A Bayesian response-adaptive dose finding and comparative effectiveness trial

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Abstract

Background/Aims: Combinations of treatments that have already received regulatory approval can offer additional benefit over the treatments individually. However, trials of these combinations are lower priority than the development of novel therapies, which can restrict funding, timelines and patient availability. Thus, this paper develops a novel trial design to facilitate the evaluation of novel combination therapies. In general, this design combines elements of phase II and phase III trials to reduce the administrative burden of undertaking these trials, whilst also maintaining a feasible sample size.

Methods: This trial design uses response adaptive randomisation to increase the level of information collected about successful novel drug combinations and Bayesian dose-response modelling to undertake a comparative-effectiveness analysis for the most successful dose combination against a relevant comparator. We used simulation methods to evaluate the probability of selecting the correct optimal dose combination and the frequentist and Bayesian operating characteristics of this design for a trial in pain management and sedation in pediatric emergency departments. We also compared the design to a standard frequentist trial with equal randomisation across the relevant comparator and all considered dose combinations.

Results: With 410 participants and 5 interim updates of the randomisation ratio, we have an 83% chance of selecting the correct optimal treatment. Based on this adaptive randomisation procedure, the comparative effectiveness analysis has a the type I error of the trial of less than 5% and a power greater than 94%, for expected values of effectiveness for the combination therapy. The trial offers an increase in power for all considered scenarios, compared to a trial with equal randomisation and the predictive power of the trial is over 90%.

Conclusions: By simultaneously determining the optimal dose and collecting data on the relative effectiveness of an intervention, we can minimise administrative burden and recruitment time for a trial. This will minimise the time required to get effective, safe combination therapies to patients quickly. Furthermore, the proposed trial has high potential to meet the dual study objectives within a feasible level of recruitment.

Keywords
Response adaptive trial, Non-inferiority trial, Bayesian Analysis, Trial Design, Clinical Trial

Introduction

Investigator-initiated trials, where clinician investigators undertake their own trials,4 are key to expanding the use of therapies that have already received regulatory approval.2 One key expansion is the development of therapies that combine two or more currently available interventions to improve outcomes compared to either treatment alone.3, 5 To develop these novel combination therapies, we must determine the optimal combination and evaluate the comparative effectiveness of this optimal therapy against the current standard of care.

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In the standard drug development process, these two aims would require two trials; a phase II trial to determine the optimal dose combination and a phase III trial to evaluate the comparative effectiveness. However, initiating a trial is a time and resource intensive process, especially when different funding sources must be sought separately for each phase. Thus, a trial design that incorporates both these elements, whilst maintaining a reasonable level of patient recruitment, would improve the efficiency of the trial process, especially for investigator-initiated trials.

Seamless phase II/III trials that use a single study protocol whilst moving between the investigative Phase II and the confirmatory Phase III are the most common type of adaptive trials. These trials typically combine two distinct phases, where successful treatments are ‘taken forward’ from Phase II to Phase III. In this setting, Kimani et al. developed a seamless design that incorporated dose selection based on safety and efficacy. However, in this study we aim to identify the optimal dose combination whilst also determining its comparative effectiveness to a standard of care. Thus, we develop a novel design to assess combination therapies whilst also avoiding a formal delineation of the two study phases. This maximises the time available to assess the relative efficacy of the different dose combinations.

To increase the expected allocation of patients to the optimal dose combination, we use Bayesian response adaptive randomisation to incrementally randomise more patients to the dose combination with the highest chance of being optimal. While adaptive randomisation has typically been found to have limited impact on the trial operating characteristics, we found that adaptive randomisation has higher power than an equal randomisation scheme. Typically, the analysis of an adaptive trial requires adjustments to ensure valid construction of confidence intervals and p-values. However, we avoid this requirement by proposing all analyses within a Bayesian framework.

