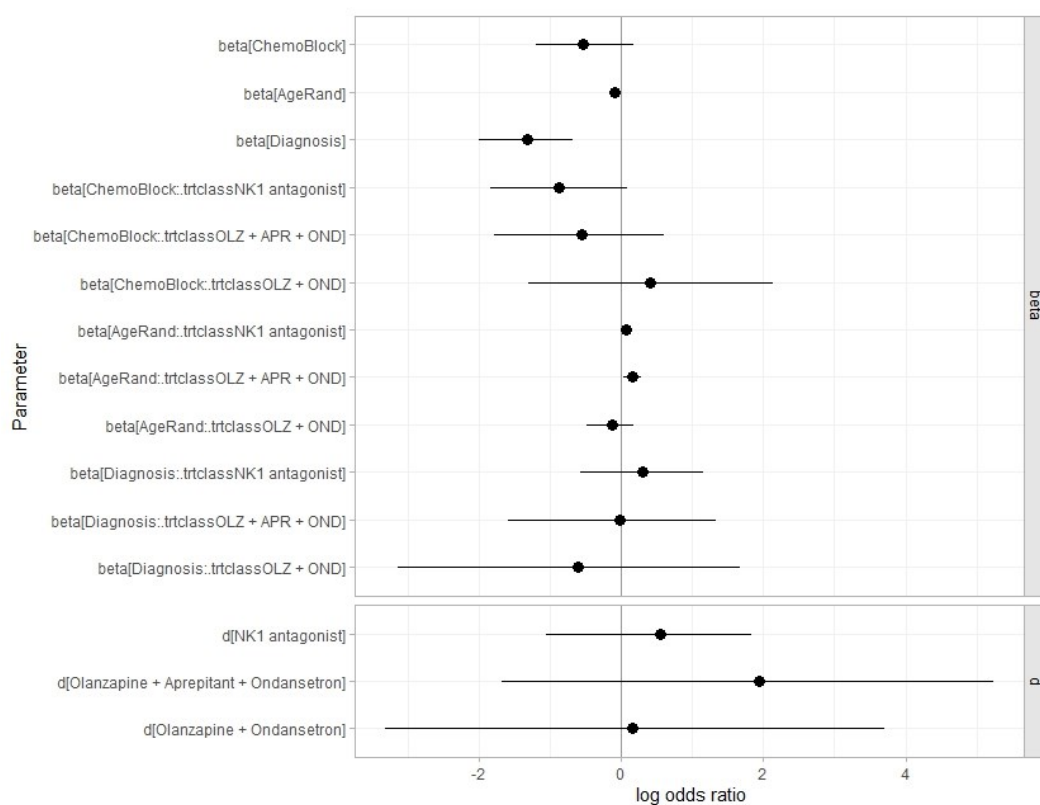


Figure 6-10 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **complete response in the overall phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' is a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.3.1 IPD meta-regression - Prognostic factors

- For every one-year increase in age, the odds of achieving a complete response in the overall phase reduce by ~10% (OR 0.905 (0.852 to 0.971))
- Those with a solid tumour diagnosis have a ~74% lower odds of achieving a complete response in the overall phase compared to those with a diagnosis of blood cancer (OR 0.270 (0.137 to 0.507)).

6.4.3.2 IPD meta-regression – interactions with treatment effect

- A one-unit increase in age translates into a ~7% increase in the relative effect of treatment effects of NK1 antagonist + ondansetron compared to ondansetron (OR 1.07 (1.00 to 1.17)) and a ~17% increase in the relative effect of treatment effects of Olanzapine + aprepitant + ondansetron compared to ondansetron (OR 1.17 (1.103 to 1.34)). Suggesting that older children derive greater relative benefit from additional antiemetics.

6.4.3.3 Sensitivity analyses- IPD meta-regression including aggregate data

The final IPD meta-regression model, inclusive of aggregate data, included the covariate of age. Here, the random effects model was preferred (DIC: fixed effects 1281 vs random effects 1255). As with the main analyses, increasing age is associated with an increased risk of CINV in the overall phase; however, no interaction effect for this covariate was identified.

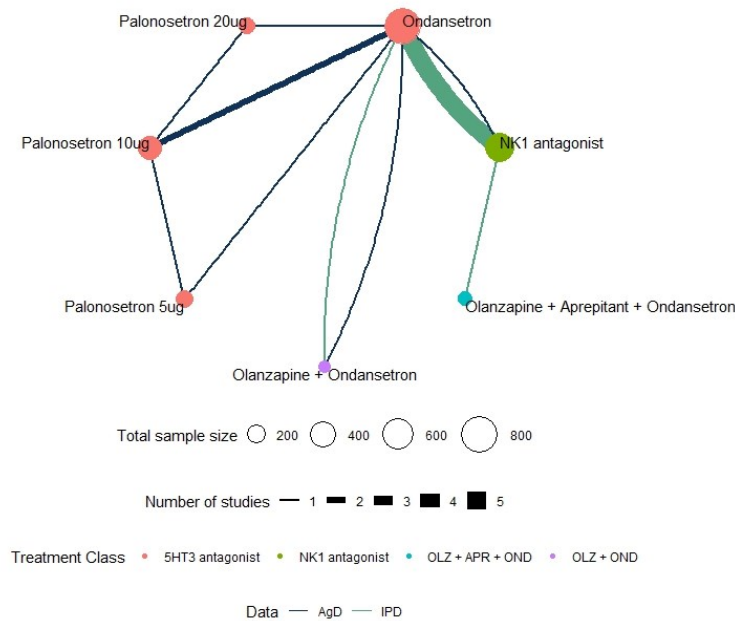


Figure 6-11 Network plot for the IPD network meta-regression, inclusive of aggregate data, for the outcome of **complete response in the overall phase**.

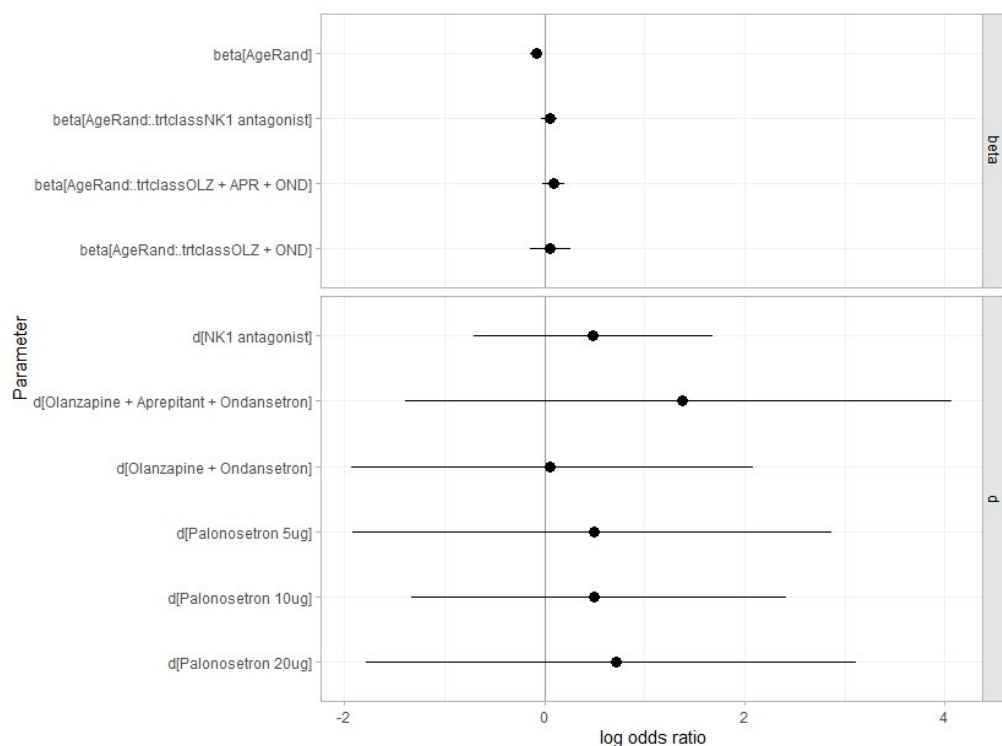


Figure 6-12 Forest plot for the IPD network meta-regression inclusive of aggregate data (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **complete response in the overall phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation.

6.4.4 Rescue medication in the acute phase

The final IPD meta-regression model for outcome ‘rescue medication in the acute phase’ included age, diagnosis and length of chemotherapy block. Here, the fixed effects model was preferred (DIC: fixed effects 456 vs random effects 456).

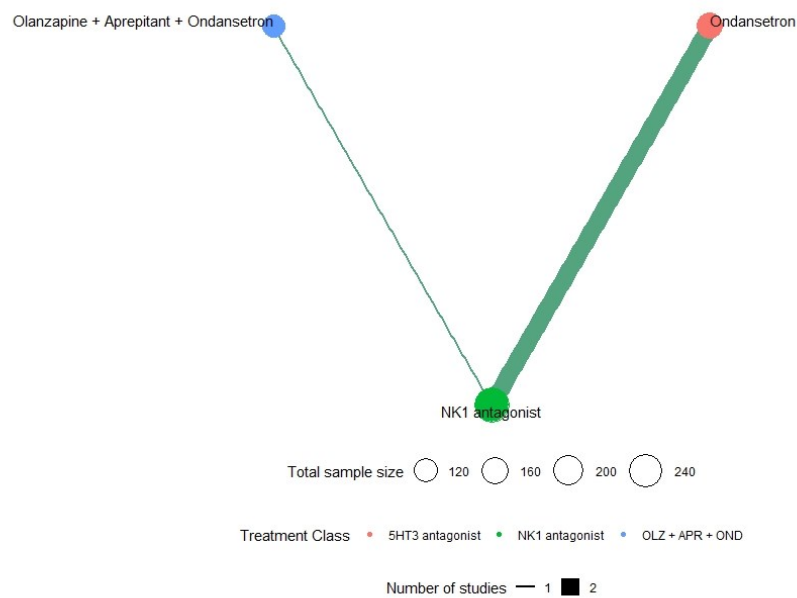


Figure 6-13 Network plot for the IPD network meta-regression, for the outcome of **rescue medication in the acute phase**

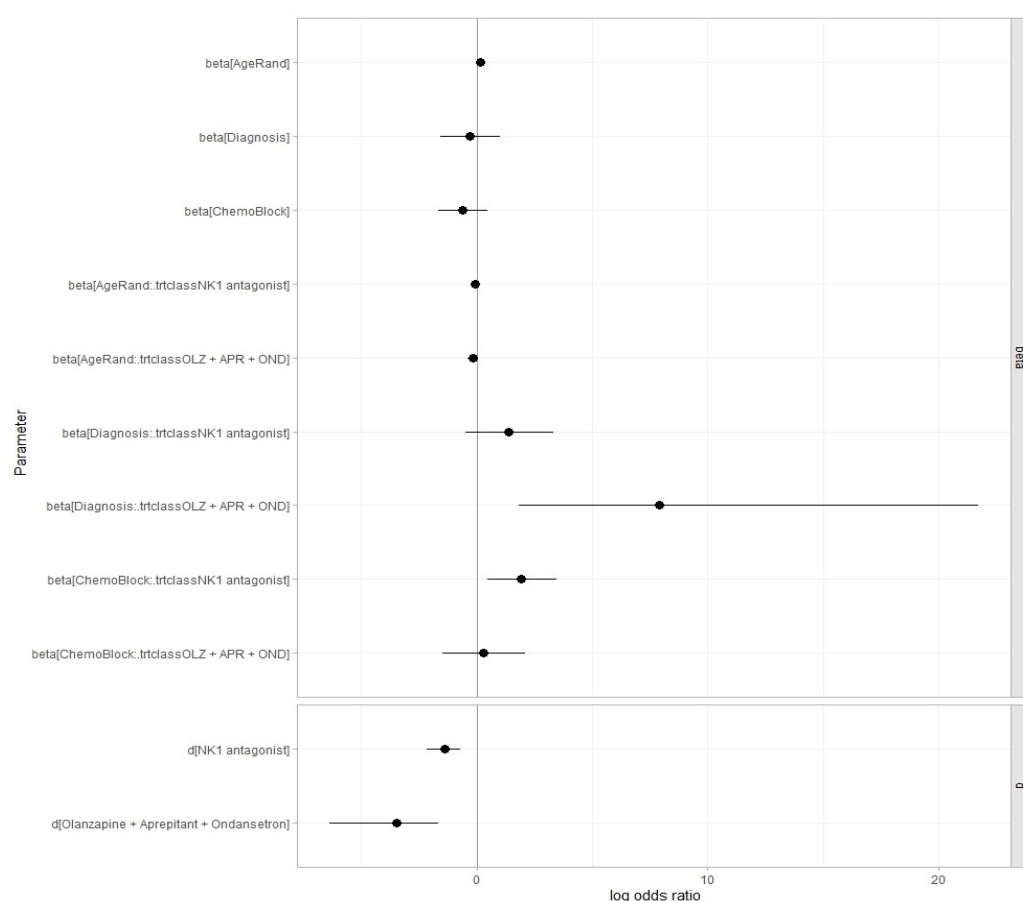


Figure 6-14 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **rescue medication in the acute phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' is a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' is a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.4.1 IPD meta-regression - Prognostic factors

- For every one-year increase in age, the odds of needing rescue medication increase by ~15% (OR 1.150 (1.068 to 1.258)).

