Backfilling cohorts in phase I dose-escalation studies

Helen Barnett¹,², Oliver Boix³, Dimitris Kontos⁴ and Thomas Jaki¹,⁵

Abstract

Background: The use of ‘backfilling’, assigning additional patients to doses deemed safe, in phase I dose-escalation studies has been used in practice to collect additional information on the safety profile, pharmacokinetics and activity of a drug. These additional patients help ensure that the maximum tolerated dose is reliably estimated and give additional information to determine the recommended phase II dose.

Methods: In this article, we study the effect of employing backfilling in a phase I trial on the estimation of the maximum tolerated dose and the duration of the study. We consider the situation where only one cycle of follow-up is used for escalation as well as the case where there may be delayed onset toxicities.

Results: We find that, over a range of scenarios, the use of backfilling gives an increase in the percentage of correct selections by up to 9%. On average, for a treatment with a cycle length of 6 weeks, each additional backfilling patient reduces the trial duration by half a week.

Conclusions: Backfilling in phase I dose-escalation studies can substantially increase the accuracy of estimation of the maximum tolerated dose, with a larger impact in the setting with a dose-limiting toxicity event assessment period of only one cycle. This increased accuracy and reduction in the trial duration are at the cost of increased sample size.

Keywords
Dose-finding, dose-escalation, backfilling, phase I trials, model-based, late-onset toxicity

Introduction

In phase I dose-finding studies, the main objective is often to find the maximum tolerated dose (MTD) or the recommended phase II dose, the dose recommended for further testing in phase II. The MTD is defined as the highest dose that has an acceptable level of toxicity,¹ most often corresponding to a certain probability of occurrence of a dose-limiting toxicity event (DLT). In oncology, a DLT is frequently defined as a grade 3 or higher toxicity by the grading scale of the National Cancer Institute.² In the following, we use the terms DLT and toxicity interchangeably.

In a phase I dose-escalation study, a set of doses is investigated, patients are recruited in cohorts and an escalation procedure is used to carefully escalate from low doses that are expected to be very safe to dose levels that have an acceptable level of toxicity and at the same time induce some desirable activity in a patient. The escalation procedure can be rule-based,¹ model-based³ or model-assisted⁴ and cohorts are most commonly small,⁵ with a size of 3 often used in such trials.

However, with such small sample sizes, comes greater uncertainty in the estimate of interest. It is, for example, desirable to establish the MTD quickly and accurately but with no more patients than necessary. As with any clinical trial, a balance must be taken between the accuracy, the duration of the study and the trial size. Typically, the larger the trial, the higher the accuracy, but also the longer the duration of the study.

An approach that has gained popularity in recent years,⁶,⁷ is the use of ‘backfilling’ of cohorts on lower doses.⁸ The principle is that, once a dose is deemed safe enough to escalate to a higher dose level, additional patients may be allocated to lower doses to increase the understanding of the safety, tolerability and activity of these doses. The decision to backfill a dose may be taken solely on the criteria that the dose is deemed

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‘safe’, or it may require the additional condition that an activity signal must be seen.

While it is clear that backfilling will result in a, potentially large, increase in patient numbers, additional insight around the safety, tolerability and potential activity of the treatment is gained. Moreover, there is the potential that the trial duration could be substantially reduced due to the improved understanding of the dose–toxicity relationship. The exact nature of this relationship between trial duration and sample size is, however, unclear – in particular in the setting where late-onset toxicities are of concern.

In this work, we investigate the impact of backfilling on the relationship between probability of correctly selecting the MTD, the duration of the study and the sample size in phase I dose-escalation trials, with a motivation of reducing the total duration.

**Motivating trial examples**

The first in-human phase I study\(^9\) investigated the safety and activity of the activin A inhibitor, STM 434, in advanced solid tumours. The study initially considered five dose levels, 0.25, 0.5, 1, 2 and 4 mg/kg administered every 4 weeks. The treatment schedule subsequently changed to bi-weekly after the half-life was estimated to be lower than anticipated and an additional dose of 8 mg/kg was added later due to lower than anticipated predicted exposures. A 3 + 3 design\(^1\) was used to guide dose escalation. DLTs were defined as any grade 3 or 4 non-haematologic toxicity, any grade ≥3 haematologic toxicity lasting 7 days, febrile neutropenia, or grade ≥3 thrombocytopenia with active bleeding and the DLT assessment period was 28 days. A minimum of 3 evaluable patients were required prior to dose-escalation and ‘Backfill’ slots were permitted at doses that had been declared safe.