This paper presents our novel trial design that simultaneously determines the optimal dose combination and its comparative effectiveness to a standard comparator. We undertake simulations to determine decision thresholds for the trial adaptions and comparative Bayesian analyses. All thresholds are chosen to ensure the trial has good frequentist operating characteristics and a high chance of detecting the true optimal treatment. We introduce a novel framework that leads to an inconclusive trial outcome to suggest additional data should be collected. We compare our design to a standard frequentist design with equal randomisation across the different dose combinations and demonstrate superior operating characteristics for our trial. Finally, we demonstrate that this design has high Bayesian predictive power.

The development of this trial design was motivated by an investigator-initiated trial looking at treatments for procedural sedation within a paediatric emergency department and is feasible conditional on the time and resource constraints of the trial.

The Ketodex Trial

Procedural sedation and analgesia (PSA) is commonly used to facilitate the realignment of a fractured or dislocated limb without surgery in children (known as a closed reduction). One drug often used to provide PSA is Intravenous (IV) Ketamine. However, IV insertion is stressful and painful and, thus, an alternative administration method would be preferred, e.g. intranasal (IN) administration. There is limited evidence that a combination of ketamine and dexmedetomidine (ketodex) given intranasally may offer adequate sedation. This combination has not be trialled in patients undergoing a closed reduction and so the Ketodex trial aims to:

(i) determine a suitable combination of IN ketodex and
(ii) compare the efficacy of IN ketodex (novel combination therapy) to IV ketamine (standard of care).

As IN delivery of sedative agents is preferable to inserting an IV, the Ketodex trial aims to determine whether IN ketodex is non-inferior to IV ketamine. The Ketodex trial has a binary primary outcome where a "success" is defined as a patient who is adequately sedated for the duration of the closed reduction procedure. As this outcome is available within 24 hours of trial enrolment, it will be used to assess both the efficacy of the different ketodex combinations and the relative effectiveness of IN ketodex to IV ketamine. Clinical expertise determined that the ketodex trial will consider three dose combinations for IN ketodex:

1. Ketamine dosed at 2 mg/kg in combination with Dexmedetomidine dosed at 4 mcg/kg (2-4 ketodex)
2. Ketamine dosed at 3 mg/kg in combination with Dexmedetomidine dosed at 3 mcg/kg (3-3 ketodex)

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3. Ketamine dosed at 4 mg/kg in combination with Dexmedetomidine dosed at 2 mcg/kg (4-2 ketodex)

Methods

Figure 1 is a graphical representation of our novel trial design, where the design and analysis consists of three key phases, adaptive randomisation, dose response modelling and a comparative effectiveness analysis.

Overall Sample Size

Before determining the full trial design, we selected the overall sample size based on pragmatic concerns and the Average Length Criterion (ALC) for Bayesian sample size estimation.\(^\text{24,25}\) In general, ALC sets the trial sample size by determining the smallest sample size required to ensure that the posterior credible interval has an average length below some fixed constant \(\xi\), to be specified. This design controls the average length of the high-density posterior credible interval of the difference in effectiveness between the standard of care and the novel combination. In addition to determining the overall sample size, we also use the ALC to determine the randomisation ratio between the novel combinations and the standard of care by selecting the randomisation ratio that respects to ALC. For the overall sample size calculation, we do not consider any adaptive elements. However, our simulations ensure that high power and well-controlled type I error conditional on this sample size and the proposed adaptive design.

Response-Adaptive Randomisation

Throughout the trial, we propose response-adaptive randomisation to increase the number of participants receiving effective dose combinations.\(^\text{12}\) To ensure enough data for the comparative effectiveness analysis, we fix the proportion of patients receiving the standard of care and consider adaptive randomisation for dose combinations. This requires a two-stage randomisation procedure. Initially, \(R_0\) is the proportion of participants randomised to receive the standard of care and \(R_1 = 1 - R_0\) is the proportion of participants randomised to receive the comparator. Following this, participants are randomised to receive a specific dose combination in a randomisation ratio that is updated at each interim analysis (first panel in Figure 1). To maintain blinding in the Ketodex trial, all participants are randomised to a dose combination, even if they are receiving the standard of care and the dose combination will be between two placebo agents.

