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Fractional design: An alternative paradigm for late-onset toxicities in oncology dose-finding studies

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ABSTRACT

Late-onset (LO) toxicities often arise in the new era of phase I oncology dose-finding trials with targeted agents or immunotherapies. The current LO toxicities modelling is often formulated in a weighted likelihood framework, where the time-to-event continual reassessment method (TITE-CRM) is commonly used. The TITE-CRM uses the patient exposure time as a weight for the censored observation, while there is large uncertainty on which weight function to be used. As an alternative, the fractional scheme formulates an efficient and robust paradigm to address LO toxicity issues in dose finding. We review the fractional continual reassessment method (fCRM) and compare its operating characteristics with those of the TITE-CRM as well as other competitive designs via extensive simulation studies based on both the fixed and randomly generated scenarios. The fCRM is shown to possess desirable operating characteristics in identifying the maximum tolerated dose (MTD) and deliver competitive performances in comparison with other designs. It provides an alternative efficient and robust paradigm for interpreting and addressing LO toxicities in the new era of phase I dose-finding trials in precision oncology. A real trial example is used to illustrate the practical use of the fCRM design.

1. Introduction

Dose finding is an essential and fundamental step in the development of a new treatment. This is particularly important in oncology, as it is believed that more than 90% of the failed large-scale randomized clinical trials (RCTs) are attributable to an inefficient or inaccurate early-phase study to some extent [1]. The primary aim of dose-finding trials is to identify the maximum tolerated dose (MTD) or the recommended phase II dose (RP2D) to be utilized in subsequent trials. From a safety and therapeutic perspective, dose finding is conducted sequentially, assuming that dose levels are assigned to patients based on the observed side effects or toxicities of the previously treated patients. The standard principle for dose-escalation trials is to control the number of patients exposed to subtherapeutic doses, preserve patients' safety and maintain efficient exploration of the dose space.

Dose-limiting toxicities (DLTs) are typically defined as grade 3 or 4 toxicities based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [2], and most of them are acute events occurring during the first cycle of treatment. However, it was shown that among 36 eligible trials, 57% of grade 3 or 4 toxicities occurred after the first treatment cycle [3]. A retrospective study including 54 trials with 35 different molecularly target agents (MTAs) showed that approximately half of the patients experienced grade 3 or higher toxicities after the first cycle of treatment [4]. Recently, a case study of dose optimization using data from bortezomib dose-finding clinical trials also indicated that almost 54% of a total of 13,008 observed patients' DLTs occurred after the first cycle of treatment [5]. If the DLT occurs after the end of the prespecified toxicity assessment period, it is called late-onset (LO) toxicity. The delayed outcome often results in censored or non-ignorable missing data that may not be available when a dose assignment decision is made for a new cohort [6].

Over the past decade, the time-to-event weighting method has been the primary framework for addressing the LO toxicity issues. The weighting scheme incorporates information from partially followed subjects who have not experienced DLTs through a weighted likelihood function. The weight is typically defined as a ratio of the completed period of follow-up and the planned, or a full weight of 1 is assigned to patients who have experienced DLTs. The time-to-event continual reassessment method (TITE-CRM) [7,8] and its variants [9–13] have been proposed along this direction. As an extension of the original CRM [14], the TITE-CRM is a sequential estimation procedure that uses a mathematical model to describe the relationship between dose levels

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and the probabilities of DLT. An attractive feature of the TITE-CRM is that it leads to a much shorter trial duration compared with the CRM by allowing patients' partial toxicity information to be incorporated into the dose-assignment decision before all patients' outcomes are fully observed [8].

Nevertheless, there are some criticisms and practical challenges associated with the TITE-CRM. First, the TITE-CRM might be associated with a higher risk of treating patients at unsafe dose levels in the settings of LO toxicities and fast patient accrual due to the incomplete follow-up [10]. Second, very limited information is contained in the binary outcome, and the simple weighting scheme cannot accommodate all the information in the censored data. Third, there is enormous uncertainty in the choice of weight functions and different weight functions may lead to different trial operating characteristics. Fourth, in general the time-to-event weighting scheme can only be adopted in the likelihood-based dose-finding methods, such as CRM, the cumulative cohort design (CCD), and the escalation with overdose control (EWOC) design.

Apart from the TITE-CRM, several other time-to-event weighting dose-finding methods have been developed. For example, the time-to-event cumulative cohort design (TITE-CCD) [15] incorporates weights into the CCD for updating the cumulative toxicity probability at each dose level. The time-to-event escalation with overdose control (TITE-EWOC) [16] identifies the optimal dose level by ensuring the probability of the dose exceeding the MTD to be less than a feasibility bound, which is equivalent to placing a higher penalty on overdosing than underdosing [17–19]. The time-to-event Bayesian optimal interval (TITE-BOIN) design accelerates phase I trials by allowing real-time dose assignment for new patients while some enrolled patients' toxicity data are still pending; and as a follow-up, a general methodology of model-assisted designs can be used to handle the LO issues [20,21].

