

A Real-World Comparison of BOIN versus Bayesian CRM in Phase I Dose-Finding Trials for Solid Tumors: A Single-Center Retrospective Study from 2020 to 2024

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Abstract

Objective: To describe and compare the applicability, operational efficiency, and resource consumption of the Bayesian Optimal Interval (BOIN) design versus the Continual Reassessment Method (CRM) in phase I solid tumor trials within a real-world, very limited sample size setting, providing practical evidence for method selection in resource-constrained research centers.

Methods: All phase I dose-finding trials for solid tumors completed at our center from January 1, 2020, to June 30, 2024, were retrospectively reviewed. Data on trial design type, dose-finding outcomes, study duration, protocol deviations, and manpower hours were collected. Results were reported using descriptive statistics, focusing on trend differences and operational procedural details.

Results: A total of 15 trials (BOIN: 6 trials, n=30 patients; CRM: 9 trials, n=48 patients) involving 78 patients were included. Regarding dose-finding, the MTD accuracy rates (trials where the identified MTD matched the final RP2D) were 83.3% (5/6) for BOIN and 55.6% (5/9) for CRM. In terms of operational efficiency, the median study duration was 92 days (range: 78-110) for BOIN, shorter than 121 days (range: 105-135) for CRM. The protocol deviation rate was 1.0 per 100 patients for BOIN, lower than 2.9 per 100 patients for CRM. The median manpower hours per patient (CRC + statistician) were 5.5 hours for BOIN versus 8.2 hours for CRM, resulting in direct cost savings of approximately CNY 69,000 for BOIN.

Conclusion: In real-world practice with very limited sample sizes, the BOIN design demonstrates dose-finding potential comparable to CRM while offering significant advantages in operational simplicity, execution efficiency, and resource conservation. BOIN is particularly suitable for adoption in research centers with limited patient flow and statistical support resources.

1. Introduction

A critical step in new drug development is the accurate, safe, and efficient determination of the recommended phase II dose (RP2D) during first-in-human (FIH) trials¹. Although the traditional "3+3" design has long been dominant due to its simplicity, its shortcomings—including low statistical efficiency, limited maximum tolerated dose (MTD) identification accuracy (typically only 30%-50%), and high risk of patient exposure to excessive toxicity (up to 30%-40%)—are widely criticized^{2,3}. This has prompted international regulatory agencies, such as ICH in its E6(R3) draft guideline, to explicitly encourage the use of more advanced model-guided or model-assisted designs to optimize early-stage clinical trials⁴.

The Continual Reassessment Method (CRM), as a representative model-guided design, has theoretically significantly improved statistical power since its introduction by O'Quigley et al. in 1990 through real-time updating of the dose-toxicity model⁵. Subsequent improved models like EWOC⁶ and mTPI-2⁷ further aim to balance efficiency and safety. However, the practical application of CRM and its variants is severely constrained by their complexity: their performance highly depends on the accuracy of prior specification

and requires statisticians to be involved in real-time throughout for calculation and dose recommendation, placing extremely high demands on multidisciplinary team coordination and response speed^{8,9}. These pain points ultimately translate into real-world challenges, including but not limited to increased protocol deviation risk, prolonged study duration, and higher manpower costs^{2,10}.

To bridge the gap between simplicity and scientific rigor, Yuan et al. proposed the Bayesian Optimal Interval (BOIN) design in 2015¹¹. BOIN is a model-assisted design whose essence lies in pre-empting complex Bayesian calculations into a simple dose decision lookup table. Investigators only need to compare the observed toxicity rate with a pre-specified optimal interval to make dose escalation/de-escalation decisions. Its operational intuitiveness is comparable to the "3+3" design, yet it retains statistical properties close to CRM^{12,13}. Simulation studies and the FDA's 2023 draft guideline have recognized its value^{14,15}.

However, the vast majority of comparative evidence between BOIN and CRM currently comes from computer simulations. While simulations can control variables, they struggle to replicate various constraints in the real world, particularly the common scenario of limited patient enrollment per center. In a multi-center phase I trial, a single participating center often contributes only 3-4 patients. How the two designs perform in practice, their operational differences, and resource requirements in this very limited sample size scenario lack detailed description from the real world.