6.4.4.2 IPD meta-regression - Interactions with treatment effect

- For diagnosis (blood cancer vs solid tumour), there is a large but uncertain interaction with treatment effect, suggesting those with solid tumours derive less benefit from the addition of olanzapine + aprepitant, but both derive some benefit.

- Those on a multiday regimen derive less benefit from the addition of an NK1 antagonist to ondansetron, compared to those on a single-day regimen, but again, both derive some benefit.

6.4.5 Rescue medication in the delayed phase

The final IPD meta-regression model for the outcome of ‘rescue medication in the delayed phase’ included the covariates of age and diagnosis. Here, the random effects model was preferred (DIC: fixed effects 514 vs random effects 506).

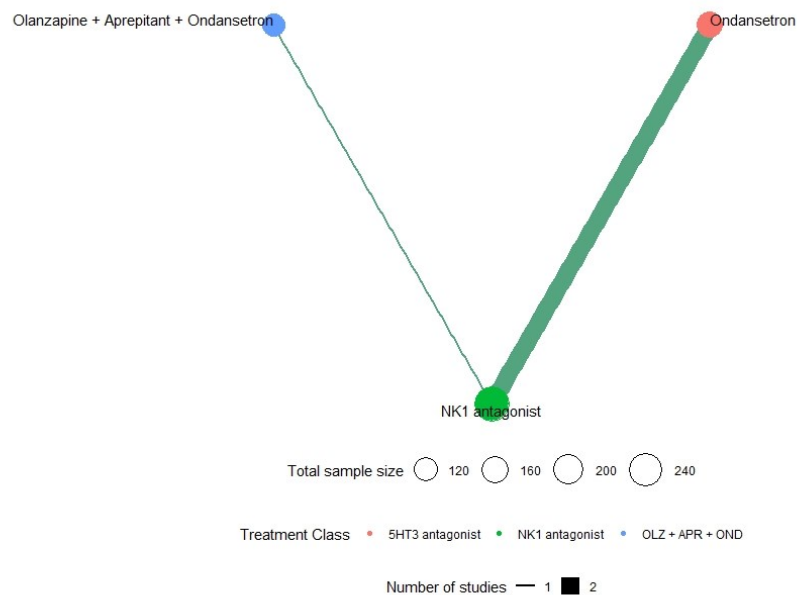


Figure 6-15 Network plot for the IPD network meta-regression, for the outcome of **rescue medication in the delayed phase**

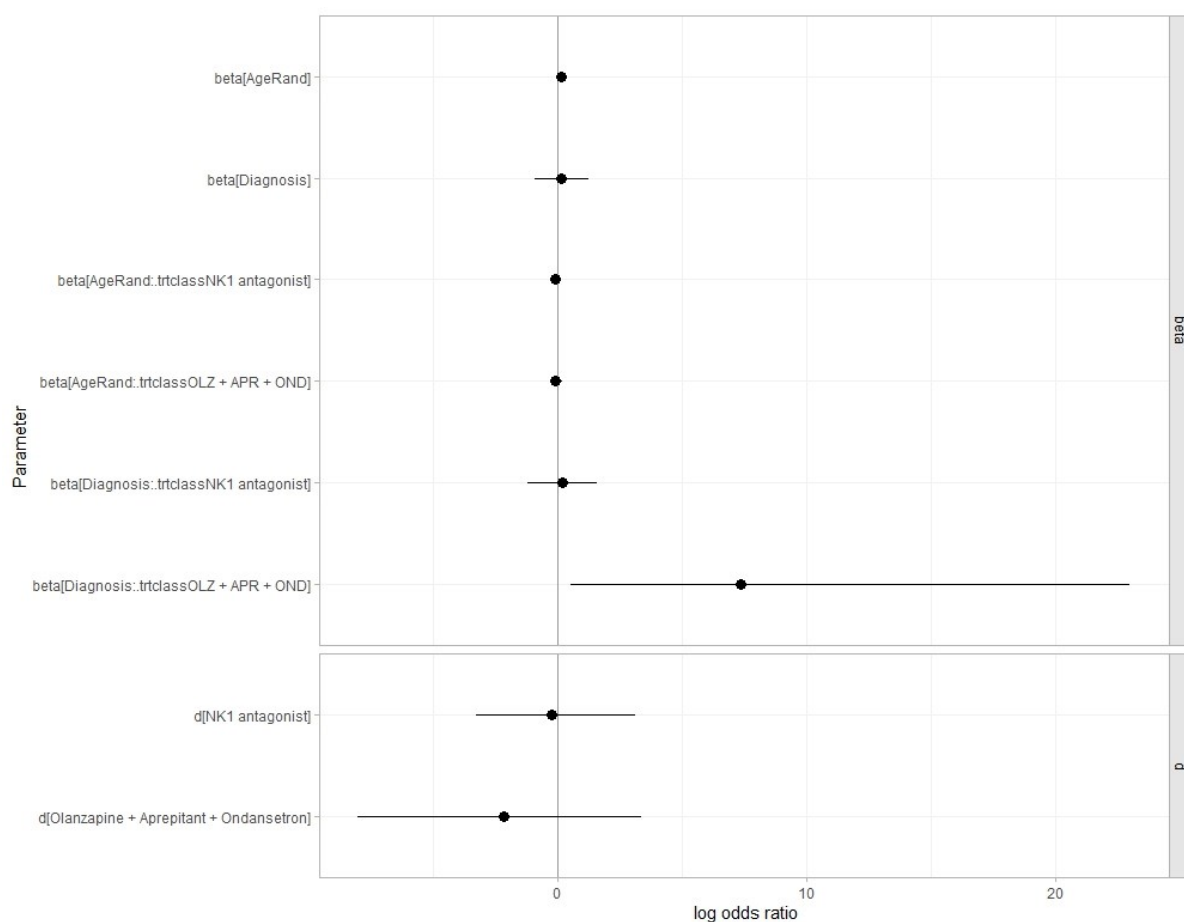


Figure 6-16 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **rescue medication in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' is a binary covariate 0- blood cancer, 1- solid tumour.

6.4.5.1 Prognostic factors

None

6.4.5.2 Interactions with treatment effect

- For diagnosis (blood cancer vs solid tumour), there is a large but uncertain interaction with treatment effect, suggesting those with solid tumours derive less benefit from the addition of Olanzapine + Aprepitant, but for both groups, predicted estimates of relative effect cross the line of no effect.

6.4.6 Rescue medication in the overall phase

The final IPD meta-regression model for the outcome ‘rescue medication in the overall phase’, included the covariates of age and diagnosis and length of chemotherapy block. Here, the random effects model was preferred (DIC: fixed effects 995 vs random effects 988).

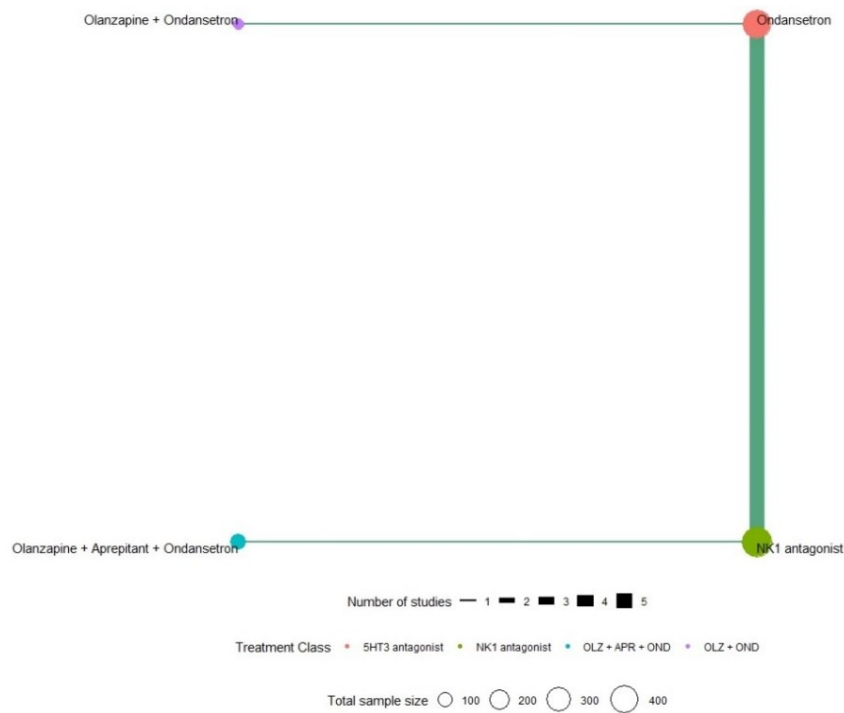


Figure 6-17 Network plot for the IPD network meta-regression, for the outcome of **rescue medication in the overall phase**

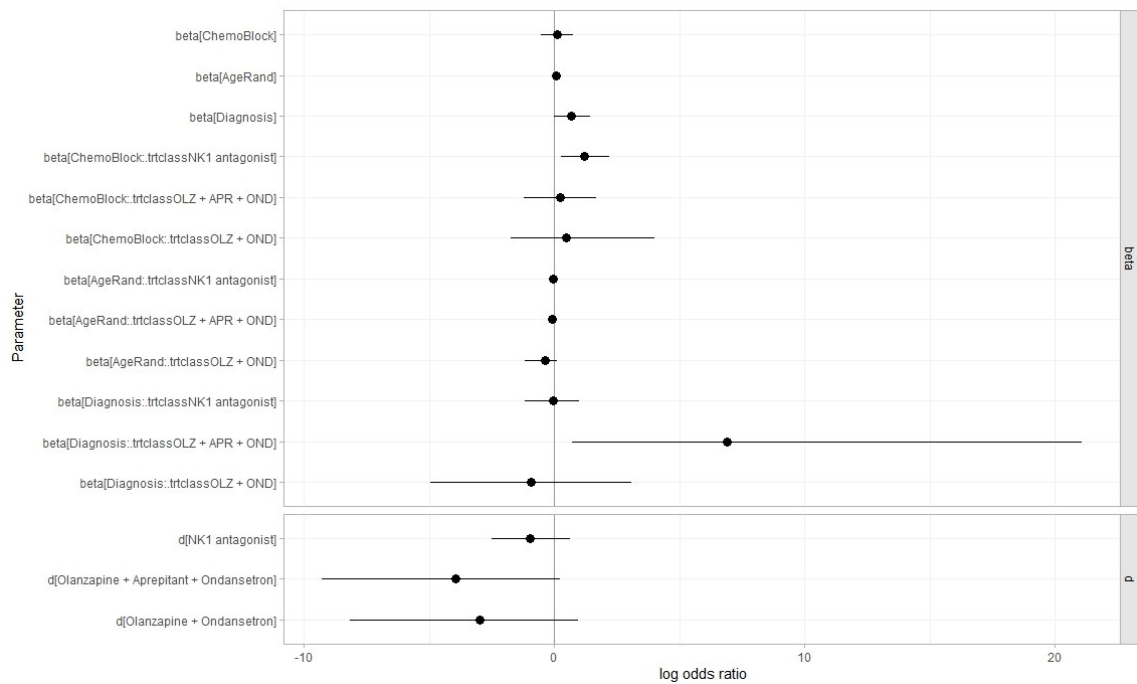


Figure 6-18 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **rescue medication in the overall phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.6.1 IPD meta-regression - Prognostic factors

- For every one-year increase in age, the odds of needing rescue medication in the overall phase increase by ~8% (OR 1.083 (1.031 to 1.150)).

6.4.6.2 IPD meta-regression - Interactions with treatment effect

- Those on a multiday regimen derive less benefit from the addition of an NK1 antagonist to ondansetron, compared to those on a single-day regimen.

- For diagnosis (blood cancer vs solid tumour) there is a large but uncertain interaction with treatment effect, suggesting those with solid tumours may derive less benefit from the addition of Olanzapine + Aprepitant.

6.4.7 Nausea in the acute phase

The final IPD meta-regression model for the outcome ‘nausea in the acute phase’ included age, diagnosis and length of chemotherapy block. Here the fixed effects model was preferred (DIC: fixed effects 399 vs random effects 399).