Currently, the landscape of drug development in oncology has evolved dramatically, primarily due to the emergence of MTAs and immunotherapies, which have different toxicity profiles from traditional cancer treatments, as they typically lead to more long-lasting mild or moderate toxicities as well as LO toxicities [22]. The time-to-event weighting paradigm for MTAs has been recommended by the NCI Radiation Therapy Oncology [23]. On the other hand, fractional designs, such as the fractional continual reassessment method (fCRM) [24] and the fractional nonparametric overdose control (fNOC) design [25], can be regarded as effective alternative strategies to addressing the LO toxicity issues, as these designs possess several desirable properties:

1. Efficiency: The fractional design can borrow information from all the doses and does not require the toxicity outcome to be ascertainable shortly after the treatment, thus substantially shortening the trial duration.
2. Safety: The fraction design does not raise the overall percentage of toxicities, which is often a vital concern for physicians.
3. Intuition and ease of interpretation: The fractional contribution is the conditional probability of experiencing toxicity in the remaining assessment period given that the patient has not yet experienced toxicity based on the nonparametric Kaplan-Meier estimator.
4. Robustness: For the LO toxicities, the accrual rate and the distribution of times to toxicity would affect the censored cases during the trial. However, the fractional design inherits the nonparametric property of the Kaplan-Meier estimator and thus is less sensitive to the time-to-event distribution and performs well even when the speed of accrual is high.
5. Flexibility: The fractional imputation approach, which is the unique scheme based on the Kaplan-Meier estimator (i.e., the nonparametric maximum likelihood estimator of the survival function), can be easily incorporated into any existing dose-finding methods, such as NOC [25] and BOIN [26]. The fractional toxicity outcome of each patient replaces the unobserved toxicity outcome that is censored prior to the complete follow-up, leading to the fractional designs: fNOC and fBOIN.

We review the fCRM methodology, illustrate the trial implementation and examine its performances in comparison with the TITE-CRM and many other weighting and fractional designs, aiming to demonstrate that the fCRM has desirable operating characteristics and can serve as an alternative approach to address LO toxicity issues.

2. Methods

2.1. TITE-CRM

Under the time-to-event weighting framework, TITE-CRM [7] addresses the late-onset toxicity issue by using patients' exposure times as weights in a pseudo-binomial likelihood function. Intuitively, a patient who has not experienced toxicity at the decision-making time is uniformly weighted by the actual follow-up time with respect to the pre-specified assessment period. As a result, the longer the follow-up time, the higher the weight since it is believed the more information is carried by the patient. Patients who have already experienced toxicity are given a full weight of 1.

Under the original CRM model [14], the true toxicity probability p_j is linked with π_j in a parametric power model via a single unknown parameter, $p_j(\alpha) = \pi_j^{\exp(\alpha)}$, $j = 1, \cdots, J$, where π_j is the pre-specified toxicity probability at dose level j, and $\pi_1 < \cdots < \pi_J$. The TITE-CRM continuously updates the posterior toxicity probabilities as more data are collected during the trial. The next cohort of patients is assigned to the dose moving one level toward the optimal dose that has an estimated toxicity probability closest to the target toxicity probability. Briefly, in the TITE-CRM, the first cohort of patients are treated at the lowest dose level or the physician prespecified dose level. Subsequently, dose escalation or de-escalation is restricted to one dose level of change between adjacent dose levels. Furthermore, a safety rule is imposed to ensure the trial would be terminated early if the lowest dose under consideration is still overly toxic. Once the maximum sample size is exhausted, TITE-CRM eventually identifies the MTD as the dose whose toxicity probability is closest to the target toxicity probability.

2.2. fCRM

In the paradigm of the fractional design, we model the time to toxicity via the Kaplan-Meier estimator by redistributing the mass of each censored case to the right [24,27,28]. This is a well-known technique to reconstruct the Kaplan-Meier estimator for censored observations [29]. Suppose that after being recruited into a trial each patient is followed up to a prespecified toxicity evaluation period $[0, \tau]$. If a patient during the follow-up period $[0, \tau]$ has experienced the DLT by the decision-making time (i.e., dose assignment for a new cohort of patients), then the corresponding toxicity outcome is $y = 1$; if a patient has not experienced the DLT by the decision-making time, we record a censored observation. By redistributing the mass of each censored observation to the right, we obtain a fraction of 1 (i.e., a value between 0 and 1) as the contribution of the censored toxicity outcome. In addition, it is worth noting that, taking τ as a boundary, subjects who have not experienced toxicity after τ (i.e., $y = 0$) still contribute to the risk set in the Kaplan-Meier estimator, because we treat those patients with $y = 0$ as censored observations at τ.

Similar to TITE-CRM, fCRM requires a pre-specified skeleton, say $\pi_1 < \cdots < \pi_J$. The true toxicity probability p_j is linked with π_j in a power model via a single unknown parameter,

$$p_j(\alpha) = \pi_j^{\exp(\alpha)}, \qquad j = 1, \cdots, J$$

We assign α a normal prior distribution, e.g., $\alpha \sim N(0, 2)$. At each decision-making time, the fCRM models the toxicity event as time-to-