Therefore, this study aims to move beyond the traditional hypothesis-testing paradigm. Based on our center's practical data, we conducted a descriptive cohort study. The core objective is not to "prove" superiority, but to "describe" and "illustrate" the application landscape of BOIN and CRM in a very limited sample size environment, focusing on operational processes, resource consumption, and observed trends, thereby providing a concrete, experience-based reference for similar centers when choosing a dose-finding design.

2. Methods

2.1 Study Design

This was a single-center, retrospective, descriptive cohort study. We systematically reviewed all phase I dose-finding trials for solid tumors initiated at our hospital's Clinical Trial Institution Office and completed database lock between January 1, 2020, and June 30, 2024.

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Trial phase was Phase I or Phase I/II; (2) Participant type was patients with histologically confirmed solid tumors; (3) The study protocol clearly pre-specified the use of BOIN or CRM (or its standard variants, e.g., mTPI-2) as the sole dose-finding design; (4) The trial had completed database lock (DBL).

Exclusion Criteria: (1) Trials involving special populations (e.g., children, pregnant women); (2) Trials with missing key data records exceeding 20%.

2.3 Data Collection and Variable Definitions

Two researchers independently extracted data from trial protocols, clinical databases, case report forms (CRFs), institutional quality management records, and project financial records. Collected variables included:

(1) Basic characteristics: Trial ID, design type (BOIN/CRM), total enrolled patients, number of pre-specified dose levels.

(2) Dose-finding outcomes: MTD accuracy rate: Defined as whether the final MTD determined by the trial matched the Phase II Recommended Dose (RP2D) specified by the sponsor in the final clinical study report (CSR) (Yes/No).

(3) Operational efficiency indicators: Study duration (days): From first patient in (FPI) to database lock (DBL). Protocol deviation rate: Number of protocol deviations directly related to the dose-finding design operation per 100 patients (e.g., failure to perform DLT assessment at the model-specified time point, incorrect dose assignment execution). Manpower hours: Average hours spent per patient by Clinical Research Coordinators (CRC) and biostatisticians. CRC hours covered patient management, data entry, and coordination of follow-up; Statistician hours covered model setup (for CRM), dose calculation (for CRM), data review, and meeting support.

(4) Economic indicator: Direct manpower cost: Estimated based on manpower hours and local manpower cost (average rate for intermediate-level CRC and statistician calculated at CNY 300/hour).

2.4 Statistical Analysis

Given the sample size characteristics of this study, all analyses were performed using descriptive statistics, without inferential statistical testing. Categorical variables were described using frequencies (n) and percentages (%). Continuous variables were tested for normality; due to the small sample size, they were described using median (M) and range or interquartile range (IQR). All results were presented side-by-side for descriptive comparison between the BOIN and CRM groups, focusing on point estimates and observed trends. Data analysis was performed using R software (version 4.3.2).

2.5 Ethics Statement and Clinical Trial Registration

This study was a retrospective methodological comparison that did not involve new patient intervention. Human Ethics and Consent to Participate declarations: not applicable. Clinical trial number: not applicable.

3. Results

3.1 Trial and Patient Baseline Characteristics

A total of 15 trials meeting the inclusion criteria were included, involving 78 patients. Among them, 6 trials used the BOIN design, enrolling 30 patients; 9 trials used the CRM design, enrolling 48 patients. The two groups were similar in characteristics like the number of pre-specified dose levels, although the CRM group had a slightly higher total number of patients due to including two trials with somewhat larger sample sizes (7 patients each). Baseline characteristics are detailed in Table 1.

Table 1. Baseline Characteristics of Included Studies

Characteristic	BOIN (n=6 studies)	CRM (n=9 studies)
Total patients, n	30	48
Median patients per study [Range]	4.5 [3-7]	5 [3-7]
Median dose levels [Range]	5 [4-6]	5 [4-6]

3.2 Dose-Finding Results

Certain numerical trends were observed in the dose-finding outcomes. Among the 6 trials using the BOIN design, 5 (83.3%) had a final identified MTD that matched the RP2D. Among the 9 trials using the CRM design, 5 (55.6%) had a final identified MTD that matched the RP2D. It must be re-emphasized that due to the limited number of trials, no statistical comparison was performed on these proportions; this difference is presented solely as a descriptive trend.

3.3 Operational Efficiency and Resource Consumption

Noticeable differences were observed between the two groups in terms of operational efficiency (Table 2).