A total of 32 patients participated in the trial of which three experienced a DLT and of 28 patients that were evaluable according to RECIST,\(^10\) 16 achieved stable disease while the remaining had progressive disease (Table 1). Since two of the DLTs occurred in the highest dose, the MTD was declared to be 4 mg/kg every 2 weeks, but no dose expansion was undertaken following the safety review committee’s recommendation on the basis of the overall safety profile observed.

From the results of the study we can see that backfilling slots were indeed used as several of the cohorts have more than three (or six) patients required for the 3 + 3 design.

| Dose (mg/kg) | DLT | Stable disease | Total subjects |
|-------------|-----|----------------|----------------|
| 0.25 (4 weekly) | 0 | 1 | 4 |
| 0.50 (4 weekly) | 1 | 3 | 6 |
| 0.50 (2 weekly) | 0 | 3 | 4 |
| 0.75 (2 weekly) | 0 | 1 | 3 |
| 1.00 (2 weekly) | 0 | 2 | 4 |
| 2.00 (2 weekly) | 0 | 3 | 4 |
| 4.00 (2 weekly) | 0 | 2 | 4 |
| 8.00 (2 weekly) | 2 | 1 | 3 |

DLT: dose-limiting toxicity.

**Table 1. Results of the first in-human phase I study reported by Tao et al.\(^9\) by number of subjects and DLT per dose level.**

To illustrate the concept of backfilling, and the difference between trials that use backfilling and those that do not, we present an example of a single trial simulation. Following the motivating study (NCT03507452) the following six doses are investigated: 1.5, 2.5, 3.5, 4.5, 6.0 and 7.0 MBq. Figure 1 illustrates a trial conducted without backfilling (left panel) and with full backfilling (right panel). Every other aspect of the trials was comparable.

Cohorts of size three enter the trial, starting at the lowest dose. If no backfilling is implemented, then cohorts are assigned to doses according to the escalation procedure, until some stopping rule is triggered. If full backfilling is implemented, when a dose is considered safe enough that the escalation continues above it, the next two cohorts are ‘backfilling cohorts’ and are recruited to that same dose. Then, the next cohort is

**Methods**

In this section, we outline the methods used in this work. First, we illustrate and discuss the concept of backfilling in more detail. We then describe the statistical models used for dose-escalation, and finally, outline the rules used in the design implementation.

**Single simulation examples**

To illustrate the concept of backfilling, and the difference between trials that use backfilling and those that do not, we present an example of a single trial simulation. Following the motivating study (NCT03507452) the following six doses are investigated: 1.5, 2.5, 3.5, 4.5, 6.0 and 7.0 MBq. Figure 1 illustrates a trial conducted without backfilling (left panel) and with full backfilling (right panel). Every other aspect of the trials was comparable.

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assigned to the escalated dose. Of course, one may also choose to backfill more cautiously, but in this illustration, we use two cohorts as standard. Patients are followed up for three cycles of treatment, with new cohorts assigned after each cycle, with a cycle lasting 6 weeks.

In this case, the trial without backfilling determined the MTD to be the 4.5 MBq dose while the trial using backfilling recommended 3.5 MBq. Figure 1 shows that the escalation in both settings is the same – they both reach the 4.5-MBq dose, but in the trial without backfilling two further cohorts are allocated to this dose before being recommended as the MTD. When backfilled cohorts were used, more information was available at the lower doses allowing the precision stopping rule to be reached quickly, and hence, the lower dose is recommended. In addition to the difference in recommended dose, one can also observe that the duration of the study is notably shorter when backfilling is used.

**BLRM and TITE-BLRM**

To investigate the impact of backfilling on the estimation of the MTD and the duration of the trial, we consider two settings. The first setting assumes that patients are followed up for one cycle of treatment only (i.e. DLT period 1 cycle), and the next cohort of patients is assigned once the previous cohort’s follow-up period has been fully observed. The second setting assumes that there may be late-onset toxicities. Patients are therefore followed up for three cycles of treatment. A new cohort of patients is admitted every cycle, so that only partial information is available for the previous two cohorts, as their full follow-up period has not yet been observed. In the first setting we use a Bayesian Logistic regression model (BLRM), and in the second setting a Time-To-Event version of the BLRM (TITE-CRM).

In each setting, a set of $J$ doses labelled $d_j$ for $j = 1, \ldots, J$ are investigated, with patients labelled $i = 1, \ldots, n$.