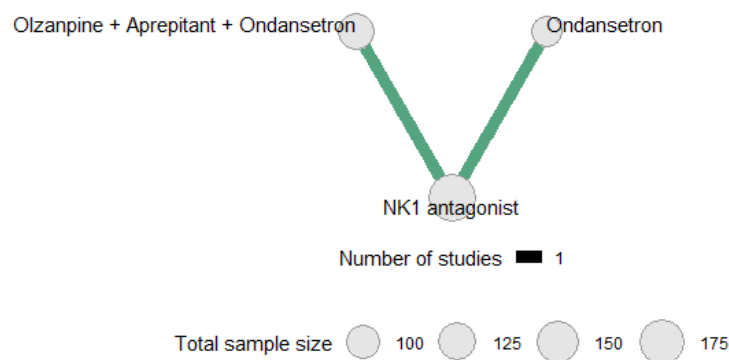


Figure 6-19 Network plot for the IPD network meta-regression, for the outcome of **nausea in the acute phase**.

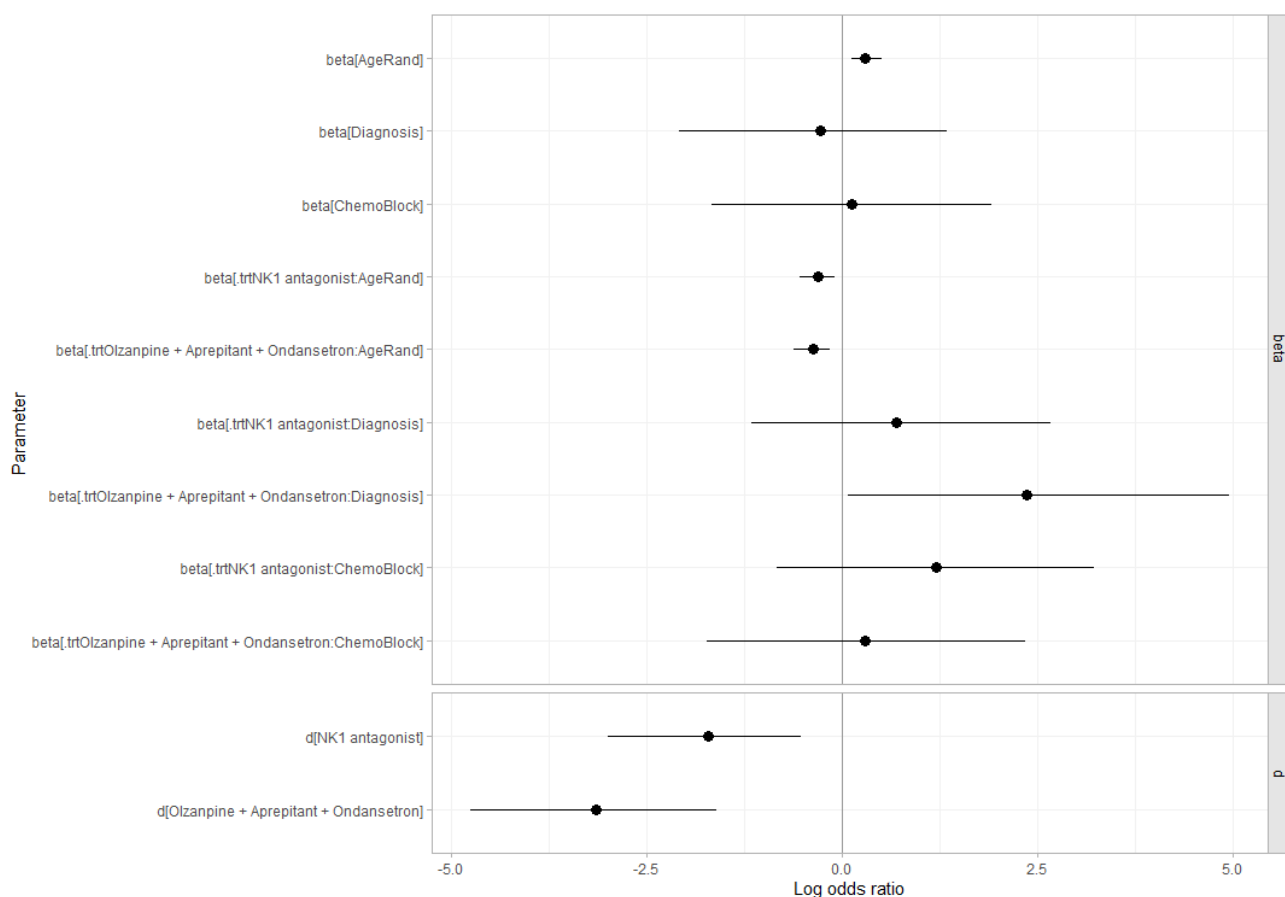


Figure 6-20 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **nausea in the acute phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. ‘AgeRand’- is a continuous covariate for age at randomisation, ‘Diagnosis’ a binary covariate 0- blood cancer, 1- solid tumour, ‘ChemoBlock’ a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.7.1 Prognostic factors

- For every one-year increase in age, the odds of experiencing nausea in the acute phase increase by ~30% (OR 1.349 (1.105 to 1.665)).

6.4.7.2 Interactions with treatment effect

- For every one-year increase in age, the relative effect of adding an NK antagonist OR Olanzapine + aprepitant to ondansetron decreases by ~27 and ~32% respectively, on the log odds ratio scale, equating to an increase in the relative benefit (as numbers below 0 favour the addition of these antiemetics). N.B. Relative benefit only seen after age 8.

- For diagnosis (blood cancer vs solid tumour) there is a large but uncertain interaction with treatment effect, suggesting those with blood cancers derive more benefit from the addition of Olanzapine + Aprepitant, but both derive some benefit.

6.4.7.3 Sensitivity analyses, inclusion of binary covariate for platinum-based chemotherapy

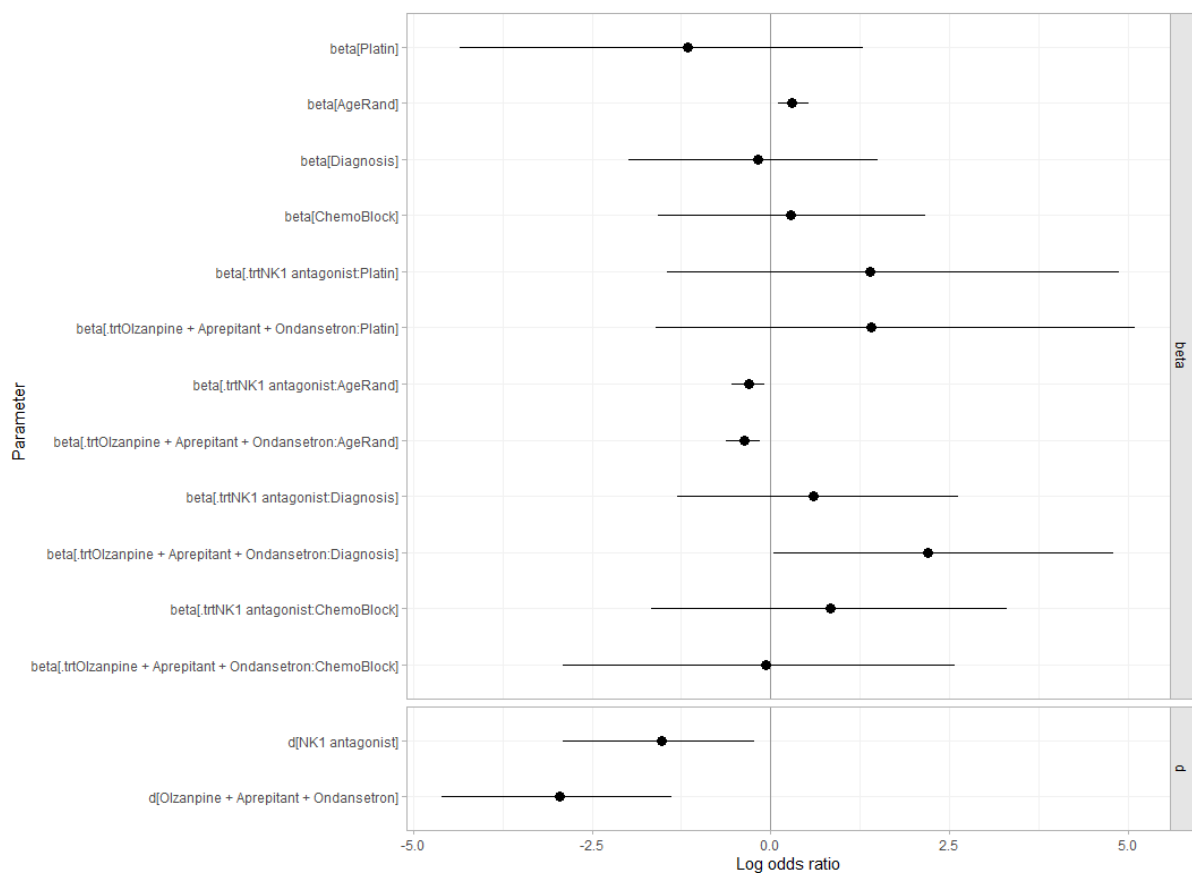


Figure 6-21 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **nausea in the acute phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen, 'Platin' is a binary covariate 0- non-platinum-based chemotherapy, 1-platinum-based chemotherapy.

6.4.8 Nausea in the delayed phase

The final IPD meta-regression model for the outcome ‘nausea in the delayed phase’ included the covariates of age, sex, diagnosis and length of chemotherapy block. Here the fixed effects model was preferred (DIC: fixed effects 391 vs random effects 391). The network plot is the same as for the outcome ‘nausea in the acute phase’ (Figure 6-19).

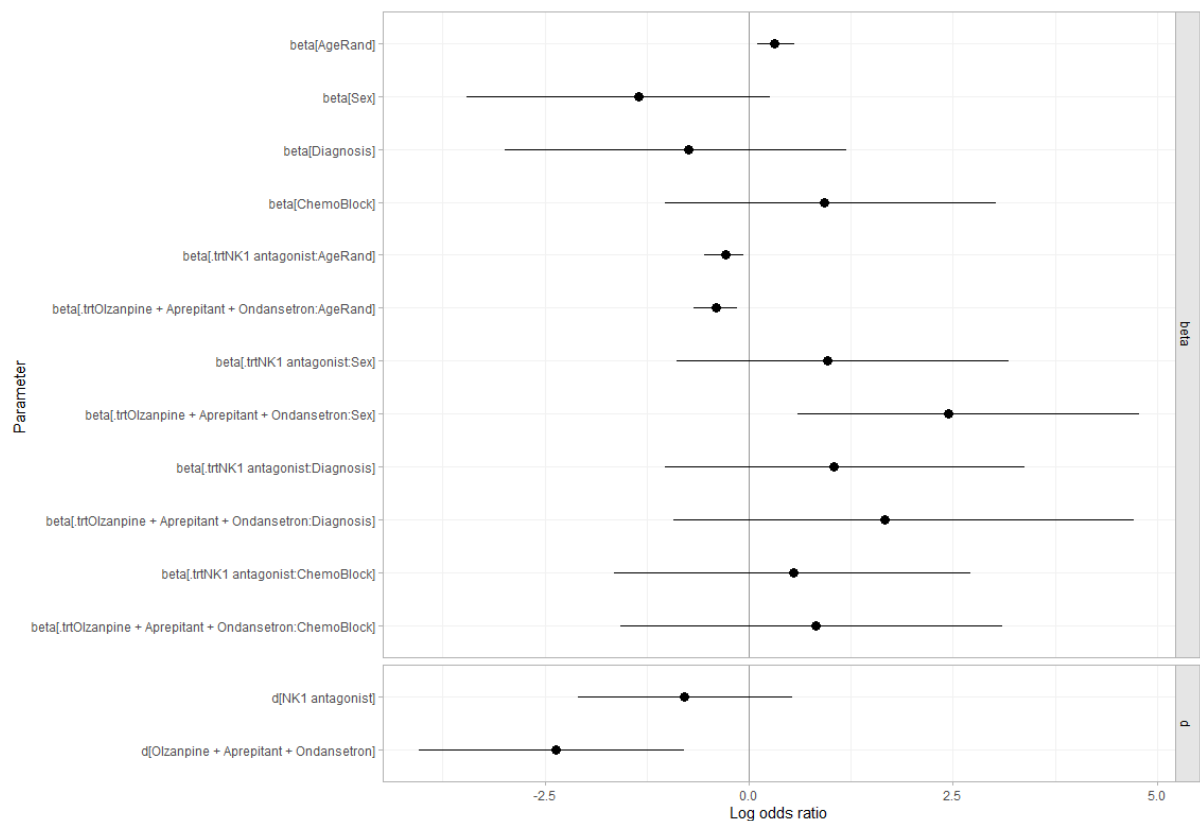


Figure 6-22 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **nausea in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. ‘AgeRand’- is a continuous covariate for age at randomisation, ‘Diagnosis’ a binary covariate 0- blood cancer, 1- solid tumour, ‘Sex’ is a binary covariate 0-male, 1-female, ‘ChemoBlock’ a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.8.1 Prognostic factors

- For every one-year increase in age, the odds of experiencing nausea in the delayed phase increase by ~36% (OR 1.363 (1.116 to 1.751)).