Formally, the second randomisation step sets the randomisation ratio \(r_{i,j}\) across the different dose combinations, \(i = 1, 2, 3\), at each trial phase \(j = 1, \ldots, J\), where \(J\) is number trial phases (6 in Figure 1). In general, we set \(r_{i,j}\) equal to the probability that dose combination \(i\) is the optimal dose combination based on the evidence gathered in all completed trial periods:

\[
r_{i,j} = \text{Prob}(p_i = \max_i p_i)
\]

where \(p_i\) is the probability of success for the dose combination \(i, i = 1, 2, 3\). The posterior distribution of \(p_i\) is obtained conditional on the data collected in trial periods 1 to \(j\).

Initially, we use the same prior distribution for \(p_i, i = 1, \ldots, 3\) so \(r_{i,1} = \frac{1}{3}\), i.e., an equal number of participants is randomised to each dose combination. To avoid randomising a small number of participants to a single arm, we use simulations to determine a value \(\gamma\) such that we set \(r_{i,j} = 0\) when \(r_{i,j} \leq \gamma\). In these settings, we will adjust the values of \(r_{i,j}\) so \(\sum_i r_{i,j} = 1\). Note that all trial data, irrespective of whether \(r_i \leq \gamma\), will be included in the final analysis and a dose combination can be reinstated in the trial randomisation scheme even if it was excluded in a previous trial phase (see Figure 1 trial periods 4 and 5).

Finally, the practicalities of the Ketodex trial mean that the second step randomisation is undertaken without knowledge of the treatment group assignment from the first randomisation. Thus, within each trial period, the number of participants receiving each active dose combination cannot be controlled and, assuming that the number of participants to be enrolled in trial period \(j\) is \(N_j\), the number of participants randomised to each active dose combination \(i\) will be a random variable

\[
M_{i,j} \sim \text{Binomial}(N_j r_{i,j}, R_1).
\]

Dose Response Modelling

To ensure maximal use of the collected data, the primary effectiveness analysis will used a dose response model to estimate the probability of success \(p_i\) for each dose combination \(i = 1, 2, 3\).\(^\text{11}\) Based on expert opinion, the Ketodex trial uses a logistic dose response model, with \(X_i\) the number of successfully sedated participants among the \(N_i = \sum_j M_{i,j}\) participants who receive dose \(i\):

\[
X_i \sim \text{Binomial}(N_i, p_i),
\]

with

\[
p_i = \beta_0 + \beta_1 \log(A_i) + \beta_2 \log(B_i),
\]
and $A_i$ is dose for drug A (ketamine) and $B_i$ is the dose for drug B (dexmedetomidine). Alternative dose response models may be more suitable in other settings. However, in general, we do not consider interaction terms as they cannot be reliably estimated and models without interactions perform well in dose finding studies.

Using this dose response model, we can determine the posterior for $p_i$, $i = 1, 2, 3$. The optimal combination is then the dose combination with the maximum expectation of $p_i$. In Figure 1, the expected values of $p_i$ are shown using vertical lines, with the highest expected value associated with the first dose combination. Thus, we set $p_1 = p_C$, where $p_C$ is the probability of a success for the optimal dose combination, used in the comparative effectiveness analysis.

**Comparative Effectiveness Analysis**

The comparative effectiveness analysis compares $p_C$ to $p_S$, the probability of success for standard of care. Specifically, we compute the posterior distribution of $d = p_S - p_C$ and then the probability that $d$ is greater than a pre-specified value $\gamma$. If $y = P(d \geq \eta)$, a standard superiority trial would set $\eta = 0$ and conclude that the novel combination is superior if $y$ is small. However, the Ketodex trial aims to determine that IN ketodex is non-inferior to IV ketamine and, therefore, $\eta$ is the non-inferiority margin of 0.178. This non-inferiority margin was estimated as the average non-inferiority margin from two surveys of 204 clinicians, undertaken by the Ketodex team. Again, evidence of non-inferiority is shown by a small value for $y$.

As seen in Figure 1, the proposed trial has three potential outcomes, that (i) the novel combination comparator is superior (non-inferior for the Ketodex trial), (ii) the trial is inconclusive or (iii) the standard of care is superior. The trial conclusion is made using two thresholds $\lambda_1$ and $\lambda_2$, chosen by simulation.