The BLRM is conducted in the following way. Starting at the lowest dose $d_1$, cohorts of patients enter the trial. After each cohort has been fully observed, the dose assignment of the next cohort is decided. A two-parameter logistic model is used to describe the dose-toxicity relationship:

$$F(d, \beta) = \frac{\exp(\beta_0 + \beta_1 d)}{1 + \exp(\beta_0 + \beta_1 d)},$$

where $F(d, \beta)$ is the probability of DLT at dose $d$, and $\beta = (\beta_0, \beta_1)$ is a parameter vector with prior:

$$\begin{pmatrix} \log(\beta_1) \\ \beta_0 \end{pmatrix} \sim N_2 \left( \begin{pmatrix} c_1 \\ c_2 \end{pmatrix}, \begin{pmatrix} v_1 & 0 \\ 0 & v_2 \end{pmatrix} \right).$$

The posterior distribution of $\beta$ is updated after each cycle using the likelihood

$$\mathcal{L}(\beta) = \prod_{i=1}^n F(d_i, \beta)^{y_i} \{1 - F(d_i, \beta)\}^{1-y_i},$$

where $y_i$ is an indicator taking the value 1 if patient $i$ had observed a DLT and 0 otherwise. The updated
posterior for $\beta$ is then used to estimate the probability of DLT at each dose. The dose assignment of the next cohort is then dose $d_j$ that minimizes $|F(d_j, \beta) - \tau_1|$, where $\tau_1$ is the target DLT rate for one cycle of follow-up, subject to certain rules – see the next section. The final dose recommendation is then the dose $d_j$ that minimizes $|F(d_j, \beta) - \tau_1|$ once a stopping rule has been triggered.

In the second setting, the TITE-CRM is used. Here, patients are followed up for three cycles of treatment. However, if it was required to wait until the entire follow-up for the previous cohort had been completely observed to assign the dose for the next patient, the trial length would be very undesirably long. Therefore, each new cohort is assigned its dose once the previous cohort has been observed for one cycle of treatment. There is therefore only partial information available for the previous two cohorts. The TITE-CRM takes this into account by weighting the observations in the following way.

The dose-toxicity model $F(d_j, \beta)$ is identical to the non-time-to-event version, and is weighted to form $G(d, w, \beta)$:

$$ G(d, w, \beta) = w F(d, \beta), $$

where the weights $0 \leq w \leq 1$ are a function of time-to-event of a patient toxicity. The posterior distribution of $\beta$ is updated after each cycle using likelihood

$$ L(\beta) = \prod_{i=1}^{n} G(d_{ij}, w_{i,n}, \beta)^{y_{i,n}} \{1 - G(d_{ij}, w_{i,n}, \beta)\}^{1-y_{i,n}}, $$

where $n$ is the number of patients that have been treated so far, $d_{ij}$ is the dose assigned to patient $i$ and $y_{i,n}$ is an indicator which takes the value 1 if patient $i$ has observed a DLT after the $n$ patients treated so far have been observed for at least one cycle, and 0 otherwise.

The updated posterior for $\beta$ is used to estimate the probability of DLT at each dose, as in the one-cycle setting. The dose assignment of the next cohort is then the dose $d_j$ that minimizes $|F(d_j, \beta) - \tau_1|$, where $\tau_1$ is the target DLT rate for three cycles of follow-up, again subject to certain rules – see the next section.

In this implementation, we use the simple specification of weights suggested by Cheung and Chapell: $w_{i,n} = u_{i,n}/S$, where $u_{i,n}$ is the current number of cycles for which patient $i$ has been observed and $S$ is the total number of cycles in the follow-up period. If patient $i$ observes a DLT, then $w_{i,n} = 1$. The final dose recommendation is the dose level that minimizes $|F(d_j, \beta) - \tau_1|$ once a stopping rule has been implemented and the follow-up for all enrolled patients has been completed.