6.4.8.2 Interactions with treatment effect

- For every one-year increase in age, the relative effect of adding an NK antagonist OR olanzapine + aprepitant to ondansetron decreases by ~25 and ~33% respectively, on the log odds ratio scale, equating to an increase in the relative benefit (as numbers below 0 favour the addition of these antiemetics).

Here, the significant benefit of adding an NK1 antagonist is only seen for children aged 13 and over. For the addition of olanzapine and aprepitant, all ages benefit to some degree.

- For biological sex, there is a large but uncertain interaction with treatment effect, suggesting that females derive less benefit from the addition of olanzapine + aprepitant; here, males derive a benefit, but for females, there is no evidence of benefit from the addition of olanzapine + aprepitant.

6.4.8.3 Sensitivity analyses, inclusion of binary covariate for platinum-based chemotherapy

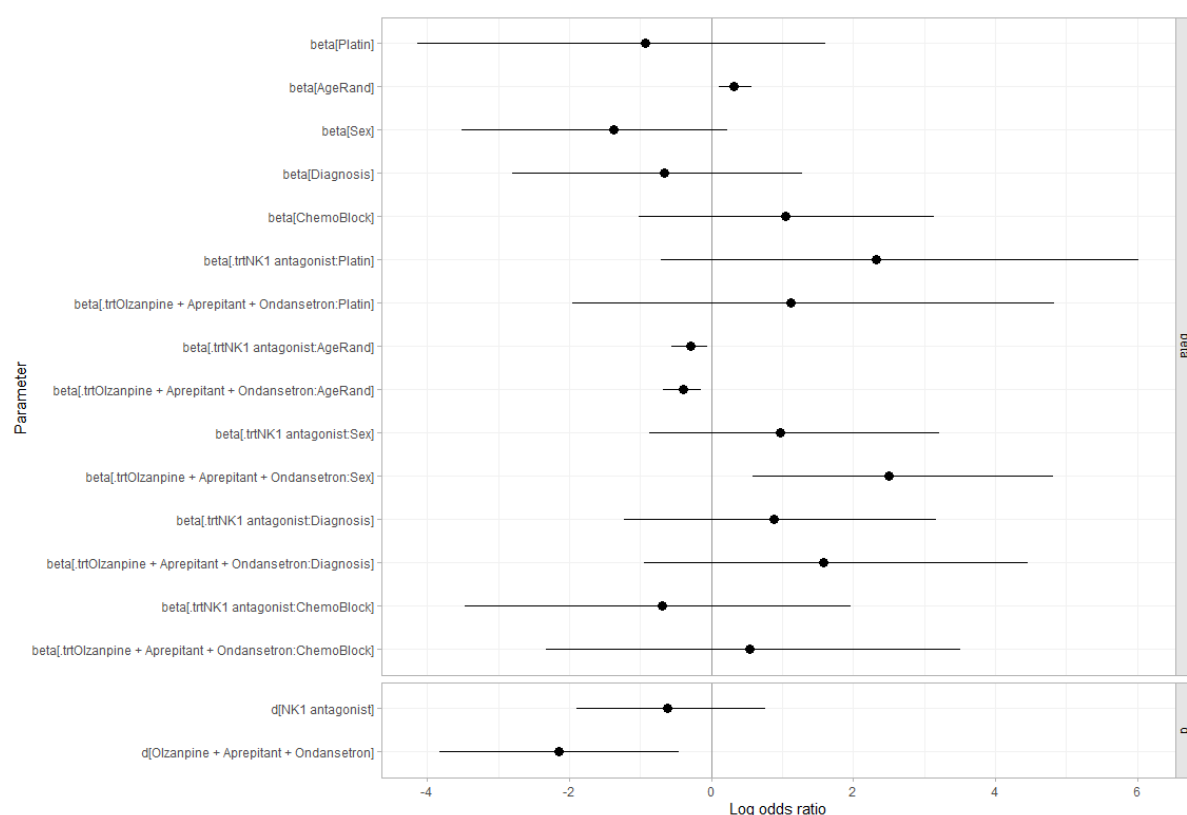


Figure 6-23 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **nausea in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' is a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen, 'Platin' is a binary covariate 0- non-platinum-based chemotherapy, 1- platinum-based chemotherapy.

6.4.9 Nausea in the overall phase

The final IPD meta-regression model for the outcome 'nausea in the overall phase' included age, diagnosis and length of chemotherapy block. Here, the fixed effects model was preferred (DIC: fixed effects 425 vs random effects 424). The network plot is the same as for the outcome 'nausea in the acute phase' (Figure 6-19).

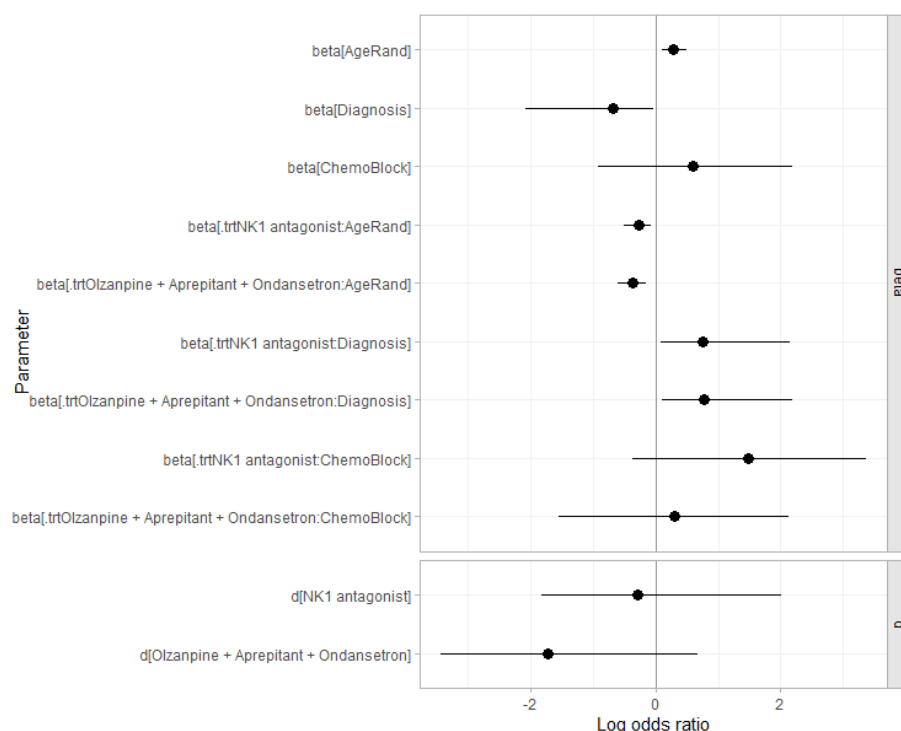


Figure 6-24 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **nausea in the overall phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.9.1 Prognostic factors

- For every one-year increase in age the odds of experiencing nausea in the overall phase increases by ~34% (OR 1.336 (1.105 to 1.649)).
- Those with a solid tumour diagnosis have a ~50% lower odds of experiencing nausea in the overall phase compared to those with a diagnosis of blood cancer (OR 0.507 (0.125 to 0.961)).

6.4.9.2 Interactions with treatment effect

- For every one-year increase in age, the relative effect of adding an NK antagonist OR Olanzapine + aprepitant to ondansetron decreases by ~27 and ~30% respectively on the log

odds ratio scale, equating to an increase in the relative benefit (as number below 0 favour the addition of these antiemetics).

- For diagnosis (blood cancer vs solid tumour) there is a large but uncertain interaction with treatment effect suggesting those with blood cancers derive more benefit from the addition of Olanzapine + Aprepitant but both derive some benefit.

6.4.9.3 Sensitivity analyses, inclusion of binary covariate for platinum-based chemotherapy

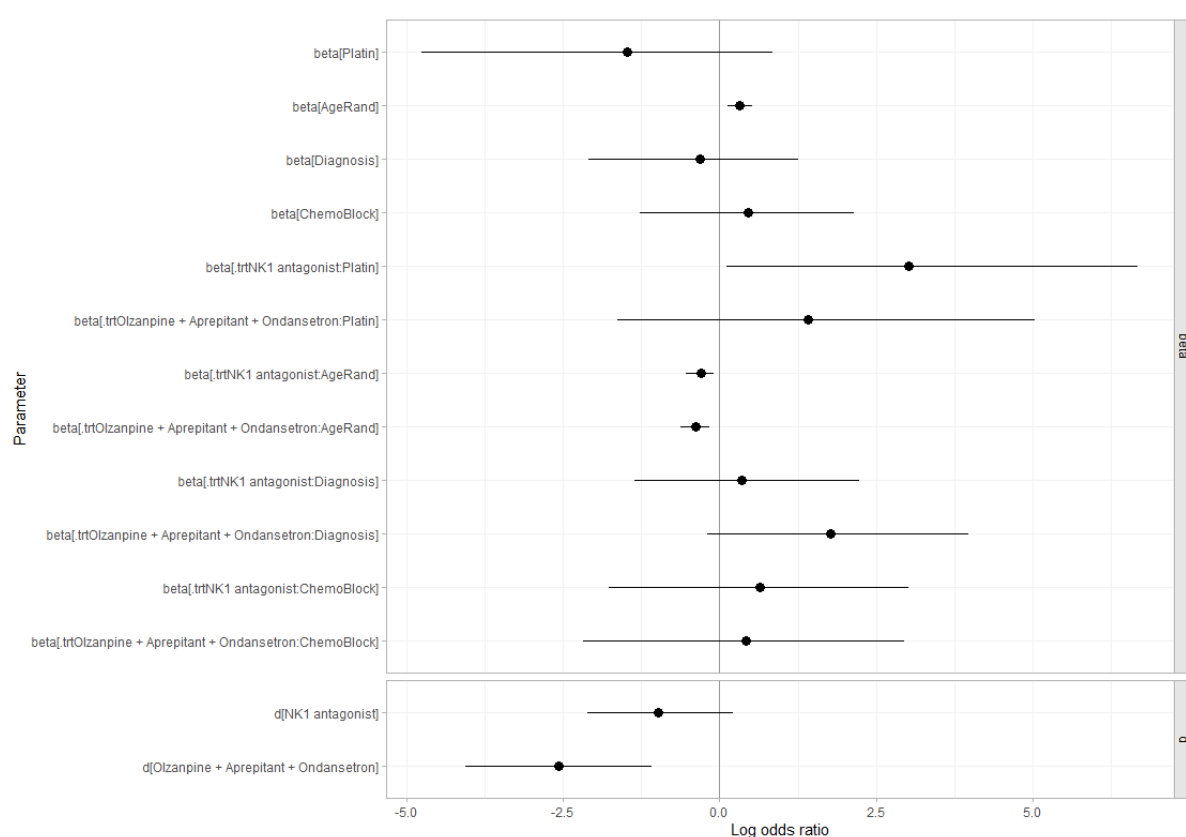


Figure 6-25 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **nausea in the overall phase**. OLAN- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'Sex' is a binary covariate 0-male, 1-female, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.10 Severe nausea in the acute phase (ESAS 7 and over)

For severe nausea in the acute phase, no covariates showed significant effects or interactions in single models; as such, the final model included no covariates and a lack of patients with an ESAS of seven or more meant that estimates of treatment effect were uncertain. The fixed effect model was preferred (DIC: fixed effects 151 vs random effects 151). The network plot is the same as for the outcome ‘nausea in the acute phase’ (Figure 6-19).

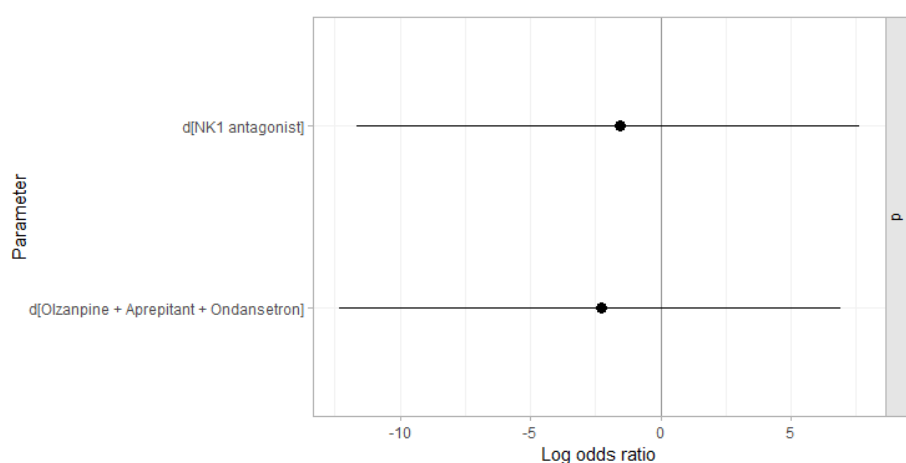


Figure 6-26 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **severe nausea (ESAS 7 and over) in the acute phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1.

6.4.10.1 Sensitivity analyses, inclusion of binary covariate for platinum-based chemotherapy

Platinum-based chemotherapy is not included as it was not identified as a prognostic factor or having an interaction effect with treatment.