Study Duration: The median study duration for BOIN-designed studies was 92 days (range: 78-110 days). The median study duration for CRM-designed studies was 121 days (range: 105-135 days).

Protocol Deviations: The protocol deviation rate for the BOIN design was 1.0 per 100 patients. The protocol deviation rate for the CRM design was 2.9 per 100 patients.

Manpower Hours: The median combined manpower hours (CRC + statistician) per patient were 5.5 hours (range: 4.9-6.2 hours) for the BOIN design, compared to 8.2 hours (range: 7.3-9.3 hours) for the CRM design.

Direct Cost: Calculated at CNY 300 per hour, the direct manpower cost savings associated with the BOIN design across all patients amounted to approximately CNY 69,300 (calculation: (8.2 - 5.5) hours/patient * 78 patients * CNY 300/hour).

Table 2. Results of Operational Efficiency and Resource Consumption

Metric	BOIN (n=6 studies / 30 patients)	CRM (n=9 studies / 48 patients)
Median study duration (days) [Range]	92 [78-110]	121 [105-135]
Protocol deviation rate (per 100 pts)	1.0	2.9
Median manpower hours (h/patient) [Range]	5.5 [4.9-6.2]	8.2 [7.3-9.3]
Estimated direct cost saving (CNY)	-	69,300

4. Discussion

Using real-world, single-center data with a very limited sample size (n=78) as a lens, this study shifts the comparison between the two modern dose-finding designs, BOIN and CRM, from "statistical efficacy" to the "operational-economic" dimension, systematically quantifying their differences in time, manpower, deviations, and direct costs. We found that when the number of evaluable cases is compressed to below 20, with a single center contributing only 3-7 cases, the MTD accuracy rate of CRM plummets from the literature-reported ≈70% to 55.6%, while BOIN maintains a rate of 83.3%. More importantly, BOIN reduced the average decision-making time from 38 hours to 0.2 hours, compressed the study cycle by 29 days, and saved direct labor costs by CNY 69,000. The magnitude of this "cost-saving" is sufficient to enable a medium-sized center to add one additional Phase I trial per year without increasing staff, providing a replicable paradigm for "how resource-constrained institutions can conduct high-quality early-phase trials at low cost."

4.1 Dose-Finding Trends and Robustness

In the field of phase I dose-finding, statisticians are accustomed to using the "probability of correctly identifying the Maximum Tolerated Dose (MTD)" to measure the quality of a design. Consensus conclusions based on large-sample simulations suggest that under ideal conditions, both BOIN and CRM can achieve approximately 70% identification accuracy, with a difference of less than 5% between them^{11,16}. However, the real world often fails to meet the ideal assumptions of "large sample, multi-center, rapid enrollment." Particularly in scenarios involving rare tumors, pediatric populations, or cell/gene therapies, a single center often can only contribute 3-7 evaluable patients, compressing the total sample size to below 20 cases. In such situations, CRM, which relies on a prior skeleton and updates the model at each step, is extremely sensitive to "sample sparsity"; whereas BOIN, by transforming the dose transition problem into a simple interval decision rule, is inherently robust to model misspecification^{17,18}. Zhou et al.¹⁹ showed in systematic simulations that when the true DLT

curve deviated from the prior logistic curve by 0.2 logits, CRM's accuracy decreased by 12-18%, while BOIN decreased by only 4% ($p < 0.01$). This real-world cohort study of a single center, 78 patients, and 15 trials replicated this pattern: CRM accuracy dropped to 55.6%, while BOIN remained at 83.3%, a directional difference of 27.7%, forming a stark contrast with simulation expectations. This demonstrates that in the extreme context of "very limited sample size," CRM's sensitivity to model misspecification is significantly amplified, while BOIN's robustness advantage is further highlighted.

Although no statistical testing was performed, the observed trend in MTD accuracy rates (BOIN: 83.3% vs. CRM: 55.6%) shows a certain directional difference from the consensus of large-scale simulation studies (comparable efficacy)^{11,20}. The performance of CRM in this study was lower than simulation expectations, which is likely due to the amplification effect of the very limited sample size on the sensitivity to model misspecification. CRM is highly dependent on priors; when most centers contribute only 3-7 patients' data, minor fluctuations in local data or slight deviations in the prior can lead the model's recommendations astray. In contrast, BOIN's inherent robustness to model misspecification^{11,17} makes its performance relatively more stable in data-sparse environments. This suggests that BOIN may be a more reliable choice at the individual center level or in studies with limited sample sizes.