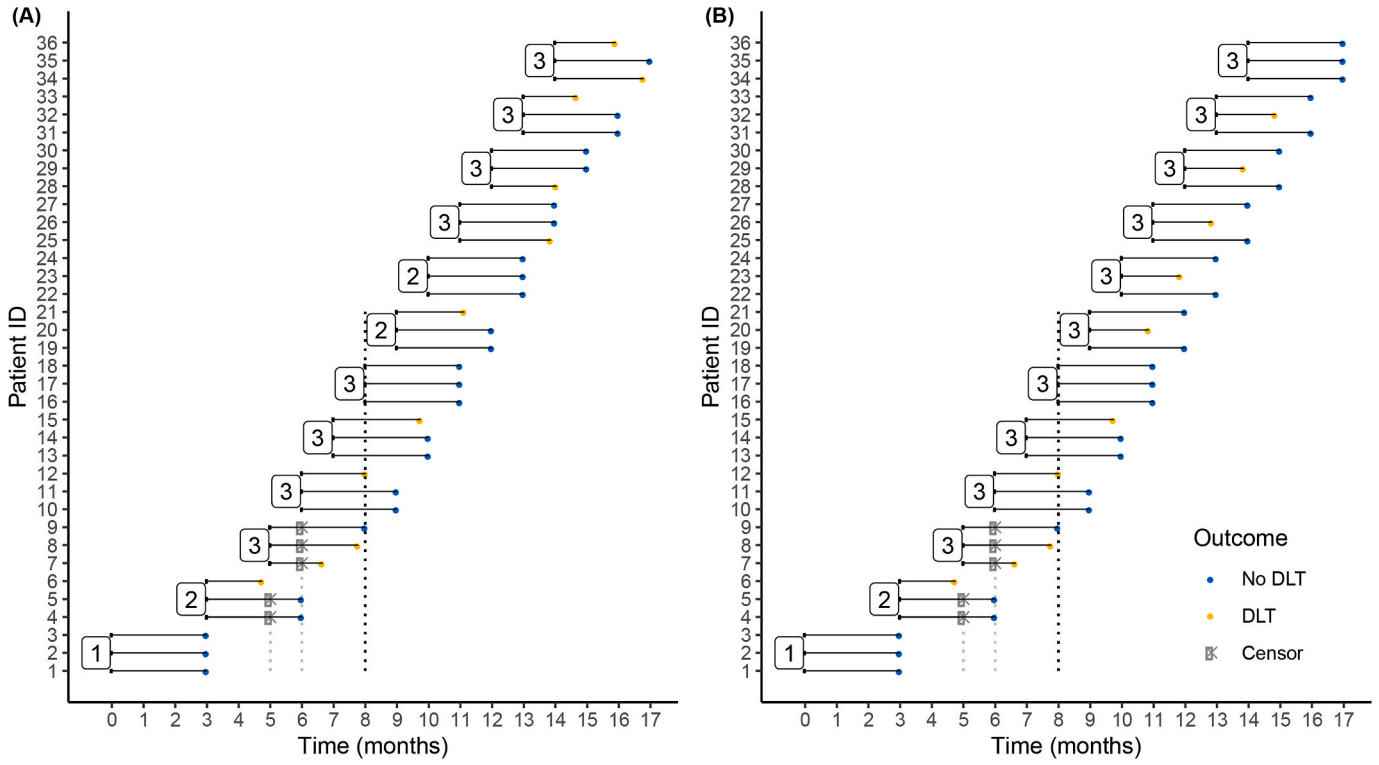

Fig. 1. A hypothetical phase I dose-finding trial using fCRM (A) and TITE-CRM (B) respectively. For each patient, horizontal line segment represents the follow-up, on which DLT is indicated by a yellow dot, no DLT by a blue dot and censoring by a cross. The number in each box indicates the dose level used for the corresponding cohort of patients. The dotted lines indicate the decision-making times for the 3rd, 4th and 6th cohorts respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

event data and redistributes censored observations to the right through the Kaplan-Meier estimator. Within the evaluation window $[0, \tau]$, if a patient experiences the DLT, we take the toxicity event $y = 1$; if a patient has not experienced the DLT by the time of decision making, the toxicity event is censored and we can split the point mass of 1 between the censoring time and the time point that is larger than τ. More specifically, for subject i, let t_i denote the time to toxicity, and let $u_i (u_i \leq \tau)$ denote the actual follow-up time that may censor t_i. Assume that u_i is independent of t_i. The toxicity event is censored for patients who have not yet experienced toxicity ($u_i < t_i$) and have not been fully followed up to $\tau (u_i < \tau)$. If the toxicity event of subject i is censored, we calculate the fractional contribution via the conditional probability of the occurrence of toxicity in the remaining follow-up period (u_i) given that the toxicity event has not occurred by u_i, that is,

$$\Pr(t_i < \tau \mid t_i > u_i) = \frac{\Pr(u_i < t_i < \tau)}{\Pr(t_i > u_i)}$$

which can be estimated by

$$\hat{y}_i = \frac{\hat{S}(u_i) - \hat{S}(\tau)}{\hat{S}(u_i)}$$

where $\hat{S}(\cdot)$ is the Kaplan-Meier estimator.

Once the censored observations are fractionalized, the fCRM continuously updates the unknown parameter as well as the estimate of the DLT probability. Each cohort is then assigned to the dose that has an estimated toxicity probability closest to the target toxicity probability, while no dose skipping is allowed. Moreover, a safety rule is imposed to ensure the trial can be terminated early if the lowest dose under consideration is still overly toxic. In detail, the procedure of fCRM can be described as follows.

1. Treat the first cohort of patients at the lowest dose level or the physician prespecified dose level.
2. At the preliminary stage, we fully follow each cohort of patients until the first DLT occurs,
   a. If no DLT occurs, escalate to the next higher dose level;
   b. If the current dose level is the highest one J, stay at the current dose level;
   c. Once the first DLT is observed, the trial seamlessly enters into the fCRM design.
3. Suppose the current dose level is j, then the optimal dose level j^* for the next cohort of patients is determined as the one whose posterior toxicity probability is closest to the target toxicity probability,
   a. If $j > j^*$, then de-escalate to dose level $j - 1$;
   b. If $j < j^*$ and $j < J$, then escalate to dose level $j + 1$;
   c. Otherwise, stay at the current dose level j.
4. Terminate the trial once the maximum sample size is exhausted or the safety rule is triggered (i.e., the lowest dose level is still overly toxic).