6.4.11 Severe nausea in the delayed phase (ESAS 7 and over)

For severe nausea in the delayed phase, the final IPD meta-regression model included the covariate ‘length of chemotherapy block’, and here the fixed effects model was preferred (DIC: fixed effects 97

vs random effects 97). The network plot is the same as for the outcome ‘nausea in the acute phase’ (Figure 6-19).

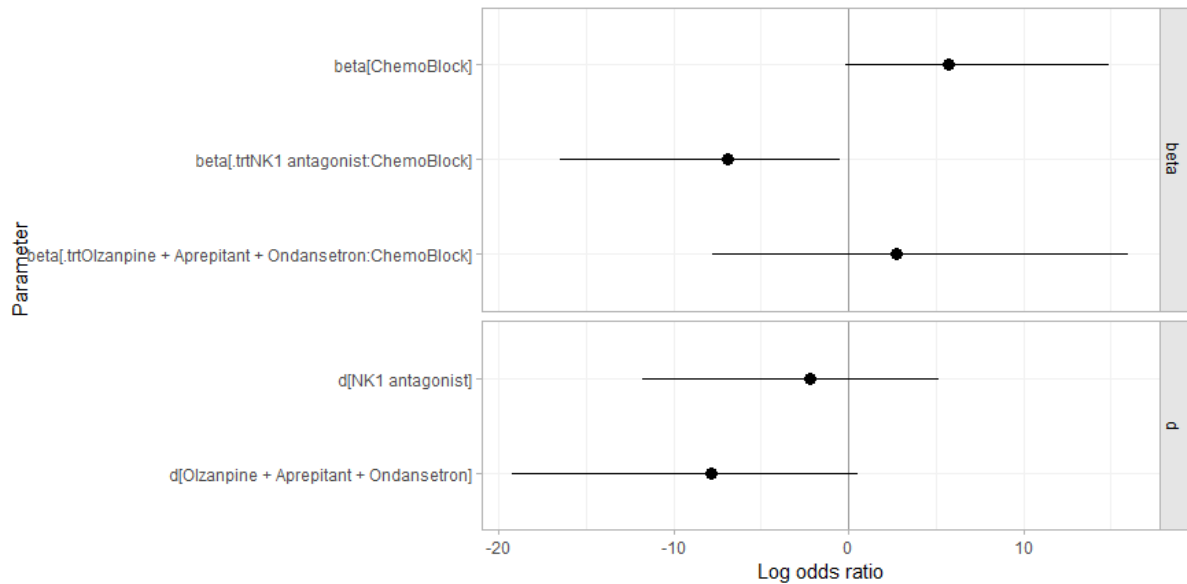


Figure 6-27 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **severe nausea (ESAS 7 and over) in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. ‘ChemoBlock’ is a binary covariate 0- single-day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.11.1 Prognostic factors

- Estimate uncertain and crosses the line of no effect, but tends in the direction of those with multi-day regimens being at increased risk of nausea.

6.4.11.2 Interactions with treatment effect

- Those on a multiday regimen derive more benefit from the addition of an NK1 antagonist to ondansetron, compared to those on a single-day regimen (large and uncertain interaction). Significant effects were seen only for those on multiday regimens.

6.4.11.3 Sensitivity analyses, inclusion of binary covariate for platinum-based chemotherapy

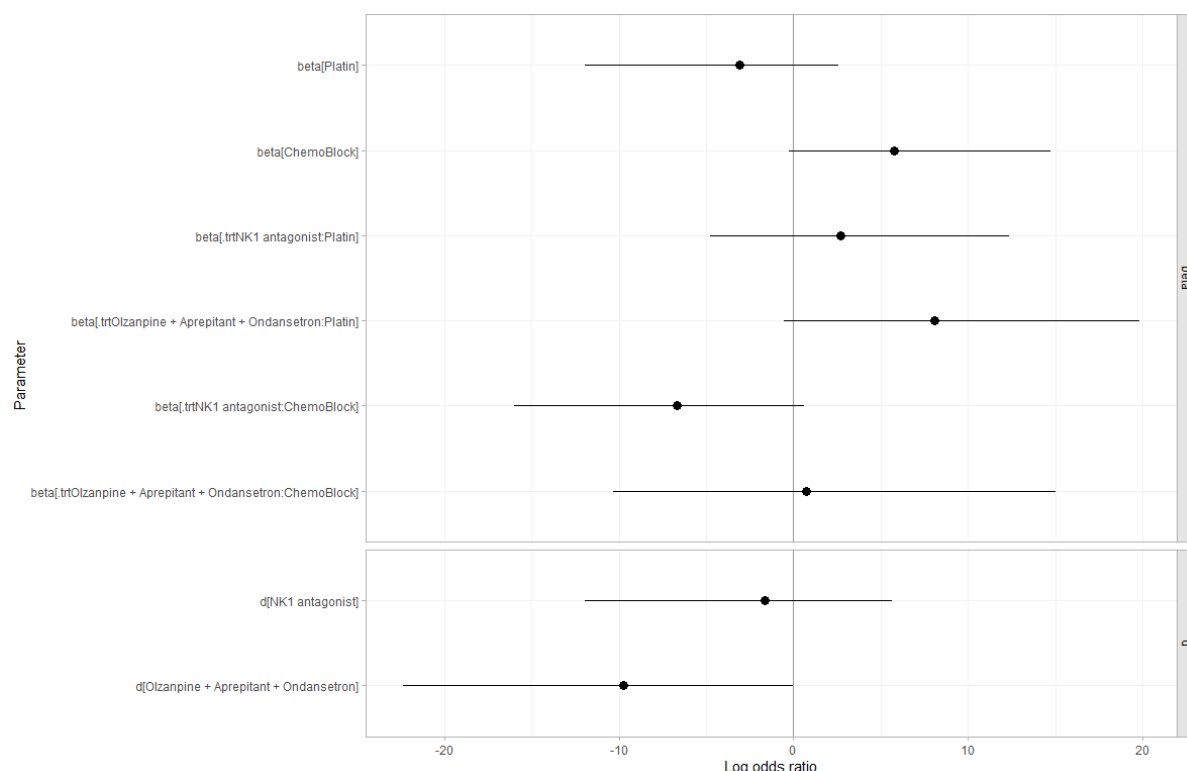


Figure 6-28 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **severe nausea (ESAS 7 and over) in the delayed phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'ChemoBlock' is a binary covariate 0- single-day chemotherapy regimen, 1- multi-day chemotherapy regimen. 'Platin' is a binary covariate 0- non-platinum-based chemotherapy, 1-platinum-based chemotherapy.

6.4.12 Severe nausea in the overall phase (ESAS 7 and over)

For severe nausea in the overall phase, the final IPD meta-regression model included the covariates 'age', 'sex' and 'length of chemotherapy block', and here the fixed effects model was preferred (DIC: fixed effects 25 vs random effects 25). The network plot is the same as for the outcome 'nausea in the acute phase' (Figure 6-19).

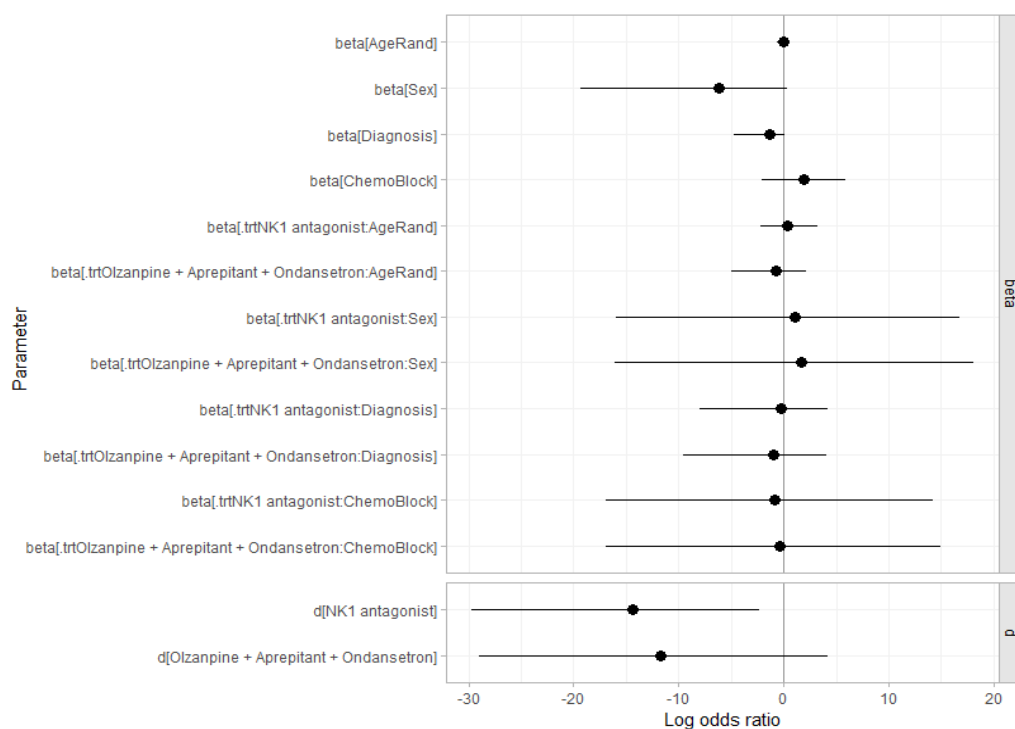


Figure 6-29 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **severe nausea (ESAS 7 and over) in the overall phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.12.1 Prognostic factors

None identified (diagnosis crosses the line of no effect)

6.4.12.2 Interactions with treatment effect

None identified

6.4.12.3 Sensitivity analyses, inclusion of binary covariate for platinum-based chemotherapy

Platinum-based chemotherapy was not included as it was not identified as a prognostic factor or having an interaction effect with treatment.

6.4.13 Constipation in the overall phase

The final IPD meta-regression model for the outcome ‘constipation in the overall phase’ included age, sex, diagnosis and length of chemotherapy block. Here, the fixed effects model was preferred (DIC: fixed effects 592.3 vs random effects 593.6). The network plot is shown in Figure 6-30.

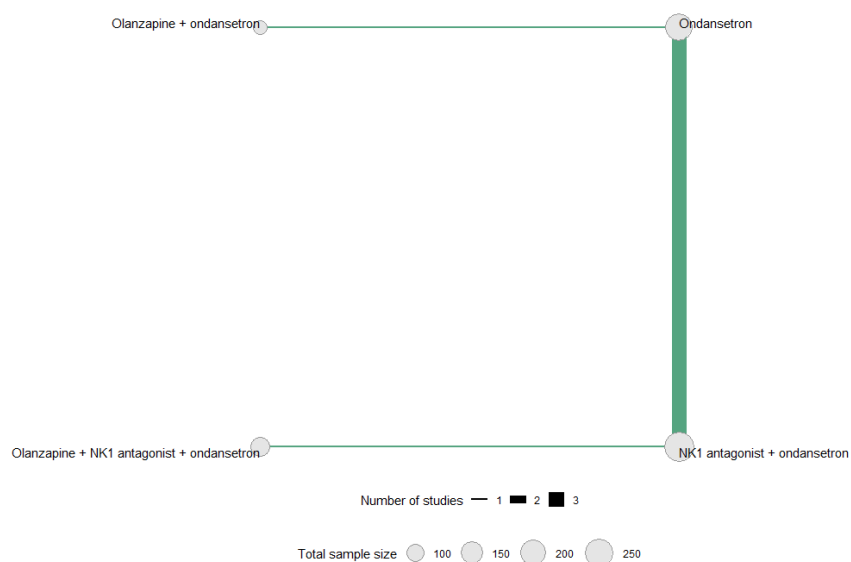


Figure 6-30 Network plot for the IPD network meta-regression, for the outcome of **constipation in the overall phase**.