Due to the added complexity of the method, the TITE-CRM uses a start-up period such that the dose assignment is escalated one level at a time until a DLT is observed. Once a DLT is observed, then the TITE-CRM

### Table 2. \( p_{i,j} = P(DLT) \) in cycle 1 for each dose \( d_j \) across 17 defined simulation scenarios.

| Scenario | 1.5 MBq | 2.5 MBq | 3.5 MBq | 4.5 MBq | 6.0 MBq | 7.0 MBq |
|----------|---------|---------|---------|---------|---------|---------|
| 1        | 0.30    | 0.40    | 0.50    | 0.60    | 0.70    | 0.80    |
| 2        | 0.20    | 0.30    | 0.40    | 0.50    | 0.60    | 0.70    |
| 3        | 0.10    | 0.20    | 0.30    | 0.40    | 0.50    | 0.60    |
| 4        | 0.05    | 0.10    | 0.20    | 0.30    | 0.40    | 0.50    |
| 5        | 0.05    | 0.10    | 0.15    | 0.20    | 0.30    | 0.40    |
| 6        | 0.02    | 0.05    | 0.10    | 0.15    | 0.20    | 0.30    |
| 7        | 0.15    | 0.20    | 0.25    | 0.30    | 0.45    | 0.60    |
| 8        | 0.05    | 0.15    | 0.30    | 0.35    | 0.40    | 0.45    |
| 9        | 0.40    | 0.45    | 0.50    | 0.55    | 0.60    | 0.65    |
| 10       | 0.05    | 0.15    | 0.25    | 0.35    | 0.45    | 0.55    |
| 11       | 0.15    | 0.20    | 0.35    | 0.40    | 0.45    | 0.50    |
| 12       | 0.05    | 0.10    | 0.15    | 0.20    | 0.25    | 0.40    |
| 13       | 0.06    | 0.07    | 0.08    | 0.09    | 0.11    | 0.12    |
| 14       | 0.10    | 0.14    | 0.21    | 0.30    | 0.46    | 0.58    |
| 15       | 0.16    | 0.30    | 0.50    | 0.70    | 0.89    | 0.95    |
| 16       | 0.55    | 0.91    | 0.99    | 1.00    | 1.00    | 1.00    |
| 17       | 0.05    | 0.05    | 0.05    | 0.80    | 0.80    | 0.80    |

MTD in bold.

model is used. Although in the original description of the methodology, this start-up period requires each patient to be followed up for their entire follow-up time before the next patient’s dose is assigned, in our implementation, only one cycle is required for follow-up before the next is assigned, which is in line with the rest of the trial.

### Simulations setup

To evaluate the performance in the setting of a phase I dose-escalation trial, we use enforcement and stopping rules that could be used in such a trial. We define $p_{s,i,j}$ as the $P(DLT)$ in cycles up to and including cycle $s$ for any given dose $d_j$. These rules are described in the online supplemental material.

To investigate the effect of backfilling on the operating characteristics of the dose-finding designs, we conduct a simulation study. The same set of six doses as used in the motivating example are used: 1.5, 2.5, 3.5, 4.5, 6.0 and 7.0 MBq. Seventeen scenarios are considered, to cover a wide range of potential dose responses.

Table 2 gives the probability of a DLT in the first 6-week cycle for each of the considered scenarios, with the MTD associated with the target, $\tau_1 = 0.3$, highlighted in boldface. Scenarios 1–6 represent cases where each level in turn is the MTD, with higher and lower doses equidistant in terms of the probability of DLT. Scenarios 7 and 8 are non-linear around the MTD. In scenarios 9–12, no dose is exactly on target, with all doses unsafe in scenario 9. Scenarios 13–17 are a set of varying scenarios, typically used to test the performance of a dose-finding algorithm.

For the setting where the follow-up period is three cycles, the conditional probability of DLT in subsequent cycles is multiplied by a factor of $1/3$. So that
\[ p_{2,d_j} = p_{1,d_j} + (1 - p_{1,d_j}) \frac{p_{1,d_j}}{3}, \]

and

\[ p_{3,d_j} = p_{1,d_j} + (1 - p_{1,d_j}) \frac{p_{1,d_j}}{3} + (1 - p_{1,d_j}) \frac{1 - p_{1,d_j}}{9}. \]

For example if \( p_{1,d_j} = 0.3 \), then \( p_{2,d_j} = 0.37 \) and \( p_{3,d_j} = 0.391 \); hence, we use \( \tau_3 = 0.391 \) as the target toxicity for three cycles of follow-up. To generate patient toxicity, a Uniform(0,1) random variable, \( U \), is generated for each patient, and a DLT is observed in cycle 1 on dose \( d_j \) if \( U < p_{1,d_j} \), in cycle 2 if \( p_{1,d_j} < U < p_{2,d_j} \), in cycle 3 if \( p_{2,d_j} < U < p_{3,d_j} \) and no DLT is observed if \( U > p_{3,d_j} \).