Once the maximum sample size is exhausted, the fCRM eventually identifies the MTD as the dose whose toxicity probability is closest to the target toxicity probability.

2.3. A hypothetical trial example

To illustrate the differences between fCRM and TITE-CRM, we consider a hypothetical phase I trial which aims to find the MTD with a target toxicity probability of 30% among six prespecified dose levels. The maximum sample size is 36 and patients are treated in a cohort size of 3. The DLT assessment period is 3 months and the inter-arrival time between two consecutive cohorts is 1 month. Fig. 1 shows the dose-assignment paths of the trial under the fCRM and TITE-CRM designs, respectively. Both the true and estimated DLT probabilities of the six

Table 1
The true and estimated DLT probabilities with cumulative cohorts of patients in the hypothetical trial with the target toxicity probability of 0.30

Cohort	True and estimated DLT probabilities						Recommended dose
	Dose 1 0.12	Dose 2 0.20	Dose 3 0.30	Dose 4 0.40	Dose 5 0.50	Dose 6 0.59	
3							
fCRM	0.157	0.231	0.316	0.406	0.497	0.583	3
TITE-CRM	0.154	0.243	0.342	0.444	0.541	0.628	3
4							
fCRM	0.121	0.190	0.273	0.365	0.460	0.550	3
TITE-CRM	0.106	0.183	0.276	0.377	0.478	0.572	3
5							
fCRM	0.137	0.213	0.302	0.397	0.492	0.581	3
TITE-CRM	0.141	0.227	0.325	0.427	0.525	0.614	3
6							
fCRM	0.169	0.253	0.347	0.444	0.537	0.622	3
TITE-CRM	0.153	0.242	0.341	0.443	0.540	0.627	3
7							
fCRM	0.176	0.262	0.357	0.455	0.548	0.632	2
TITE-CRM	0.152	0.241	0.340	0.442	0.539	0.626	3
8							
fCRM	0.188	0.277	0.373	0.472	0.564	0.646	2
TITE-CRM	0.152	0.240	0.339	0.441	0.538	0.625	3
9							
fCRM	0.151	0.234	0.329	0.428	0.523	0.611	3
TITE-CRM	0.146	0.232	0.331	0.433	0.531	0.619	3
10							
fCRM	0.154	0.239	0.336	0.434	0.529	0.616	3
TITE-CRM	0.146	0.233	0.332	0.433	0.530	0.619	3
11							
fCRM	0.124	0.201	0.293	0.392	0.490	0.582	3
TITE-CRM	0.146	0.233	0.332	0.434	0.531	0.619	3
12							
fCRM	0.128	0.206	0.300	0.399	0.497	0.587	3
TITE-CRM	0.146	0.233	0.332	0.434	0.5731	0.620	3
MTD Selection							
fCRM	0.162	0.249	0.346	0.446	0.541	0.627	3
TITE-CRM	0.146	0.233	0.332	0.434	0.531	0.620	3

dose levels step-by-step are presented in Table 1. The trial starts with the first cohort of patients assigned to dose level 1, and no DLT is observed. According to the dose-escalation rule, the first cohort of patients is fully followed and so is the second cohort until the first DLT is observed (between months 4 and 5); the trial then enters into the main phase. For the fCRM design, the fractional contributions of the censored observations in the first two cohorts are calculated using the Kaplan-Meier estimator, which are $\{(0,0,0),\ (0,0,1)\}$, and the next cohort is assigned to dose level 3. The same dose level is also recommended by the TITE-CRM design, in which the weights for the first six patients are $\{(1,1,1),(0.67,0.67,1)\}$ and the estimated toxicity probabilities of the six dose levels are also presented in Table 1. The next four cohorts of patients are treated at dose level 3, which are the same under both the fCRM and TITE-CRM designs. However, the difference occurs for cohort 7 on month 9. Based on the data from the first six cohorts, the posterior toxicity probabilities of the six dose levels are $(0.169, 0.253, 0.347, 0.444, 0.537, 0.622)$ and, as a result, the fCRM recommends dose level 2 to cohort 7. By contrast, the TITE-CRM with the posterior toxicity probabilities of the six dose levels $(0.153, 0.242, 0.341, 0.443, 0.540, 0.627)$ recommends dose level 3. The subsequent cohort under fCRM remains at dose level 2 while that under TITE-CRM remains at dose level 3. Afterwards, the remaining four cohorts are all treated at dose level 3, which is the same in both designs. At the end of the trial, a total of 11 DLTs are observed under the fCRM design which recommends dose level 3 as the MTD with the estimated toxicity probability $\widehat{p}_3 = 0.346$. With 11 DLTs observed under the TITE-CRM design, the same dose level 3 is recommended to be the MTD with $\widehat{p}_3 = 0.332$.

2.4. Simulation studies

To examine the operating characteristics and evaluate the performances of fCRM and two commonly used approaches (i.e., TITE-CRM and CRM) for the late-onset toxicities, simulations with ten scenarios given in Table 2 are performed. The power model is adopted, where the skeleton is chosen using the model calibration method [30] with a halfwidth of the indifference interval of 0.05. We consider a total of six dose levels and a maximum sample size of 36 patients with a cohort size of 3. The first cohort is treated at the lowest dose level. The toxicity assessment period is 3 months and the inter-arrival time between two consecutive cohorts is 1 month. We assume that the time to toxicity at each dose level follows a Weibull distribution, whose shape and scale parameters are chosen such that the survival function at the end of the follow-up is equal to one minus the toxicity probability of that dose, and only 10% of toxicity outcomes would occur in the first half of the assessment period. The target toxicity probability is 30%. For each scenario, 5000 replications are carried out. We also remove the stopping rule to achieve a fair comparison. Three types of statistics are used to quantify the operating characteristics of each design: (i) accuracy assessment, including the percentage of correct selection (PCS) of the

Table 2
Ten toxicity scenarios with the target toxicity probability of 0.3 (in boldface).