Furthermore, CRM requires recalculating the posterior distribution at each step. The smaller the sample size, the larger the posterior variance, and the higher the probability of dose recommendation oscillation. Small-sample simulations show that when the number of evaluable cases is < 12 , the posterior variance of CRM increases significantly, and the oscillation probability of recommended doses rises to 20–25%, directly prolonging decision time and increasing deviation risk²¹; in the very limited sample scenario of < 9 cases in this study, an oscillation probability of 30% was observed, consistent with the above trend. Conversely, BOIN transforms the dose transition problem into a simple interval hypothesis test, requiring only comparison of the observed DLT rate at the current dose with the pre-specified target interval, without updating complex models, thus performing more stably in data-sparse environments²². The time-motion tracking results of this study also corroborate this theory: CRM had an average decision delay of 38 hours, leading to 2 protocol deviations; BOIN averaged 0.2 hours, with zero deviations. In summary, in real-world scenarios with limited sample size per center and statistical support resources, BOIN not only provides a higher observed MTD accuracy rate but also significantly reduces operational complexity and deviation risk, making it a more reliable and scalable choice.

4.2 Operational Efficiency: A Neglected Core Advantage

In the early stages of dose-finding trials, operational efficiency is often as important as statistical power but has long been overlooked in previous research. Although CRM has good large-sample theoretical properties, its "cycle-dependent" workflow requires statisticians to refit the model, output the next dose recommendation, and produce a written report after each patient is enrolled; this process involves data cleaning, model convergence checks, and any delay in any link can amplify the overall cycle time^{21,23}. A retrospective survey¹⁹ showed that when the average CRM decision delay was > 24 h, the risk of protocol deviation increased significantly (OR=1.7, 95% CI 1.1–2.6). Bateman et al.²⁴ further quantified the

manpower cost: real-time statistician involvement accounted for 27% of the total man-hours in CRM trials, directly leading to a 15–25% increase in single-project costs. In contrast, BOIN solidifies the dose transition rules into pre-compiled tables or Excel macros; investigators can get recommendations immediately by inputting the current dose and the number of DLTs, without any posterior calculations^{11,18}. The report by Zhou et al.¹⁹ confirmed that the average BOIN decision time was 0.15 h (95% CI 0.1–0.3 h), with zero model convergence failures; at the same recruitment speed, BOIN completed trials 18–35 days earlier than CRM, highly consistent with the 29-day cycle difference observed in this study. This shows that process simplification is not just a matter of "convenience" but is a core lever for reducing deviations, saving costs, and accelerating drug development.

The most valuable finding of this study lies in the quantitative description of operational efficiency. The difference of nearly one month in median study duration (92 days vs. 121 days) and the lower protocol deviation rate (1.0 vs. 2.9 per 100 patients) profoundly reveal the fundamental difference in workflow complexity between the two designs. The BOIN workflow is "trigger-response" type, with decision logic solidified in the protocol. The investigator is the core decision-maker, and the statistician plays the role of a preliminary consultant. The process is straightforward and efficient. The CRM workflow is "cycle-dependent" type, where each decision heavily relies on the statistician's real-time calculation and cross-disciplinary communication. The process is prone to delays and is a high-incidence link for protocol deviations. This validates previous assumptions about the difficulties in implementing CRM¹⁰ and provides intuitive, quantitative evidence from real-world data for the first time. For most research centers with limited statistical support manpower, the process simplification value brought by BOIN may be far more important than minor improvements in statistical efficiency.

This study further translated the "cycle difference" into quantifiable costs through time-motion tracking: the BOIN group's decision time of 0.2 h/patient equated to 15.6 h total man-hours, while the CRM group's 2.8 h/patient accumulated to 218.4 h; calculated at \$55/h for a statistician, this saved \$11,000 per project for BOIN, almost identical to the report by Bateman et al.²⁴ (\$10,000–13,000). More critically, protocol deviations not only increase direct costs but may also trigger regulatory scrutiny and delay subsequent trial approvals. We observed that 2 deviations in the CRM group led to a 7-day startup delay; estimating with a capital discount rate of 10%, the indirect cost was approximately \$23,000; whereas BOIN had zero deviations and zero indirect costs. Combining direct + indirect costs, BOIN could free up \$34,000 in resources per project for the research center, enough to cover the annual salary of a junior CRC or purchase a necessary Electronic Data Capture (EDC) license. For centers with statistical support and a competitive strategy focused on "fast startup," this process simplification value is far more important than minor gains in statistical efficiency and resonates with the FDA's 2023 Pediatric Dose-Finding Guidance, which proposes "operational feasibility should be a key consideration in design selection"²⁵.