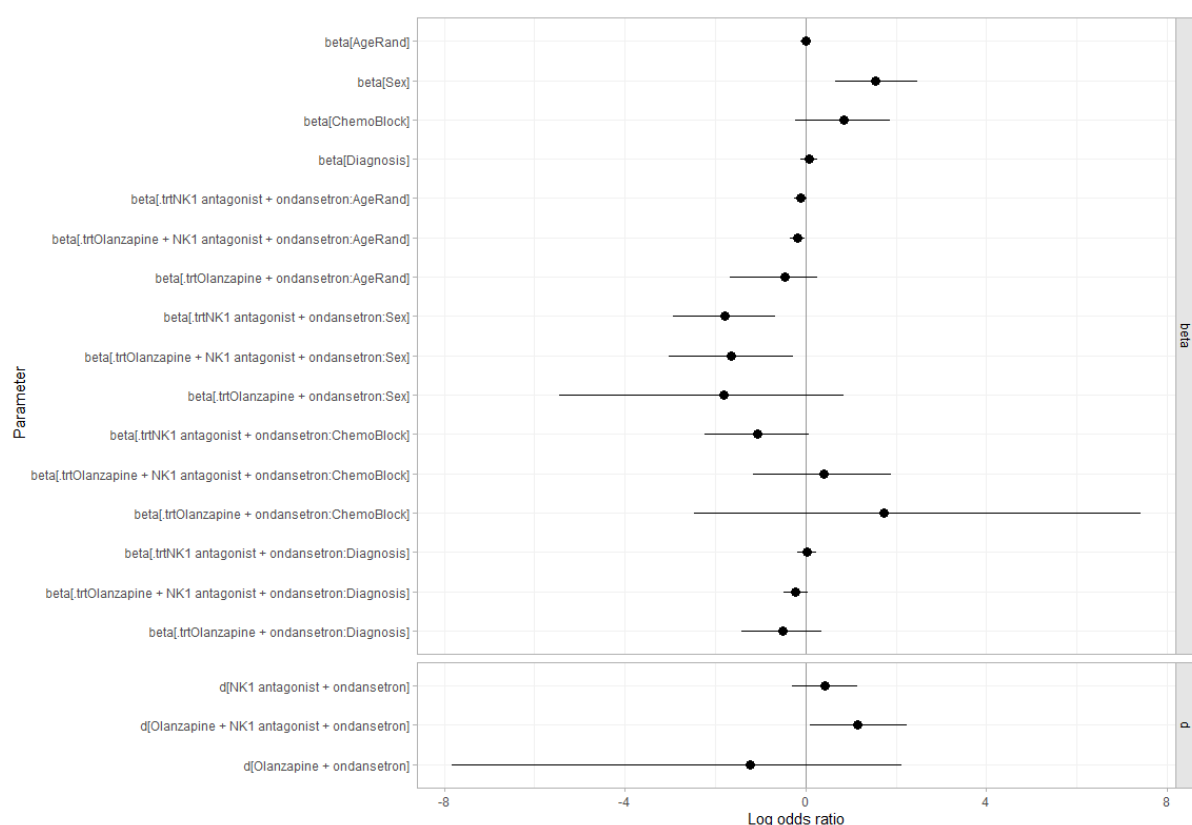


Figure 6-31 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **child population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **constipation in the overall phase**. OLZ- olanzapine, APR- aprepitant, OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, 'Diagnosis' a binary covariate 0- blood cancer, 1- solid tumour, 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.4.13.1 Prognostic factors

Being female may increase the odds of experiencing constipation (OR 4.66 (1.97-11.58), but this estimate is uncertain, so it should therefore not be overinterpreted.

6.4.13.2 Interactions with treatment effect

The increased odds of constipation with multi-antiemetic regimens may be less for older children (OR 0.835 (0.697 to 0.980) - Olanzapine + NK1 antagonists + ondansetron vs ondansetron) and for females (OR 0.170 (0.052 to 0.512) - NK1 antagonists + ondansetron vs ondansetron alone, and OR 0.196 (0.0491 to 0.771) - Olanzapine + NK1 antagonists + ondansetron vs ondansetron). Again, these estimates are uncertain, and so over-interpretation should be avoided.

6.5 Results of interaction analyses by outcome for the adult population

Analysis of adult data was planned for both complete and partial response outcomes; however, partial response outcomes were inconsistently available in the paediatric IPD to produce an estimate for comparison. As such, only complete response outcomes were analysed in adults.

6.5.1 Complete response in the acute phase

The final IPD meta-regression model with adult data for outcome complete response in the acute phase included covariates of age, diagnosis and length of chemotherapy block. Here, the fixed effects model was preferred (DIC: 1215 fixed effects vs DIC:1216 random effects).

N.B. Network plot not exportable from R but is the same as Figure 6-33 without the aggregate data.

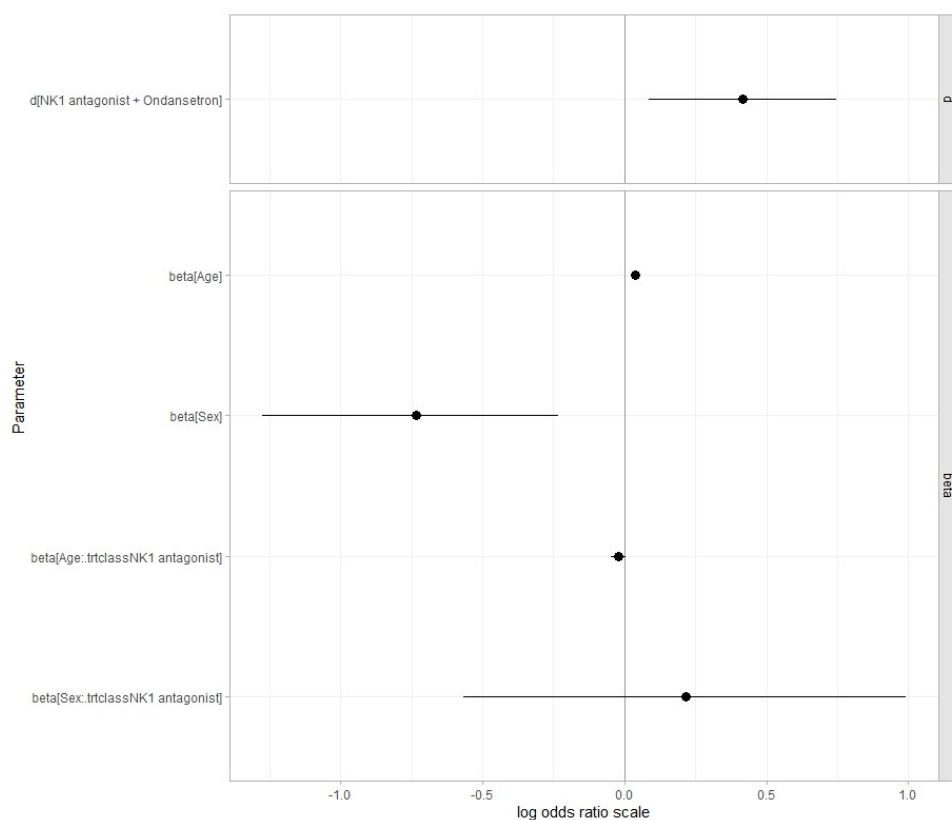


Figure 6-32 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **adult population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **Complete response in the acute phase**. OND- ondansetron, NK1 - Neurokinin 1.

‘AgeRand’- is a continuous covariate for age at randomisation, and ‘Sex’ is a binary covariate 0 - male, 1 - female.

6.5.1.1 IPD meta-regression - Prognostic factors

- Females have ~52% lower odds of achieving a complete response in the acute phase compared to males (OR 0.481 (0.278 to 0.795)).
- For every one-year increase in age, the odds of achieving a complete response in the acute phase increase by ~4% OR 1.041 (1.020 to 1.062).

6.5.1.2 IPD meta-regression - Interactions with treatment effect

- For every one-year increase in age, the relative benefit of adding an NK1 antagonist to ondansetron decreases by ~2% OR 0.980 (0.951 to 1.00).

6.5.1.3 Sensitivity analyses- IPD meta-regression including aggregate data

The final IPD meta-regression model, inclusive of aggregate data, included the covariates of age and sex. Here, the fixed effects model was preferred (DIC: 1237 fixed effects vs 1237 random effects).

As with the main analyses, being female is associated with an increased risk of CINV (i.e. a decrease in the odds of experiencing a complete response) and increasing age is associated with a decreased risk of CINV in the acute phase in adults. Age is also identified as being an effect modifier.

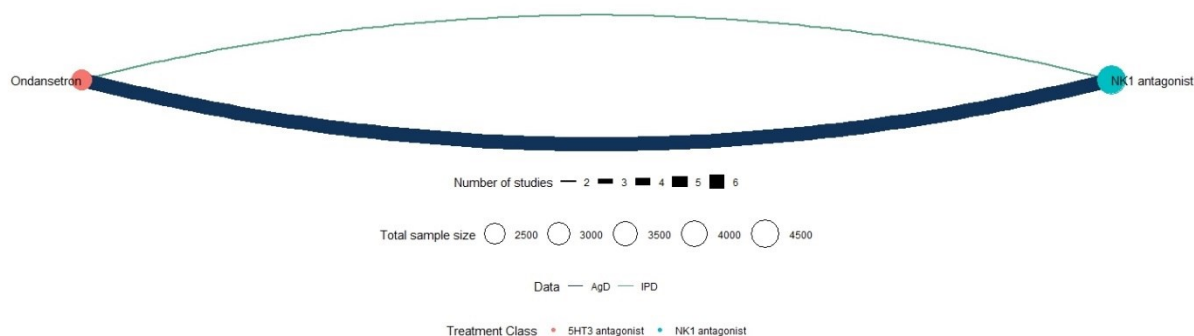


Figure 6-33. Network plot for the IPD network meta-regression, inclusive of aggregate data in adults, for the outcome of complete response in the acute phase.

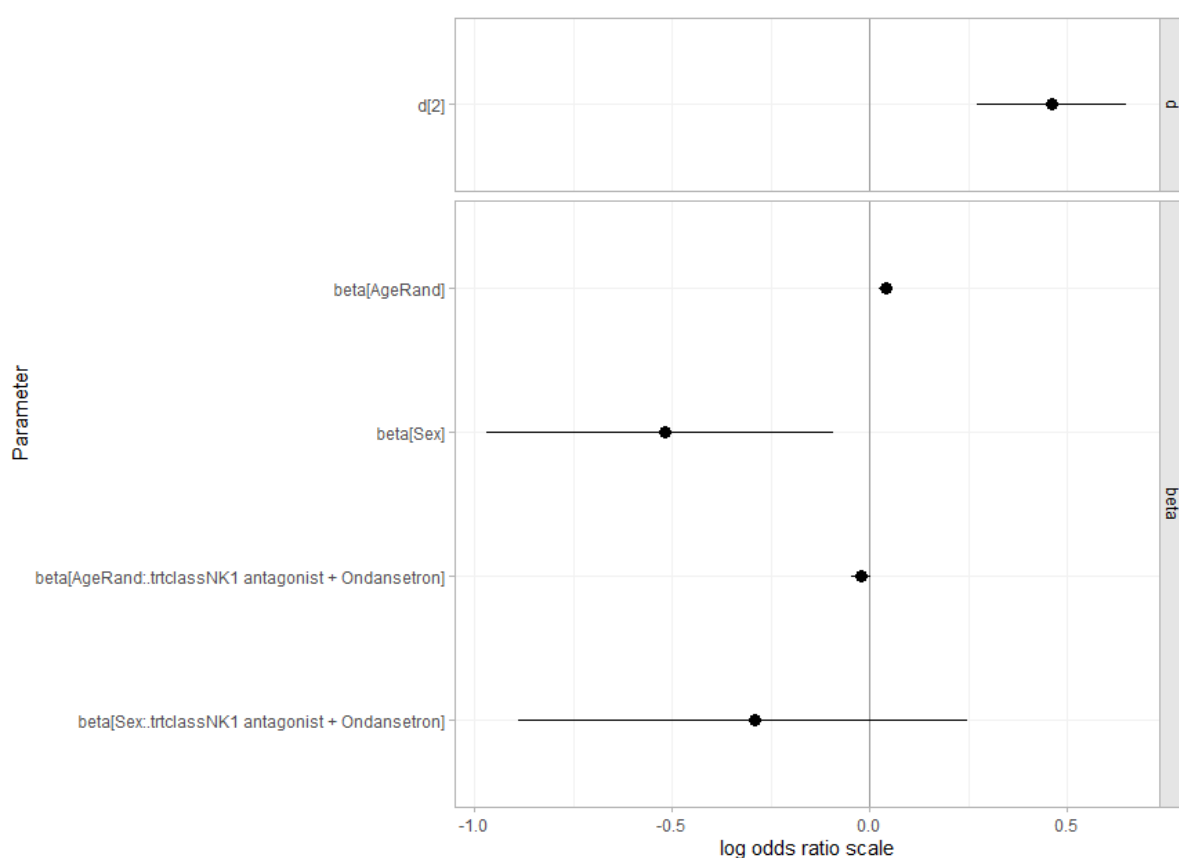


Figure 6-34 Forest plot the IPD network meta-regression inclusive of aggregate data (reference treatment ondansetron) in the **adult population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **Complete response in the acute phase**. OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, and 'Sex' a binary covariate 0- male, 1- female.

6.5.2 Complete response in the delayed phase

The final IPD meta-regression model with adult data for outcome complete response in the delayed phase included covariates of age, diagnosis and length of chemotherapy block. Here the fixed effects model was preferred (DIC: 2157 fixed effects vs DIC: 2158 random effects).

N.B Network plot not exportable from R but is the same as Figure 6-36 without the aggregate data.