![Diagram of trial design and analysis](image-url)
Simulation Scenarios

We use simulation methods to develop and evaluate our trial design. To achieve this, we use five different simulation scenarios to:

1. Evaluate the ALC to determine the overall sample size and value for $R_0$.
2. Determine the value of $\gamma$, the threshold under which we drop a dose combination from the randomisation procedure.
3. Determine the values of $\lambda_1$ and $\lambda_2$, the thresholds for concluding superiority (non-inferiority) of the novel combination or the standard of care.
4. Compare the Bayesian design with a frequentist design with equal randomisation.
5. Compute the predictive power of the trial.

These simulation scenarios are undertaken sequentially, i.e., the overall sample size is determined in the first simulation and then used as the sample size throughout the remaining simulation scenarios. The following sections outlines the parameters of these five simulations and the criteria used make conclusions from the each simulation for the Ketodex trial.

Determining the Overall Sample Size

For the Ketodex trial, we set $\zeta = 0.07$ and control the length of the 95% highest density posterior credible interval. The value for $\zeta$ represents a posterior credible interval that is six times shorter than the credible interval from the prior and was chosen considering the budget and time constraints that limited our maximum recruitment.

$ALC$ determines the overall trial sample size and $R_0$, the proportion of participants randomised to the standard of care. We consider four alternative values for $R_0$, 0.2, 0.3, 0.4 and 0.5, and compute the ALC for each $R_0$ for sample sizes increasing in increments of 10 from 350 to 500. Initially, we select the smallest sample size that respects the ALC and then, for that sample size, we select the value of $R_0$ that leads to the most balanced trial, provided the ALC is respected.

For each sample size and value of $R_0$, we simulate 2000 datasets from the prior-predictive distribution of the data, using the priors defined below. For each dataset, we obtain 2000 simulations from the posterior distribution of $p_S$ and $p_C$ and compute the highest density posterior 95% credible interval. We then estimate the average length for each sample size and value of $R_0$ across all 2000 prior-predictive datasets.

Determining $\gamma$ for the adaptive randomisation

Next, we use simulations to determine the value of $\gamma$, the threshold for dropping a given dose combination from randomisation in a specific trial period. We consider values of $\gamma$ between 0.05 and 0.3, increasing in increments of 0.05, with 0.3 chosen as the maximum because an even randomisation ratio would have 0.33 randomised to each arm. For the simulations, we fix, $p_1 = 0.93$ with $p_2 = 0.88$ and $p_3 = 0.83$ and determine the number of participants randomised to each treatment option for each value of $\gamma$. Across all simulations, we estimate the probability of randomising the highest number of participants to dose $i = 1$. We select the value of $\gamma$ that maximises this probability. If two values for $\gamma$ give the same probability, then we will chose the smallest threshold $\gamma$.

This allows us to maximise the amount of information collected for the optimal treatment, if the incorrect optimal treatment is selected.

We run 7000 simulations of the complete trial recruitment for each value of $\gamma$. We use 7000 simulations as it gives a greater than 99% chance of estimating the probability of 0.8 to 2 decimal places. Thus, we base all conclusions on simulations results rounded to 2 decimal places.

Thresholds for Comparative Effectiveness Analysis

Based on the adaptive randomisation scheme finalised in the previous section, we then use simulation to determine the decision thresholds for the comparative effectiveness analysis, $\lambda_1$ and $\lambda_2$. As $\lambda_1$ controls the type I error of the trial, we set $p_S = 0.97$ and $p_C = 0.97 - \eta = 0.792$ and select $\lambda_1$ such that 5% of the trials incorrectly conclude non-inferiority. For $\lambda_2$, we set $p_C = 0.78$, undertake the same trial simulation process and specify that 50% of the simulated trials should declare superiority for the standard of care. In both simulation settings, we set 3-3 ketodex as the optimal treatment $p_1 = p_C$, based on expert guidance, with 4-2 ketodex as the second best treatment $p_2 = p_C - 0.05$ 2-4 ketodex as the worst $p_3 = p_C - 0.1$.

