Incorporating Historical Information to Improve Phase I Clinical Trial Designs

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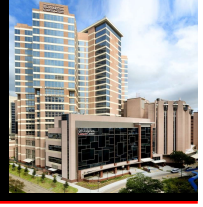


Abstract

Motivation To improve the efficiency of the model-assisted designs, we propose a unified framework that allows incorporating historical data into the derivation of the decisions rules in these designs.
Innovation The proposed approach adapts the well-established ``skeleton" approach, combined with the concept of effective sample size, making it easier to understand by the clinical community.
Significance The proposed approach is easy to understand and maintains the hallmark of the model-assisted design: the dose escalation/de-escalation rules can be tabulated prior to the trial. Our user-friendly software can provide timely interactive feedback for practitioners or researchers to evaluate the accuracy, safety, and reliability of the design.

Methods

❑ Unified framework for informative prior incorporation

The proposed method (Figure 1B) takes a similar approach as the CRM skeleton (Figure 1A), combined with the concept of effective sample size, to allow the incorporation of prior information into the model-assisted designs (mTPI, BOIN, Keyboard, etc.). We referred to these new designs as informative designs, e.g., iTPI, iBOIN, and iKeyboard.

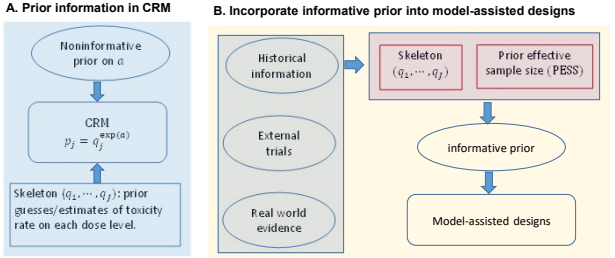


Figure 1. The skeleton approach for informative prior incorporation in CRM and model-assisted designs, where p_j is the true toxicity probability and J is the number of doses in the trial.

❑ Robust prior

To avoid a substantial loss of performance when the prior is severely mis-specified. Based on numerical studies, we recommend $PESS \in [1/3(N/J);\ 1/2(N/J)]$ as the default value that improves trial performance while maintaining reasonably robust.

❑ Evaluate the operating characteristics of the informative designs through extensive simulation

- **General trial setting:** target DLT probability is 0.3; prior effective sample size $\text{PESS} = 3$; maximum sample size is 30; patients are enrolled in cohort size of 3.
- **Scenarios:** ten fixed scenarios and 2000 random scenarios.
- **Prior specifications:** prior is (1) correctly specified or (2) mis-specified with different level of severity (e.g., prior MTD is one dose or two doses off the true MTD.
- **Designs in comparison:** $\text{CRM}, \text{iCRM};\ \text{BOIN}, \text{iBOIN}, \text{iBOIN}_R;\ \text{Keyboard}, \text{iKeyboard}, \text{and iKeyboard}_R$. The iCRM indicates that informative prior is used for α and the corresponding PESS is matched to those in other informative model-assisted designs. The subscript R means that robust prior is used.
- **Four metrics to evaluate:** shown in Figures 2-4.

Results

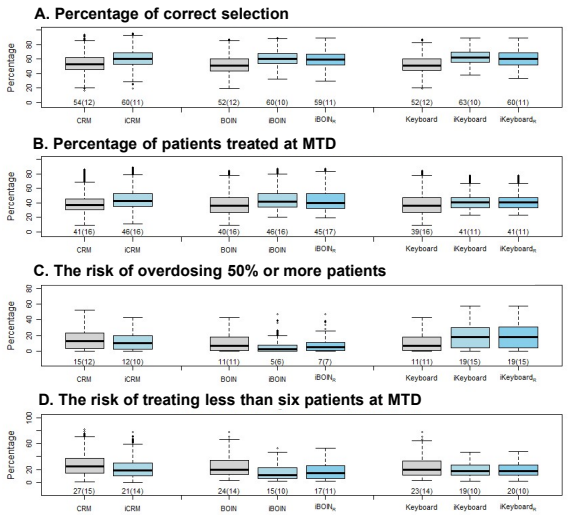


Figure 2. Operating characteristics under random scenarios where ***the prior MTD is correctly specified***.