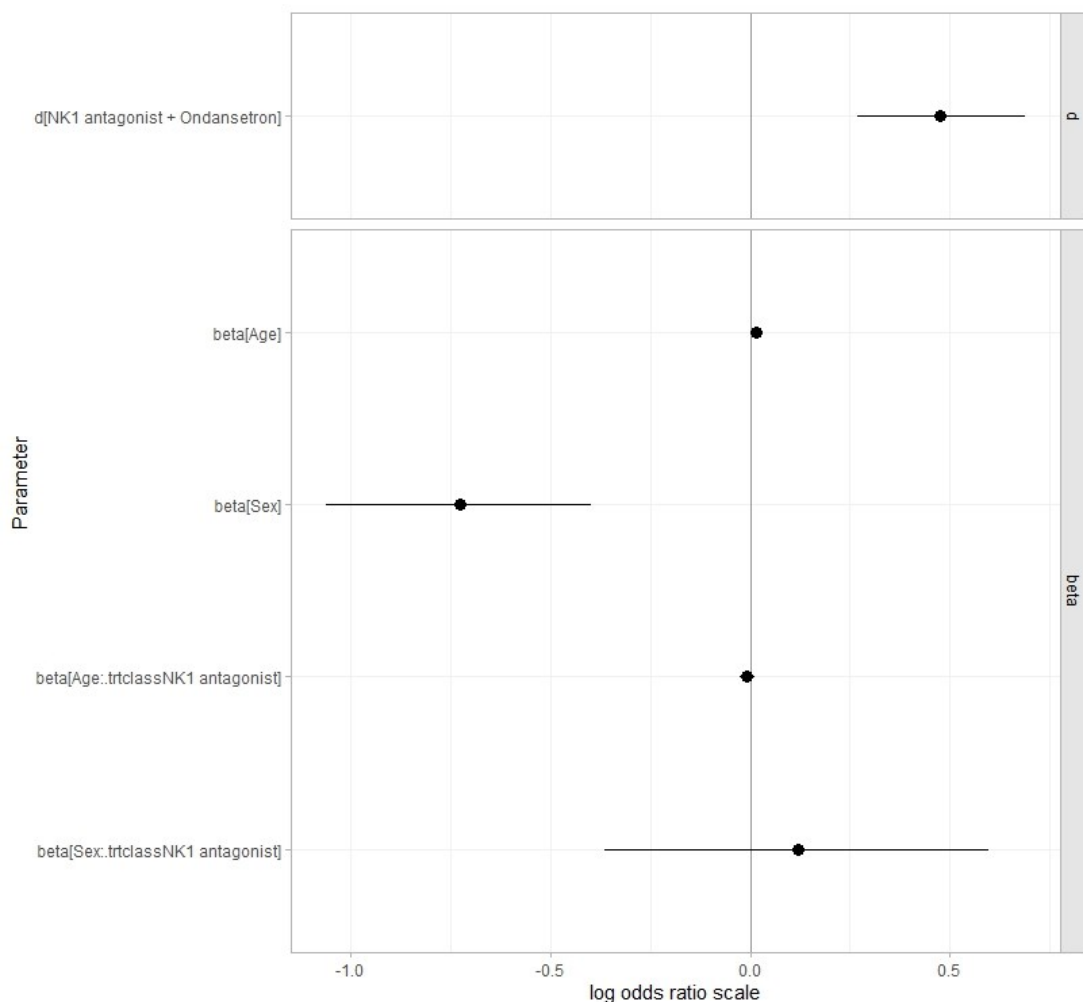


Figure 6-35 Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **adult population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **Complete response in the delayed phase**. OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, and 'Sex' a binary covariate 0 - male, 1 - female.

6.5.2.1 IPD meta-regression - Prognostic factors

- Females have ~52% lower odds of achieving a complete response in the delayed phase compared to males (OR 0.481 (0.346 to 0.670)).
- For every one-year increase in age, the odds of achieving a complete response in the delayed phase increase by ~2% OR 1.020 (1.000 to 1.030).

6.5.2.2 IPD meta-regression - Interactions with treatment effect

- No identified interactions

6.5.2.3 Sensitivity analyses- IPD meta-regression including aggregate data

The final IPD meta-regression model, inclusive of aggregate data, included the covariates of age and sex. Here, the fixed effects model was preferred (DIC: 1283 fixed effects vs 1281 random effects).

As with the main analyses, increasing age and being female are associated with decreased odds of experiencing a complete response in the delayed phase in adults, whilst increasing age increases the odds of experiencing a complete response. Neither covariate was identified as being an effect modifier.

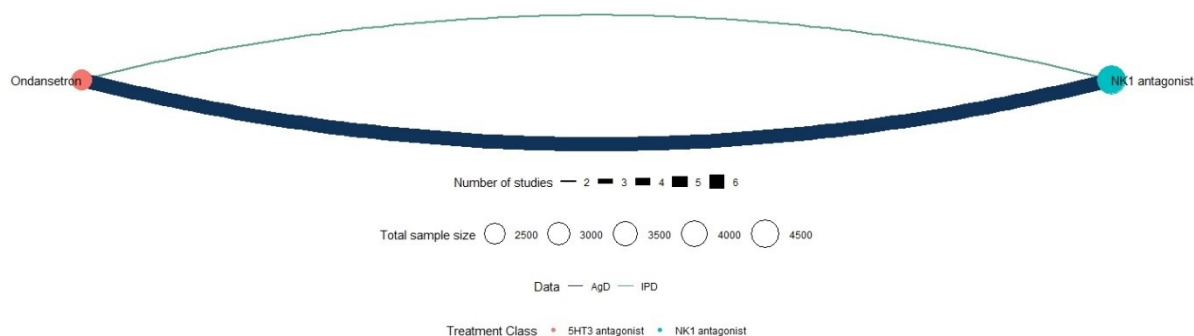


Figure 6-36 Network plot for the IPD network meta-regression, inclusive of aggregate data in adults, for the outcome of complete response in the delayed phase.

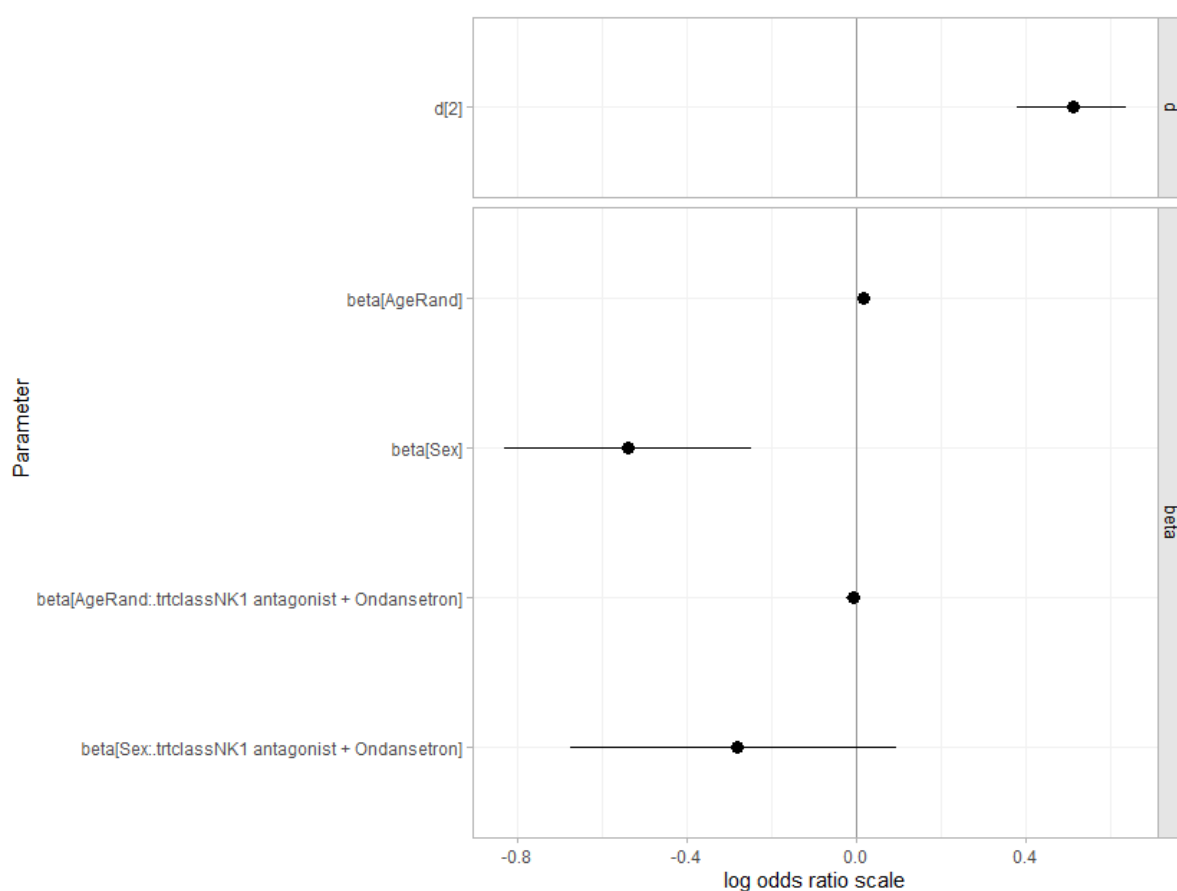


Figure 6-37 Forest plot the IPD network meta-regression inclusive of aggregate data (reference treatment ondansetron) in the **adult population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **Complete response in the delayed phase**. OND- ondansetron,

NK1 - Neurokinin 1. 'AgeRand' - is a continuous covariate for age at randomisation, and 'Sex' a binary covariate 0- male, 1- female.

6.5.3 Complete response in the overall phase

The final IPD meta-regression model with adult data for outcome complete response in the overall phase included covariates of age, diagnosis and length of chemotherapy block. Here, the fixed effects model was preferred (DIC: 2201 fixed effects vs DIC: 2202 random effects).

N.B. Network plot not exportable from R, but is the same as Figure 6-39 without the aggregate data.

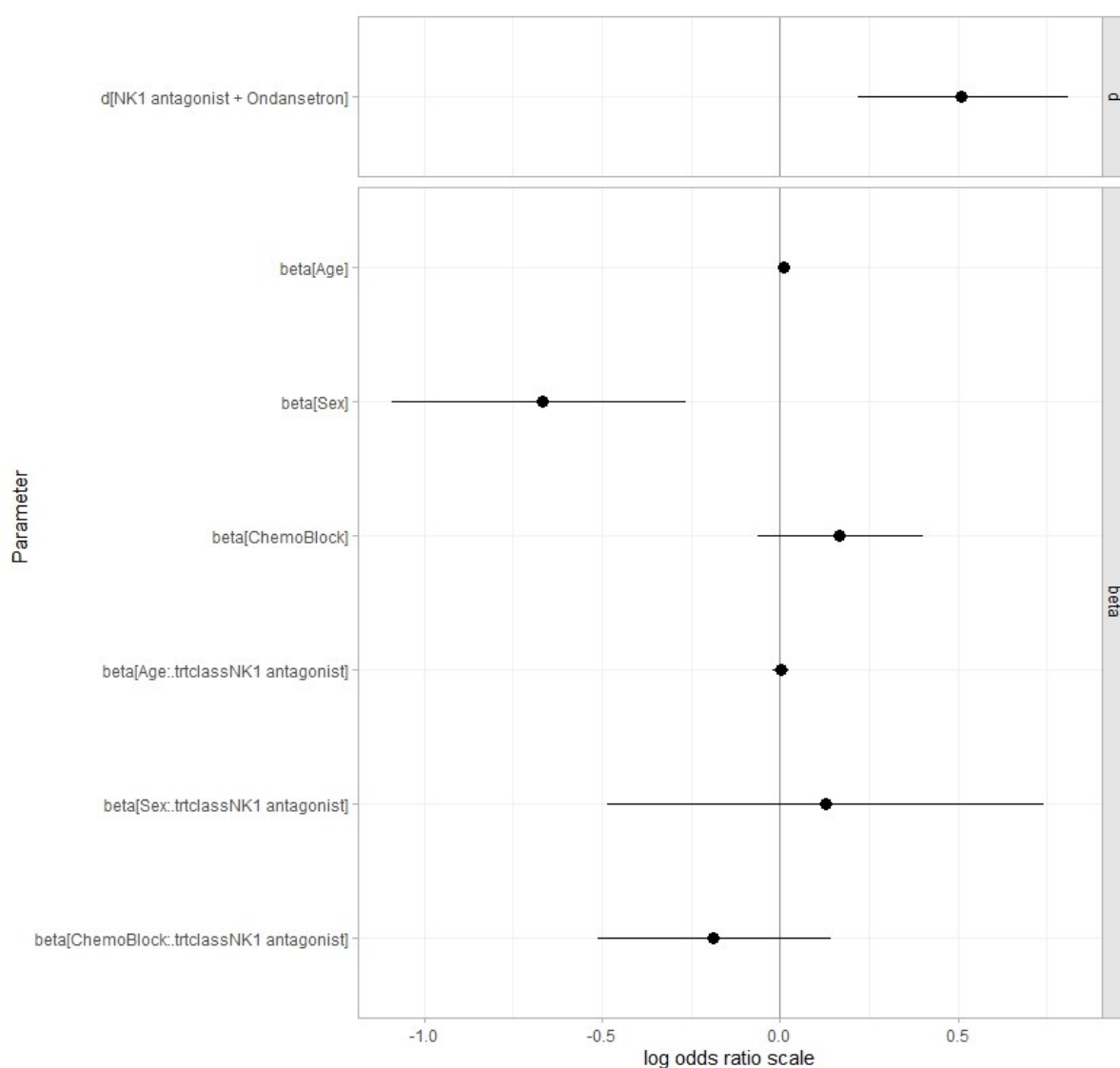


Figure 6-38. Forest plot the IPD network meta-regression (reference treatment ondansetron) in the **adult population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **Complete response in the overall phase**. OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, and 'Sex' a binary covariate 0- male, 1- female and 'ChemoBlock' a binary covariate 0- single day chemotherapy regimen, 1- multi-day chemotherapy regimen.