Scenario	Dose Level					
	1	2	3	4	5	6
1	**0.30**	0.38	0.45	0.60	0.68	0.75
2	0.17	**0.30**	0.43	0.55	0.65	0.80
3	0.05	0.13	**0.30**	0.38	0.65	0.85
4	0.08	0.12	0.15	**0.30**	0.45	0.65
5	0.06	0.08	0.10	0.20	**0.30**	0.50
6	0.01	0.04	0.08	0.10	0.15	**0.30**
7	0.08	0.10	0.12	0.15	**0.31**	0.55
8	0.05	0.10	0.15	**0.28**	0.40	0.58
9	0.15	**0.29**	0.36	0.43	0.52	0.59
10	0.06	0.12	0.18	**0.27**	0.37	0.45

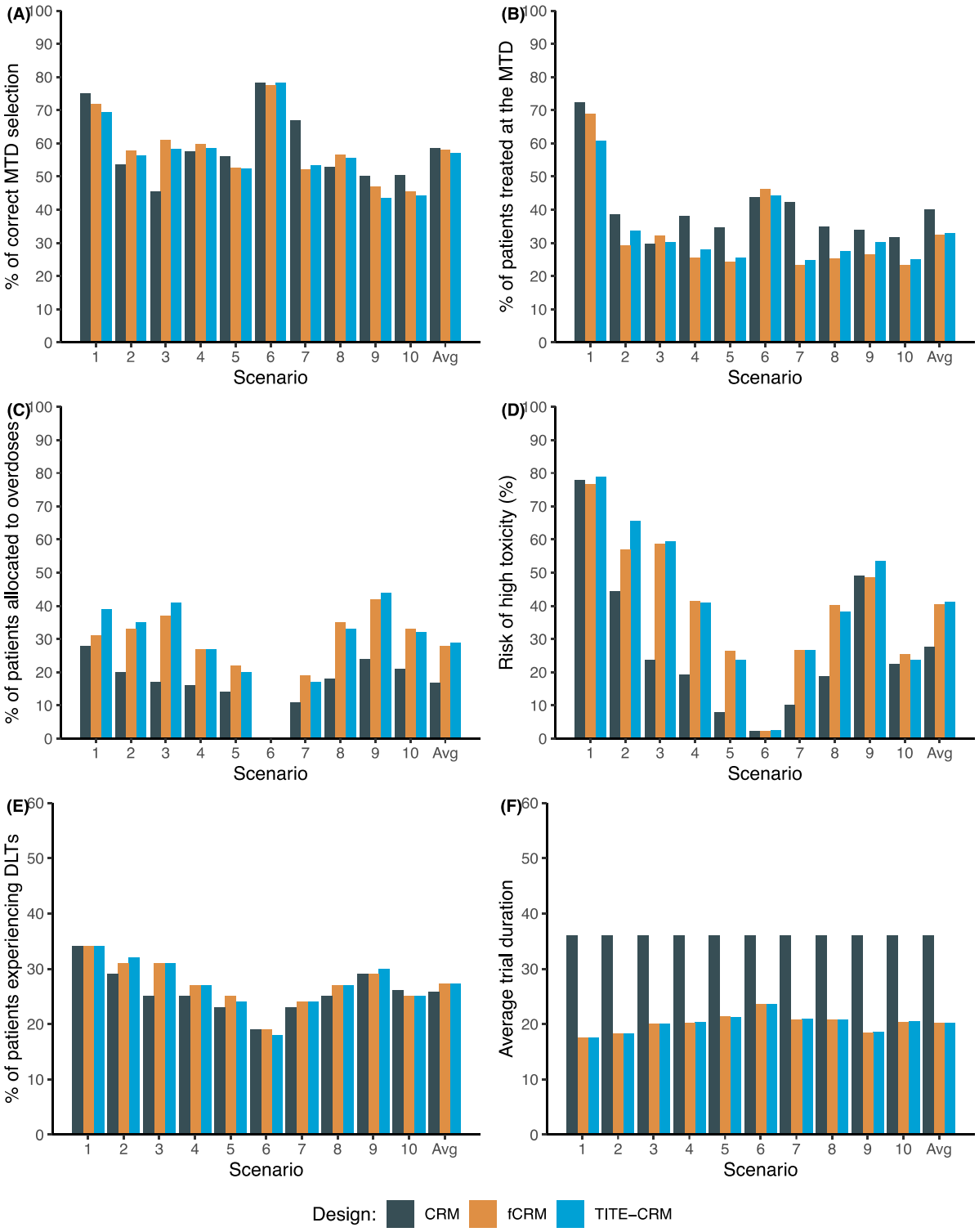

Fig. 2. (A) The percentage of correct MTD selection, (B) the percentage of patients treated at the MTD, (C) the percentage of patients allocated to overdoses, (D) risk of high toxicity (%), (E) the percentage of patients experiencing DLTs, and (F) the average trial duration of the CRM, fCRM and TITE-CRM designs. Avg represents the average value over 10 scenarios.

MTD and the percentage of patients treated at the MTD, for which the larger the better; (ii) safety statistics, including the percentage of patients allocated to overdoses; the risk of high toxicity, defined as the percentage of trials leading to the DLT rate greater than the target toxicity probability; and the percentage of patients experiencing DLTs, for which smaller values are considered more desirable and ethical as they reflect the safety aspects of a trial; and (iii) trial duration, which is calculated as the average trial duration over all simulated trials, for which the shorter the better.