Main findings in Figure 2:

- iCRM and iBOIN outperformed their non-informative counterparts with a higher PCS and better patient allocation to MTD.
- Compared to iCRM, iBOIN had a lower risk of overdosing and poor allocation.
- iKeyboard yielded a higher PCS than its non-informative counterpart, but increased the risk of overdosing due to its aggressive dose escalation.

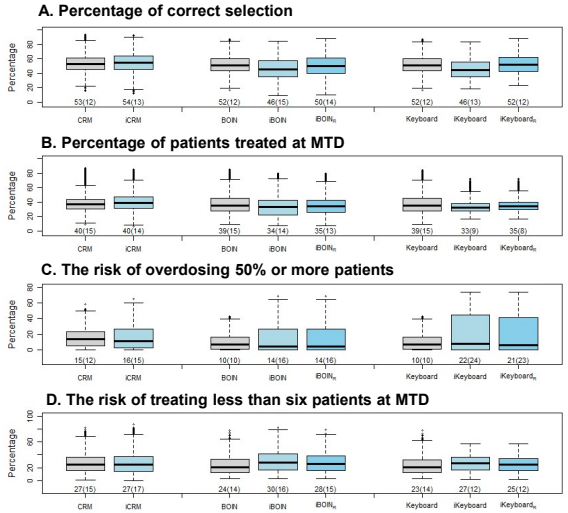
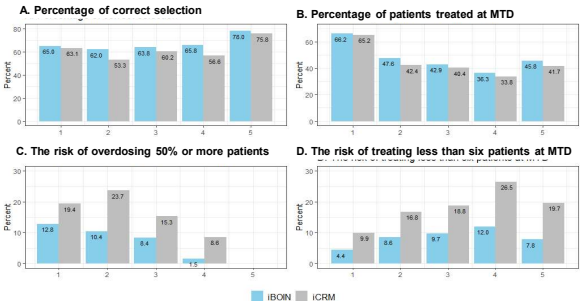


Figure 3. Operating characteristics under random scenarios where ***the prior MTD is two doses off the true MTD***.

Main finding in Figure 3: iCRM was more robust than iBOIN; however, by using the proposed robust prior, iBOIN_R showed competitive performance.



PESS for the first five scenarios

Scenario	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
1	6	3	3	2	1
2	3	7	3	1	1
3	2	4	7	1	1
4	1	2	4	7	1
5	2	2	2	4	5

Figure 4. Operating characteristics of iBOIN and iCRM when ***different amount of prior information (i.e., PESS) is available for different doses*** under the first five fixed scenarios (see Zhou et al., 2020 for specific performance of the designs in the ten fixed scenarios).

Main findings in Figure 4: Compared to CRM, iBOIN offered a higher PCS and allocated a larger percentage of patients at the MTD, as well as a lower risk of overdosing and poor allocation. This is because CRM does not allow for specifying dose-specific PESS as it uses a single parameter (α) to control prior information in all doses, thus it cannot take full advantage of the prior information.

Recommendation: iBOIN appear to be the most efficient design among the informative designs when the same prior information is available. We have developed a user-friendly App for implementing this design. Figure 5 shows how to obtain the App for use.

Scan the QR code: →Phase I→BOIN Suite→Single Agent→BOIN/iBOIN→Lauch→iBOIN

Figure 5. The flowchart to find the iBOIN web-based application to design and implement phase I clinical trials.

Conclusions

Our unified framework to incorporate historical data or real-world evidence has improved the efficiency of phase I trial design. When prior MTD is correctly specified, all the informative designs greatly improve both PCS and patient allocation, with the largest improvement in iBOIN. Both iCRM and iKeyboard are riskier than iBOIN. Thus, we recommend iBOIN for phase I clinical trial designs when good prior information is available, due to the simplicity and superior performance of the design. Note that iBOIN with robust prior or standard BOIN should be used if it is anticipated that the prior may not well approximate the true DLT probability curve. A user-friendly software is available to implement the iBOIN design at www.trialdesign.org.

Key References

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4. Yan, F., Mandrekar, S. J., & Yuan, Y. (2017). Keyboard: a novel Bayesian toxicity probability interval design for phase I clinical trials. *Clinical Cancer Research*, *23*(15), 3994-4003.