The maximum sample size is chosen to be \( n_{\text{max}} = 54 \), which is relatively large for a phase I trial, but has been chosen to allow escalation to dose \( d_6 \) with backfilling implemented.

We conduct 5,000 simulations for each scenario and compare the performance to the non-parametric benchmark.\(^{14}\) This benchmark gives an indication of the ‘difficulty’ of a scenario so that we can quantify any differences between the approaches accordingly. Note that this uses the maximum sample size in every simulation, and is not subject to any stopping rules.

In these implementations, as well as comparing backfilling all doses considered safe (Fully Backfilled), and not (Not Backfilled), we also consider the setting where a dose level is only backfilled once an activity signal has been observed at that dose or any dose below (Partially Backfilled). For example, if an activity signal is first seen in the third dose level and not the first or second, then the decision to escalate to the fourth dose level would mean the additional backfilling cohorts are assigned to dose three but not doses one and two. Since we employ backfilling once an activity signal has been seen, we use the probability of at least one complete response in a cohort. In this partially backfilling setting, the underlying probability of observing an activity signal is 0.00, 0.15, 0.30, 0.45, 0.50, 0.75 at each of the six doses, respectively, corresponding to an individual’s activity probability of \((0, 0.05, 0.11, 0.18, 0.26, 0.37)\) at each of the six doses.

We consider two options for the values of the hyper-parameters of the prior distribution; non-calibrated and calibrated. In the first option, the hyper-parameters for the prior used are chosen so that the prior is relatively vague, with a mean effective prior sample size of 1.3 patients per dose level. These choices are in line with those used by Neuenschwander et al.\(^{12}\) The second option is to calibrate the values of these hyper-parameters over a small range of scenarios, to choose the values yielding the best performance across a wide range of settings (see, e.g. Mozgunov et al.\(^{15}\)). Further details including the values of hyper-parameters are available in the online supplemental material.

**Results**

The most often considered metrics of performance in dose-finding trials are the proportion of correct selections and the proportion of acceptable selections. A correct selection is defined as selecting the MTD as defined in Table 2, or as a safety stopping rule being correctly triggered. An acceptable selection is defined as a dose whose true probability of toxicity during the first cycle is between 0.18 and 0.33, based on the overview of Phase I trials by Iasonos and O’Quigley.\(^{16}\)

Here, we discuss the results for the non-calibrated prior, with the calibrated prior discussed in the online supplemental material. The online supplemental material also contains details of the stopping reasons for the simulations.

**Non-calibrated prior**

Figures 2 and 3 show the proportion of correct and acceptable selections in the setting with one cycle and three cycles, respectively. The Monte Carlo simulation errors are at most ±1.4%. From Figure 2, it can be seen that, when one cycle of follow-up is considered, employing backfilling increases the proportion of correct and acceptable selections in almost all scenarios, as expected. The only scenario which did not see an increase in the proportion of correct selections is scenario 7, where there is a marginal decrease in the proportion of correct selections, but a noticeable increase in the proportion of acceptable selections. This is a particularly challenging scenario, where the dose below the MTD has a true probability of DLT only 5% below the target. The largest increase is seen in scenario 13, where full backfilling gives a 9% increase in correct selections. In nearly all scenarios, partial backfilling gives a performance between no backfilling and fully backfilling as expected. Interestingly in scenario 17, the performance of partial backfilling is worse than both no and full backfilling. With such an ‘easy’ scenario, the proportion of correct selections is already very high, and the decrease is due to a shift to recommending the unsafe fourth dose. The average increase in correct selections from no backfilling to fully backfilling is 4% and is 5% for acceptable selections. The approach to partially backfilling we have taken means the probability of backfilling any given level dose increases with dose. Therefore when the lower doses are more toxic, fewer doses will be backfilled and partial backfilling gives more similar results to no backfilling. Although in all cases it is noticeable that the performance is well below that of the benchmark, it is worth noting that the benchmark has the advantage of a much larger sample size on average.

To compare the measures of trial sizes of the two approaches, Figure 4 shows the relationship between the mean total sample size and the mean trial duration...
for each scenario and most importantly how this relationship changes for differing levels of backfilling. The diamonds represent the setting with one cycle of follow-up, with blue indicating that full backfilling was used, purple indicating partial backfilling and black indicating no backfilling. It is clear to see that the use of full backfilling substantially increases the total sample size in scenarios where the MTD is at least the second dose level. This increase in sample size owed to the use of backfilling decreases the average trial duration notably, seen by the upwards left drift of the blue diamonds compared to their black counterparts. On average across scenarios, full backfilling increases the sample size by 12 patients on average but reduces the trial duration by 6 weeks (one treatment cycle). It appears that on average each additional patient reduces the duration by half a week. For partial backfilling, although the overall increase in sample size is smaller, as is the decrease in trial duration, the trade-off is still on average each additional patient reduces the duration by half a week. Although such a trade-off may seem small, it also brings with it the increase in precision of MTD estimation.