Fig. 2 provides the comparison among CRM, fCRM, and TITE-CRM. In terms of PCS of the MTD, fCRM performs slightly better than TITE-CRM with an average of 2% improvement, and achieves a comparable

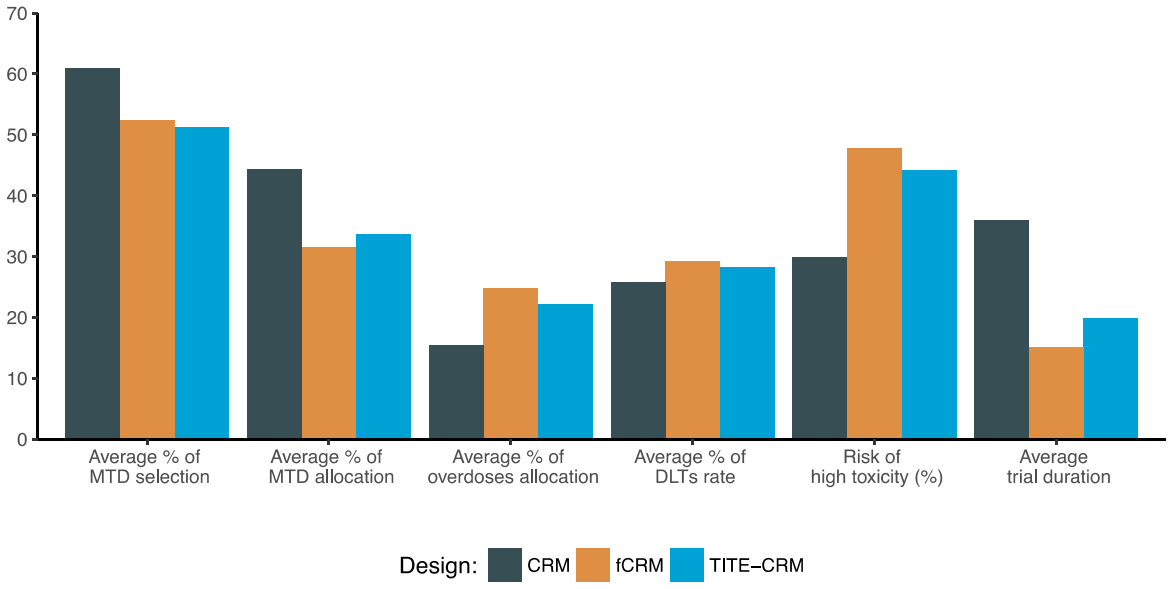

Fig. 3. The average percentages of correct MTD selection, patients treated at the MTD, patients allocated to overdoses, patients experiencing DLTs, risk of high toxicity and the average trial duration under the CRM, fCRM and TITE-CRM designs based on 1000 randomly generated scenarios each with 1000 simulated trials.

performance to CRM. For the percentage of patients treated at the MTD, fCRM yields a similar performance to TITE-CRM, while CRM performs the best as it uses the complete information with a full follow-up for estimating the toxicity probabilities. Regarding the safety of the three designs, fCRM performs similarly to TITE-CRM in terms of all three metrics. The average trial durations of fCRM and TITE-CRM are comparable but much shorter than that of CRM.

Furthermore, to overcome the subjectivity in choosing specific toxicity scenarios, we randomly generate 1000 scenarios, as illustrated in the Supplementary Fig. S1, via a modified pseudo-uniform algorithm [1]. A total of 1000 replications are conducted under each scenario. As shown by Fig. 3, the simulation study based on 1000 randomly generated scenarios further corroborate the similar performances of fCRM and TITE-CRM.

2.5. Sensitivity analysis

The percentage of censored observations is controlled by two factors: the ratio of the assessment period and inter-arrival time (A/I ratio) and the time-to-event distribution. When the A/I ratio is high, each new cohort arrives rapidly, and the trial requires more frequent decision making on dose assignment. As a result, the cohorts that have already entered the trial are only followed for a short period of time, which thus would result in a high percentage of unobserved or censored toxicity outcomes. On the other hand, if the distribution of the time to toxicity is highly skewed toward the end of the assessment period, more unobserved toxicity outcomes are expected when a new cohort arrives. This can be controlled via the adjustment of the proportion of DLT occurrences in the first half of the assessment period. To evaluate the