We use 7000 simulated trials with the proposed comparative effectiveness analysis based on 7000 posterior simulations from the dose response curve and the posterior for $p_S$.

Finally, to gain a fuller understanding of the design, we then evaluate the probability of each trial outcome, for 8 different values of $p_C$: $p_C = 0.93, 0.9, 0.87, 0.85, 0.83, 0.792, 0.78$ and 0.75, using the specified values of $\lambda_1$ and $\lambda_2$.

Frequentist Trial with Equal Randomisation

We compare our novel trial design with a trial that randomises participants equally across all four treatments, i.e., the standard of care and the three dose combinations. We use the same sample size for the our design and this “equal randomisation” trial. We assume that the final analysis for this equal randomisation trial will compare each dose combination to the standard of care.
using an exact test for non-inferiority. We use an exact test as $p_C = 0.97$ making normal approximations insufficiently accurate. We do not adjust for multiple comparisons as we are expecting differences in the treatment success. We estimate the size/power of this trial for $p_C = 0.93, 0.9, 0.87, 0.85, 0.83, 0.792, 0.78$ and $0.75$, using the same assumptions about the relative effectiveness of the dose combinations as the simulations from the previous section and 7000 simulated trials for each value of $p_C$.

Bayesian Predictive Power Finally, we calculate the expected probability of a conclusive trial, i.e., conclusively concluding superiority of the novel combination or the standard of care, using Bayesian predictive power. We take 2000 simulations from the prior predictive distributions of $p_C$ and $p_S$, using the priors outlined below. We consider three scenarios where the relative effectiveness of the three dose combinations to $p_C$ is varied. Scenario 1 sets the relative effectiveness at $0.9$, $0.95$ and $1$ for $4$-$2$, $2$-$4$ and $3$-$3$ ketodex, respectively. Similarly, Scenario 2 uses $0.95$, $0.98$ and $1$ and Scenario 3 uses $0.95$, $0.1$ and $1.05$. We undertake the comparative effectiveness analysis using 2000 posterior simulations for each prior predictive sample.

Prior Specification

To develop the design, we must specify priors for $p_S$, the probability of success for the standard of care, $\beta_0$, $\beta_1$ and $\beta_2$, the parameters of the log-logistic model. For the prior predictive analysis, we must also specify a prior for $p_C$. We use either previously published evidence or minimally informative priors.

For IV ketamine, Kannikeswaran et al. had a 97% success rate with ketamine dosed at 1.5 mg/kg, as proposed in the Ketodex trial. To account for differences between this trial and the Ketodex trial, we down-weighted this information to an effective sample size of 16:

$$p_S \sim \text{Beta}(15.6, 0.44).$$

For IN ketodex, Bhat et al. published a trial in which 2 out of 27 participants were inadequately sedated. To account for substantial differences between the two trials, including in dosing and the setting, we discount this information to an effective sample size of 6.5:

$$p_C \sim \text{Beta}(6.25, 0.25).$$

The effective sample size of the prior for $p_C$ was chosen to give a 90% chance a priori that IV ketamine is superior to IN ketodex, based on our non-inferiority margin $\eta = 0.178$.

For the regression coefficients, we use non-central Student t-distributions with precision 0.001 and degrees of freedom 1, as suggested in Gelman et al. We set the mean for $\beta_1$ and $\beta_2$ to be 0, as we have minimal information on the dose response. For $\beta_0$, we set the prior mean $p_i$ at 0.93, the success rate observed in the literature.

Results

Average Length Criterion

Figure 2 displays the results from the ALC analysis. The average length of the posterior credible interval falls below 0.07, represented by the black horizontal line, with a sample size of 410 and $R_0 = 0.4$. For all sample sizes, $R_0 = 0.4$ results in the shortest credible intervals.