The other important metrics used in dose-finding trials concern the safety of the patients within the trial. Figures in the online supplemental material show the

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**Figure 2.** Proportion of correct and acceptable selections across scenarios for one cycle of follow-up.

**Figure 3.** Proportion of correct and acceptable selections across scenarios for three cycles of follow-up.
distribution of mean percentage of DLTs and the mean number of patients assigned to overly toxic doses. Although backfilling increases the number of DLTs observed in every scenario, the percentage of patients observing a DLT decreases slightly when full backfilling is used, and is largely unchanged for partial backfilling. For the most part, the increase in numbers of patients exposed to overly toxic doses is in scenarios where all doses are unsafe. Hence, one mistaken escalation increases this exposure by three cohorts when backfilling instead of one when not. The benefit in reducing the number of patients exposed to overly toxic doses comes in scenarios where the MTD is in the middle of the dose range, and the backfilling expansion provides more information on the lower doses, resulting in more cautious escalation.

Interestingly, the patterns observed in the setting with one cycle of follow-up are not all duplicated in the setting with three cycles of follow-up. It is not the case here that the proportion of correct and acceptable selections increase across all scenarios when backfilling is employed. In fact in some scenarios, there is a noticeable decrease in the proportion of correct selections when backfilling is employed. For example, in scenarios 5–7, where the proportion of correct selections is low in both settings, it is lower when backfilling is used. This reflects further the point raised earlier that the backfilling leads to a more cautious escalation. In most cases, the proportion of acceptable selections is higher when backfilling is implemented.

In terms of mean sample size and trial duration, the circles in Figure 4 display this relationship. This relationship is similar to that observed with one cycle. For every additional patient, the trial duration decreases by 0.3 weeks, for both full and partial backfilling. Again, the magnitude of this overall increase or decrease is larger for fully backfilling. Likewise, the comparisons of the safety aspects of the trials are similar. With three cycles of observation, fully backfilling increases the total number of DLTs in all scenarios, decreases the percentage of DLTs overall, decreases the number of patients exposed to overly toxic doses in some scenarios and increases in others. On average across scenarios, there is a slight decrease in the number of patients exposed to overly toxic doses.

**Conclusion**

In this work, we have investigated the effect of backfilling on the operating characteristics of dose-escalation studies. The main reasons to utilize backfilling include to gain better understanding of the safety, tolerability and activity of the treatment under investigation and to aid determining the recommended phase II dose. In this work, we have focussed on the implications of backfilling on the estimation of the MTD and the duration of the study. We found that backfilling increases the chance of identifying the MTD while reducing the duration of the study, on average by 14%. This comes at the cost of an increased number of patients required in studies that use backfilling. The impact of backfilling on the accuracy is larger in the setting with a DLT assessment period of one cycle than when three cycles of follow-up are used. The added value of backfilling depends on the escalation scheme used, with most value potentially added for a less conservative scheme.

Here, we have used a target DLT rate of 0.391 for the setting with three cycles of follow-up, as this corresponds to the target of 0.3 for one cycle of follow-up. However, similar patterns of results have been observed when the target is 0.3 over three cycles.

In our evaluations, patients for backfilling are available for recruitment immediately which clearly is an optimistic assumption. Moreover, the use of backfilling does increase the number of patients in the study. Nevertheless, we did see consistent benefits of backfilling. Specifically, one additional patient did yield a reduction of the study duration of approximately half a week.

Our investigations explore two different settings with respect to the prior distributions used. In the first
setting, the prior is chosen with a study in mind that does not plan to use backfilling, while the second considers backfilling as an option at the outset. Encouragingly, we find that, irrespective of the setting, the benefits of backfilling on the estimation of the MTD and duration of the study are fairly consistent.

Data availability statement
All data is simulated according to the specifications described.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This report is supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care (DHSC). T Jaki and H Barnett received funding from UK Medical Research Council (MC_UU_00002/14).

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Supplemental material
Supplemental material for this article is available online.

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