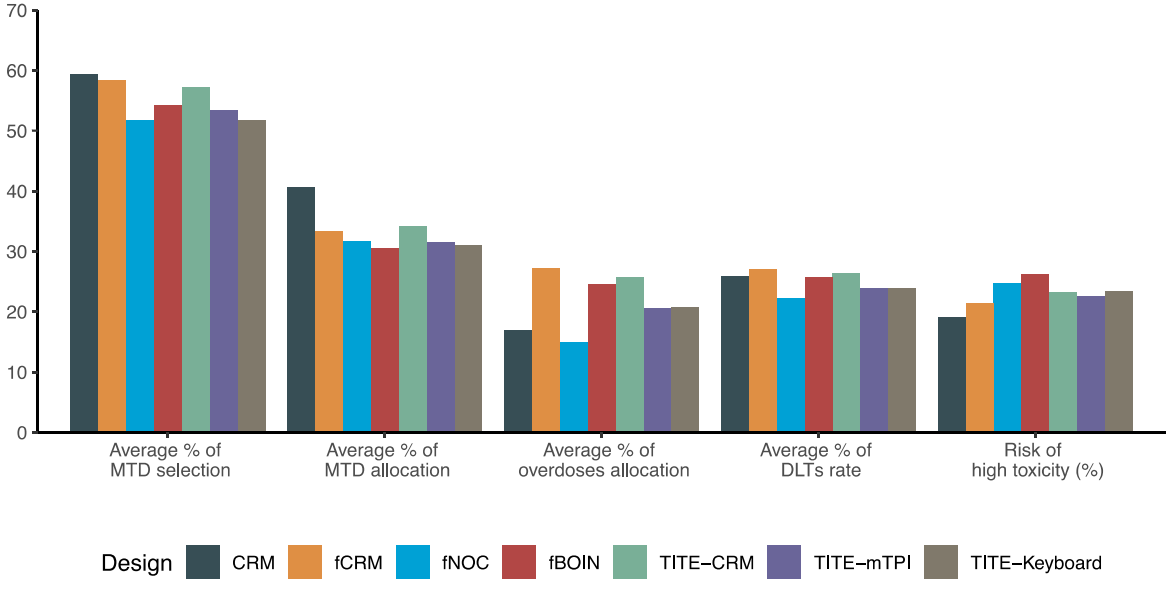

Fig. 4. The average percentages of correct MTD section, patients treated at the MTD, patients allocated to overdoses, patients experiencing DLTs, and risk of high toxicity under the CRM, fCRM, fNOC, fBOIN, TITE-CRM, TITE-mTPI, and TITE-Keyboard designs based on 1000 simulated studies over the ten fixed scenarios.

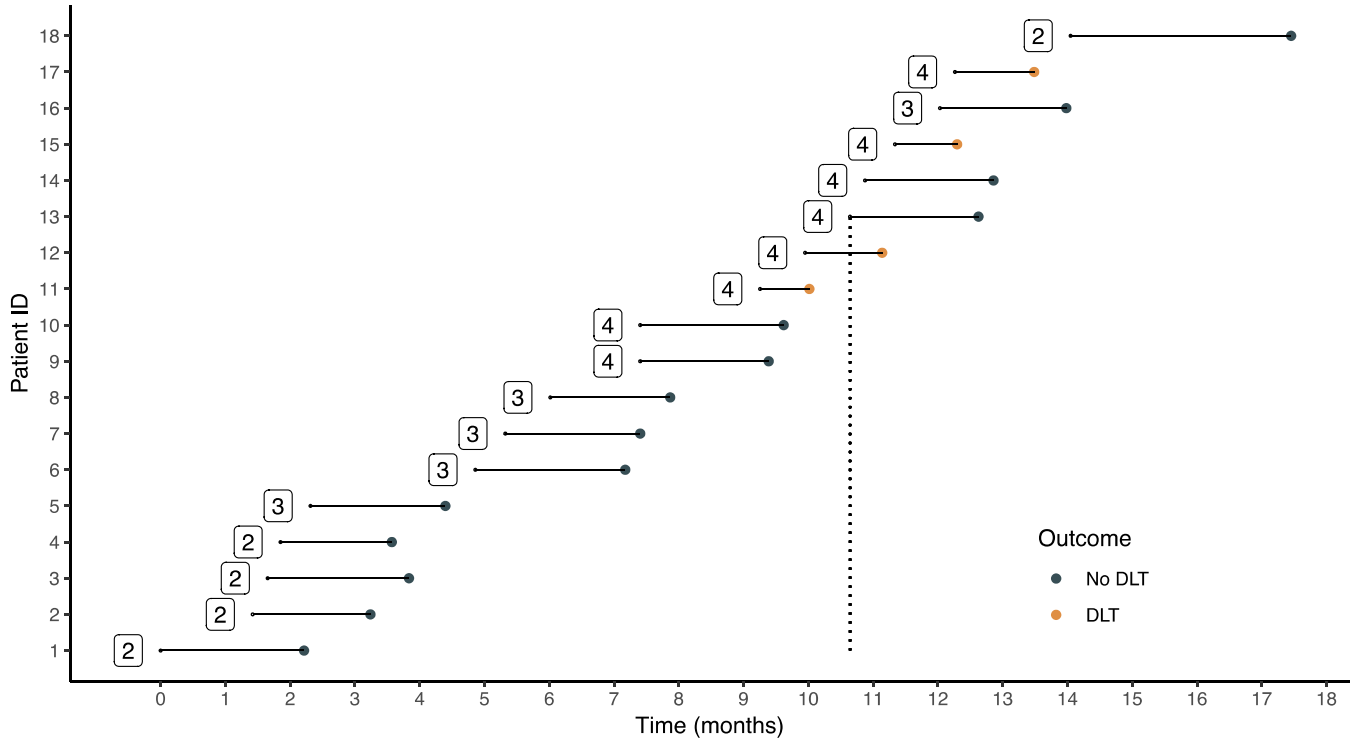

Fig. 5. The dose assignment path of the cisplatin trial using the fCRM design. For each patient, the horizontal line segment represents the follow-up time, on which the DLT is indicated by a yellow dot, no DLT by a blue dot. The number in each box indicates the dose level assigned to the corresponding patient. The dotted line indicates the decision-making time when patient 13 was ready for treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

influence of these trial aspects, we take the A/I ratio to be 4 or 6 and consider three different Weibull distributions by tuning the proportion of DLT occurrences in the first half of the assessment period (i.e., 10% or 30%).