6.5.3.1 IPD meta-regression - Prognostic factors

- Females have ~55% lower odds of achieving a complete response in the overall phase compared to males (OR 0.449 (0.326 to 0.618)).
- For every one-year increase in age, the odds of achieving a complete response in the overall phase increase by ~2% OR 1.02 (1.01 to 1.030).

6.5.3.2 IPD meta-regression - Interactions with treatment effect

- No identified interactions

6.5.3.3 Sensitivity analyses- IPD meta-regression including aggregate data

The final IPD meta-regression model, inclusive of aggregate data, included the covariates of age and sex. Here, the fixed effects model was preferred (DIC: 1224 fixed effects vs 1224 random effects).

As with the main analyses, increasing age is associated with an increase in the odds of experiencing a complete response, and being female is associated with a decrease in the odds of experiencing a complete response. Neither covariate was identified as being an effect modifier.

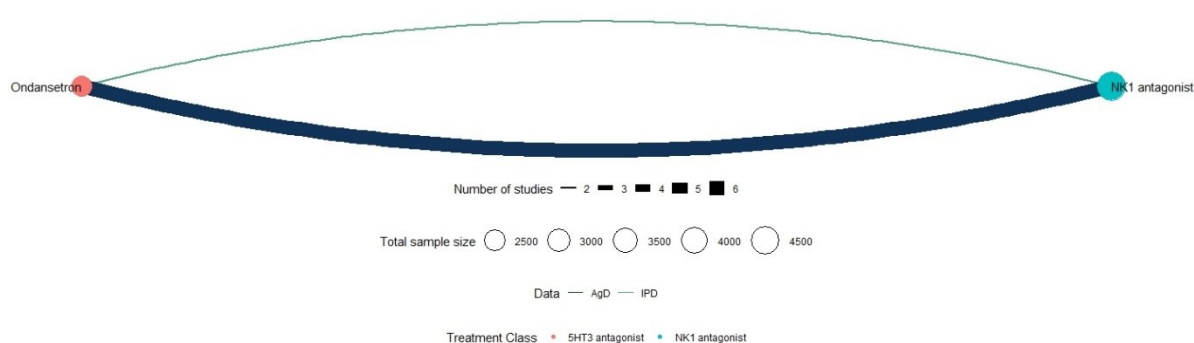


Figure 6-39 Network plot for the IPD network meta-regression, inclusive of aggregate data in adults, for the outcome of complete response in the overall phase.

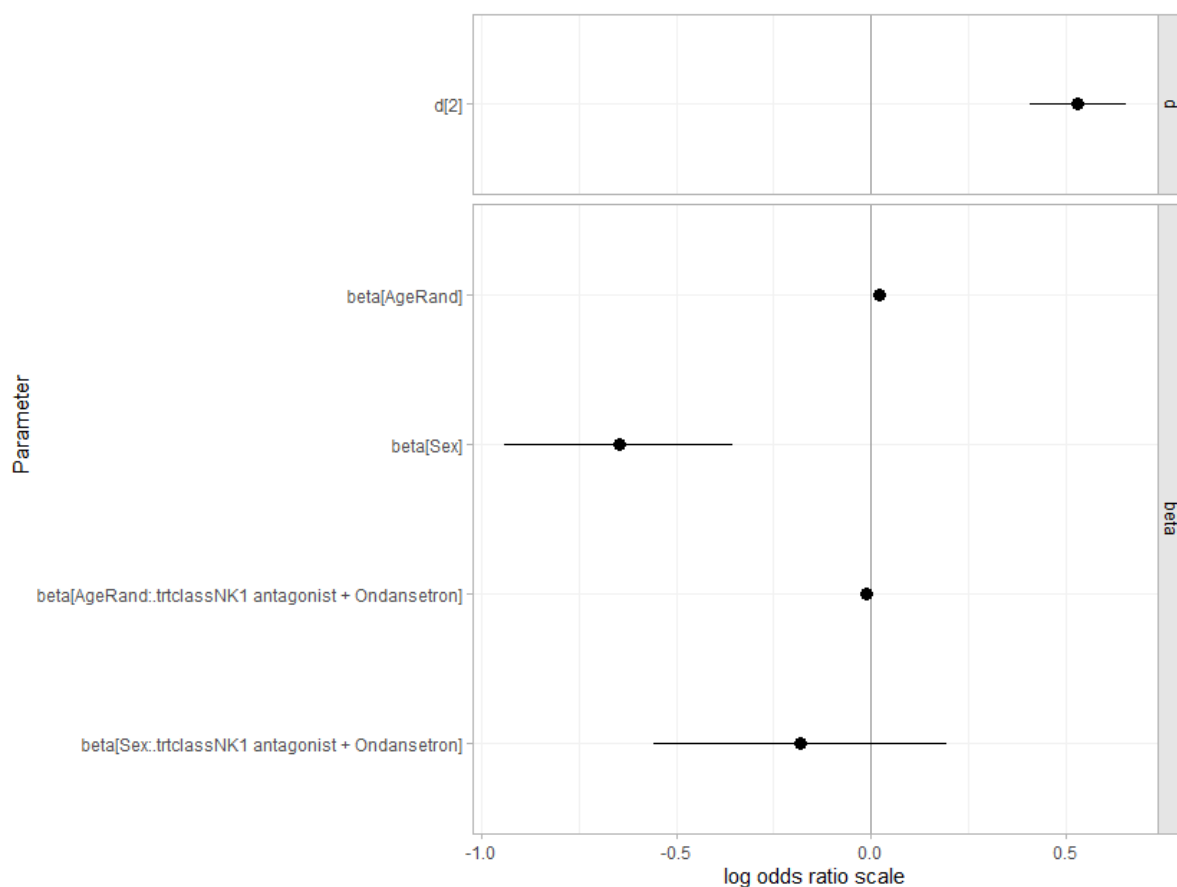


Figure 6-40 Forest plot the IPD network meta-regression inclusive of aggregate data (reference treatment ondansetron) in the **adult population**, indicating the beta and interaction coefficients for each covariate and the adjusted treatment effect for the outcome of **Complete response in the overall phase**. OND- ondansetron, NK1 - Neurokinin 1. 'AgeRand'- is a continuous covariate for age at randomisation, and 'Sex' is a binary covariate 0 - male, 1 - female and 'ChemoBlock' is a binary covariate 0 - single day chemotherapy regimen, 1 - multi-day chemotherapy regimen.

6.6 The co-occurrence of benefit and adverse effect in children.

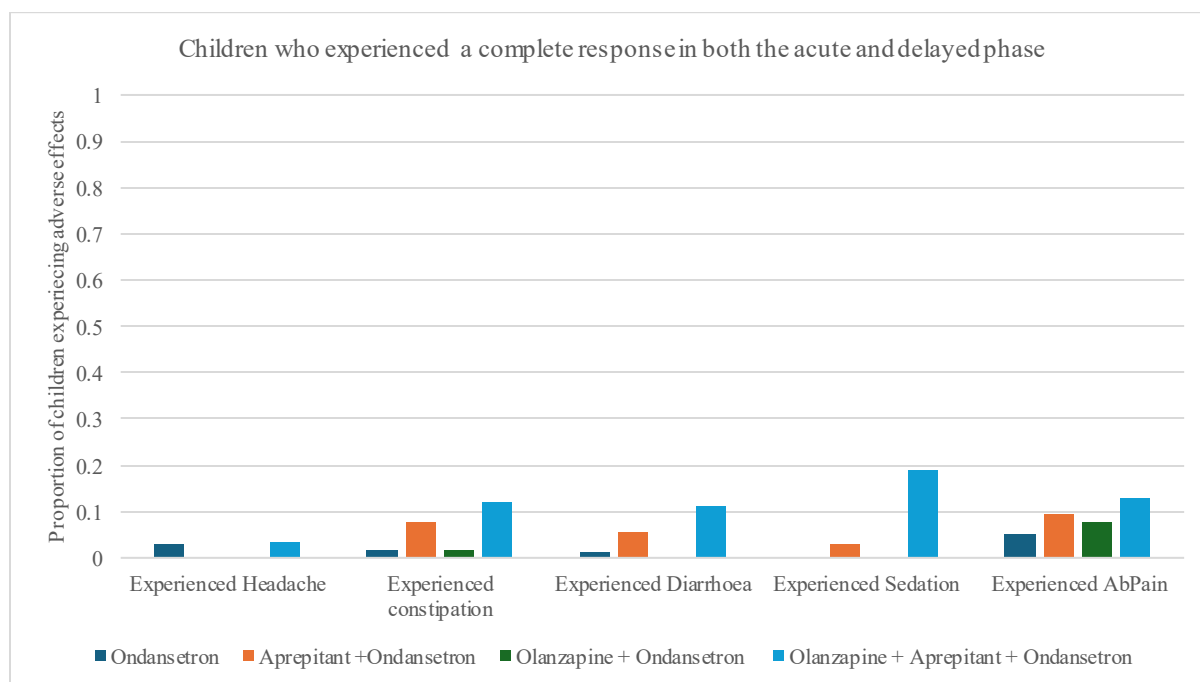


Figure 6-41 Proportion of children who experienced benefits (complete response in the acute and delayed phase) and adverse effects (Abpain- abdominal pain).

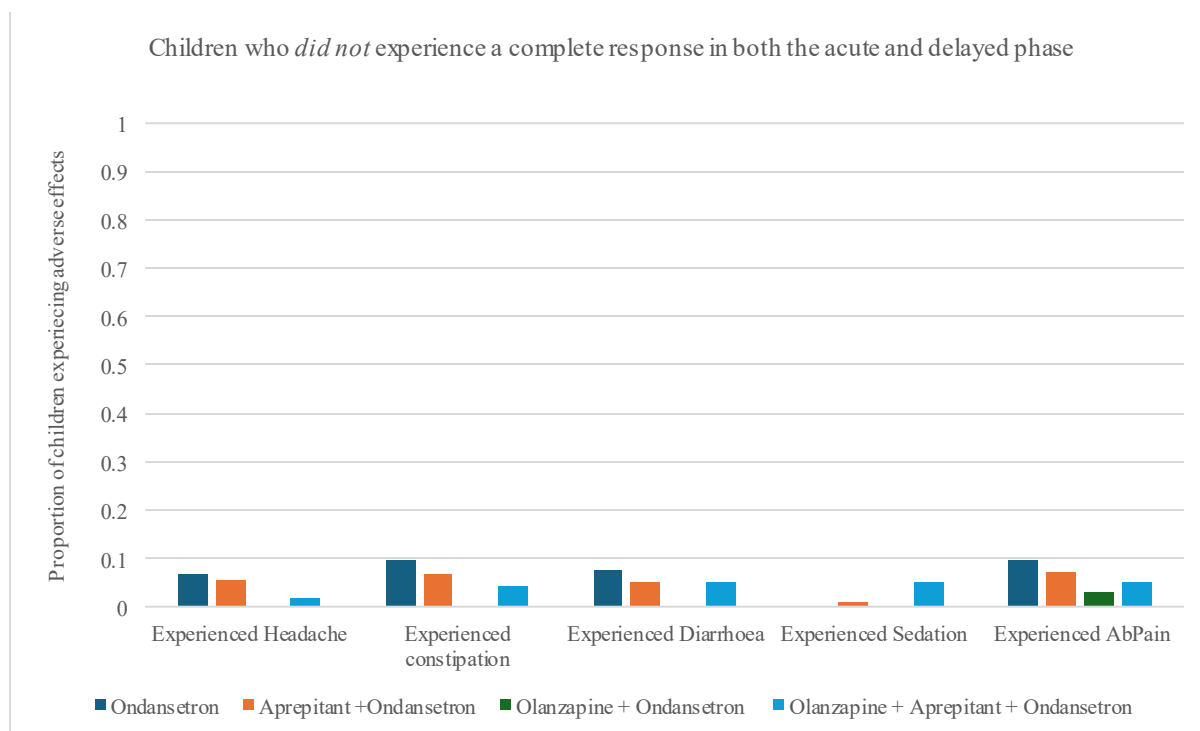


Figure 6-42 Proportion of children who did not experience benefits (complete response in the acute and delayed phase) and adverse effects (Abpain- abdominal pain).

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