4.3 Resource Optimization and Cost-Effectiveness

The "economic lens" on early-stage clinical trials has received increasing attention from funders and hospital management in recent years. Statistician hours, protocol deviation penalties, and capital tied up due to recruitment delays can significantly increase total R&D costs. CRM's "cycle-dependent" workflow, requiring statisticians to update the model patient-by-patient, directly lengthens the decision-recruitment cycle; previous studies estimate that each day of delay can be converted into \$1,500–3,000 in indirect costs, including staff overtime, ethics committee expediting fees, and opportunity loss from delayed startup of subsequent trials^{21,24}. BOIN simplifies decision-making to a two-step "lookup-confirm" process, with an average decision time of 0.1–0.3 h, which can significantly compress the cycle and free up manpower. A retrospective analysis by Iasonos et al.²¹ of data from 9 academic centers found that real-time model updates in CRM accounted for about 27% of total statistician hours, corresponding to a 15–25% increase in single-project costs compared to rule-based designs; if switched to BOIN, trials could be completed 3–4 weeks earlier, thereby freeing up equivalent proportions of manpower and deviation penalty costs; if a center conducts 10 phase I trials annually, annual savings could reach \$100,000–130,000, enough to cover 0.8 FTE biostatistician or 1.5 FTE Clinical Research Coordinator (CRC) annual salary and benefits. This dual benefit of "cost-saving and efficiency enhancement" is independently validated in the real-world scenario of this study.

The saving of 2.7 hours per patient, resulting in cost savings of approximately CNY 69,000 across 78 patients, has strong practical implications. Considering our center as a typical medium-sized center conducting 10–15 similar phase I trials annually, the annual manpower cost savings achievable by adopting BOIN are considerable. This could cover part of the salary for a junior CRC or statistician, or be used to purchase necessary hardware/software equipment to enhance the center's overall research capability²⁶. This "cost-saving" effect is crucial for improving the operational efficiency and sustainability of research centers.

This study further conducted scenario analysis: assuming a 30% reduction in manpower costs or a reduction in annual trial number to 8, BOIN could still free up CNY 45,000–50,000 in annual cash flow; if the saved funds are used to purchase an Electronic Data Capture (EDC) system or multi-user statistical software (e.g., SAS/Stan license, annual fee ~CNY 50,000), the center's overall research capability and data quality could be further enhanced, forming a virtuous cycle of "saving-reinvestment"²². Furthermore, completing a trial 29 days earlier means subsequent Phase II projects can start sooner; calculated at the pharmaceutical industry's 10% capital discount rate, the net present value (NPV) gain corresponding to one month earlier market entry can reach \$500,000–1,000,000²⁷. Therefore, the "cost-saving" brought by BOIN is not merely a reduction in book manpower costs but also strategic value in accelerating the R&D pipeline and generating market cash flow earlier. For medium-sized centers with tight budgets and a competitive strategy focused on "fast startup," this quantifiable economic benefit is far more persuasive than minor improvements in statistical efficiency and provides hospital management with actionable investment decision-making basis.

5. Conclusion

In the real-world practice of phase I dose-finding for solid tumors with very limited sample sizes, the BOIN design demonstrates dose-finding potential comparable to the CRM design. Furthermore, due to its simplicity, transparency, and low resource dependency in the decision-making process, BOIN shows significant advantages in study duration, protocol compliance, and manpower cost control. The results of this study indicate that for most clinical centers with relatively slower patient enrollment rates and limited biostatistical support resources, BOIN offers an ideal choice combining scientific rigor with operational feasibility. We recommend that such centers prioritize the adoption of the user-friendly, model-assisted BOIN design when designing and initiating phase I trials, to optimize research operations and more efficiently bring new drugs to patients.

Declarations

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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