As shown in the Supplementary Figs. S2–S4, fCRM is robust and yields desirable PCS of the MTD and the percentage of patients treated at the MTD is comparable with that under TITE-CRM. As expected, the safety statistics of both fCRM and TITE-CRM are slightly deteriorated as the A/I ratio and the proportion of DLT occurrences in the first half of the assessment period become large. The average trial duration of fCRM is similar to that of TITE-CRM, while both are much shorter than that of CRM.

2.6. Comparisons with other methods

Moreover, we carry out a comprehensive comparison among several popular designs, including the CRM, fCRM, fNOC, fBOIN, TITE-CRM, and TITE-mTPI [31] as well as TITE-Keyboard [21]. As shown in Fig. 4, fCRM outperforms fNOC, fBOIN, TITE-mTPI, and TITE-Keyboard in terms of both the percentage of correct MTD selection and the percentage of MTD allocation. The safety of fCRM is slightly deteriorated in terms of the percentage of overdoses allocation.

2.7. Cisplatin trial in pancreatic cancer

To illustrate the fCRM with a real trial, we consider a cisplatin trial in pancreatic cancer [32]. Preclinical studies had shown that the combination of gemcitabine and cisplatin could produce synergistic cytotoxicity without loss of radiosensitization, which might lead to improved control of pancreatic cancer. The objective of the trial was to identify the MTD of cisplatin which would be combined with the full-dose gemcitabine and radiation therapy. The trial involved four doses of cisplatin: 20 mg/m^3, 30 mg/m^3, 40 mg/m^3, and 50 mg/m^3. The sample size was 18 and patients were treated in a cohort size of 1. The target probability of DLT was 0.20. The initial dose of cisplatin was 30 mg/m^3 and the assessment window was 9 weeks. The dose assignment for each incoming patient was determined by TITE-CRM [32].

Table 3
The estimated DLT probabilities up to enrollment of patients 13–18 in the cisplatin trial using the fCRM with the target toxicity probability of 0.20

Patient ID	Currently estimated posterior DLT probability				Optimal dose (mg/m^3)
	20 mg/m^3	30 mg/m^3	40 mg/m^3	50 mg/m^3	
13	0.050	0.078	0.109	0.143	50
14	0.043	0.070	0.099	0.131	50
15	0.087	0.128	0.170	0.214	50
16	0.074	0.112	0.152	0.193	50
17	0.105	0.152	0.190	0.244	40
18	0.088	0.130	0.173	0.217	50
MTD Selection	0.118	0.167	0.216	0.264	40

We reran the trial using fCRM, for which Fig. 5 shows the path of the dose assignments for all patients. The fCRM kicked in after patient 11 experienced DLT, and patient 12 was assigned to dose 50 mg/m^3. As shown in Table 3, the DLT probability estimates for the four doses given all the previously treated 12 patients were $(0.050, 0.078, 0.109, 0.143)$ and the fractional contribution from patient 12 was 0.091, and thus patient 13 was assigned to dose 50 mg/m^3. At the end of the trial, dose 40 mg/m^3 was selected as the MTD with the estimated DLT probability of 0.216.

3. Discussion

The TITE-CRM, embodying the spirit of the time-to-event weighting

method, has gained enormous popularity in addressing the issue of LO toxicities, which has been successfully implemented in several major academic cancer centers, such as Columbia University [33,34], University of Michigan [8,35] and the NCI Radiation Therapy Oncology Group [23]. As an alternative approach, we illustrate the fCRM design and make a comprehensive comparison of fCRM with other time-to-event weighting methods. As demonstrated in the simulation studies and sensitivity analysis, fCRM possesses a competitive performance with other time-to-event weighting counterparts. Therefore, fCRM can serve as an alternative paradigm to addressing the issue of LO toxicities, commonly arising in dose-finding studies with novel MTAs [35] and immunotherapies [36]. Unlike the weighting scheme which may lead to different design properties depending on weighting functions, the fractional scheme delivers a unique solution using the Kaplan-Meier estimator, which is nonparametric and thus robust. It simply fractionizes the outcome to a value between 0 and 1 if it is not observed yet. As a result, the fractional scheme is universally applicable to all dose-finding methods, which can be viewed as a response to the call for innovative adaptive phase I trial designs from the FDA [37] and the American Society of Clinical Oncology (ASCO) [38].

Moreover, the fractional contribution delivers a more clinically meaningful interpretation as it represents the conditional probability of experiencing DLT in the remaining assessment period given that the patient has not yet experienced it by the decision-making time [39,40]. In contrast, the weight in the TITE-CRM solely reflects the partial follow-up time for patients who have not experienced DLT. The fCRM, inheriting the robustness property of the Kaplan-Meier estimator, is less sensitive to the distribution of the time to toxicity. Note that we observe slight deterioration in the performance as the A/I ratio increases. This is expected as the larger the A/I ratio, the faster the enrollment as well as the higher frequency of decision making. In this case, decision making becomes more difficult and may result in aggregative dose escalation owing to the short follow-ups. In practice, due to the safety consideration, seldom do we use such a high A/I ratio (i.e., 6), and the probability of DLT occurrence in the first cycle of treatment is generally less than 50% [3–5].

Extensive simulation studies should be conducted to evaluate the operating characteristics of the fractional design prior to the launch of a new trial. To facilitate the use of the fCRM, we have developed a Shiny App (https://demoyang.shinyapps.io/clinicaltrialdesignapp_fcrm/) and R software codes, which can be freely downloaded from the GitHub (https://github.com/ZhaoYangCICAMS/fCRM).

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Declaration of competing interest

The authors declare no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2020.100650.

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