Based on this sample size, we specify the interim analyses using pragmatic concerns. The first interim analysis will take place after an expected enrolment of 30 participants for each dose combination to ensure sufficient data is collected before changing the randomisation ratio. Thus, the first interim analysis will take place once 150 participants have been enrolled. Further updates of the randomisation ratio will take place at intervals of 50 participants, i.e., at 150, 200, 250, 300, 350, before the final comparative effectiveness analysis at 410.
Based on the overall sample size and the values for $R_0$ and $\gamma$, we determine that $\lambda_1 = 0.0434$ ensures a type I error of 5% size. Following this, setting $\lambda_2 = 0.621$ ensures that 50% of trials declare superiority for IV ketamine when $p_C = 0.78$. Based on these thresholds, Table 2 displays the probability of each trial outcome for all the considered scenarios. The power of the Ketodex trial is very high at the prior mean of 0.93 and remains high provided the true probability of success for the optimal dose combination is over 0.9. The probability of an inconclusive trial is high for values of $p_C$ close to the non-inferiority threshold. Finally, the trial is more likely to be inconclusive above the non-inferiority boundary, i.e., the probability of an inconclusive trial is equal for $p_C = 0.85$ and $p_C = 0.78$, while 0.85 is 0.058 above the boundary and 0.78 is 0.012 below.

Predictive Power

The Bayesian predictive power of the Ketodex trial, i.e., the prior probability that the Ketodex trial is conclusive, is 0.92, 0.92 and 0.95 for scenarios 1, 2 and 3, respectively. The predictive power is higher for scenario 3 as the optimal combination is assumed more effective than the combination used in the literature. In all considered settings, the predictive power is over 90%, which is higher than the prior probability that IN ketodex is superior to IV ketamine. This is possible as we allow conclusions that declare that IV ketamine is superior to IN ketodex. The predictive power of declaring non-inferiority is 0.83, 0.84 and 0.88 for scenarios 1, 2 and 3, respectively.

Discussion

We have developed a novel Bayesian trial design that simultaneously evaluates to comparative effectiveness of a novel combination therapy and determines the optimal dose combination. We use response adaptive randomisation to maximise the number participants who receive the higher performing dose combinations and dose-response modelling to maximise the power of the comparative effectiveness analysis. This trial design minimises the administrative burden of evaluating novel combination therapies and, although it has been developed in a non-inferiority setting, can easily be applied to trials to evaluate superiority of the novel combination.

Our novel design has higher power than a trial with equal randomisation and has high potential to select the optimal dose combination. However, this may be due to the fact that the Ketodex trial is a non-inferiority trial with a rather large non-inferiority margin, as estimated from a survey of clinicians. As the non-inferiority margin gets smaller, the sample size requirements for this novel design will increase and other designs may be more suitable. Additionally, the components of this novel design will need to be re-estimated for alternative settings and this may change the operating characteristics. To facilitate this re-estimation, we the code to undertake the simulations in the supplementary material. Furthermore, note that there are other potential designs that could have been considered alongside the proposed equal randomisation trial such as separate phase II and phase III studies or an alternative seamless design. However, as the Ketodex trial included both dose combinations and a non-inferiority analysis these designs would have required adaptations to be relevant to our setting.

This novel design introduces the concept of an inconclusive trial based on posterior probabilities. To
compute posterior probabilities, we must have a one-sided test, i.e., we need to compute the probability that novel combination is superior to standard of care. This analysis would not be possible if we wanted to consider a point hypothesis. Thus, an adaptation of this decision rule would be required to be equivalent to a two-sided test. Nonetheless, the advantage of this inconclusive trial outcome and a Bayesian trial analysis is that further information could be collected, past the initial completion date of the trial, and incorporated with the data from the currently proposed trial to assess the comparative effectiveness going forward.

Finally, this novel design and decision making framework could be extended to standard dose finding settings to reduce the administrative burden of undertaking phase II and phase III trials. However, in this setting, the safety of the novel intervention would also be needed an alternative potential designs may be more suitable. The advantage of dose combination studies is that the safety of the agents is well understood so explicit safety monitoring and its use in the response-adaptive randomisation may not be required.

Conclusion

We have developed a novel trial design to undertake dose finding and comparative effectiveness analysis to subject to time and resource constraints of an investigator initiated trial.

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