Simulating maximum tolerated dose-finding oncology trials using the InSilicoTrials cloud-based platform

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INTRODUCTION

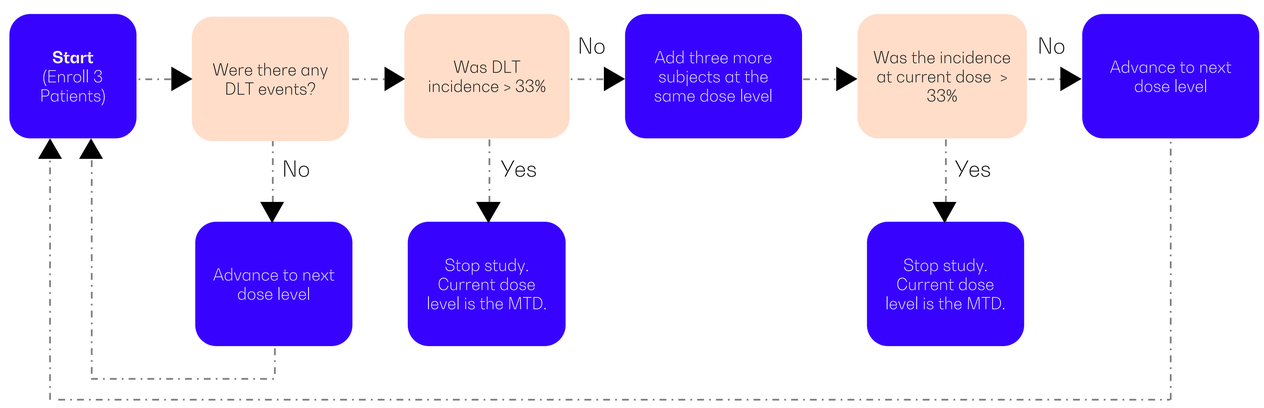
In silico clinical trials are expected to play an increasingly important role in guiding the design of oncology phase I studies aiming at determining an optimal recommended dose for subsequent Phase II trials. Such trials typically involve a design where successive cohorts of patients receive increasing dose levels until a maximum tolerated dose (MTD) associated with a predefined level of acceptable toxicities is reached [1].

OBJECTIVES

- To develop a simulation framework for oncology phase I dose-escalation studies using the InSilicoTrials cloud platform [2]
- To illustrate the implemented trial simulator using modeled exposure-response data of neutropenia grades from a first-in-human (FIH) study of a thymidylate synthase inhibitor [3].

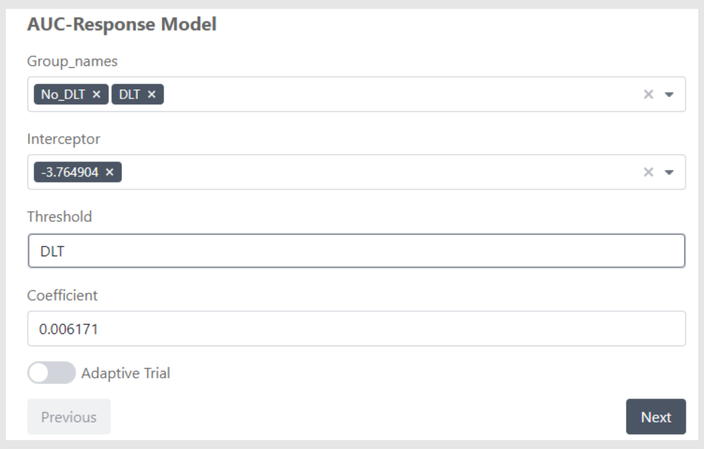
METHODS

Our cloud-based technology supports simulation of FIH studies for cytotoxic oncology products. Such studies typically employ a 3+3 dose escalation approach. This strategy involves enrolling three subjects at the first dose level and conducting a safety assessment to determine the enrollment of the next three subjects, either at the same dose (if there is a safety signal) or at the next higher dose (if there is not a safety signal). This safety assessment is repeated after each three patients are enrolled to either escalate the dose, expand the current group, or stop the trial. At the end of the study each dosing cohort will consist of either three or six patients.

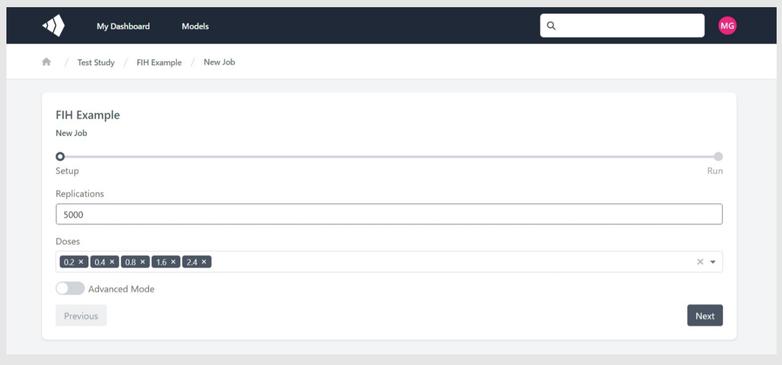


INPUT

Specify the dose-exposure and exposure-response models and the safety signal threshold



Specify the sequence of dose levels to be tested, and the number of study replicates



Meta-analysis of all replicates:
- **Summary distribution of MTD levels across replicates**
- **Average number of subjects in each cohort across replicates**

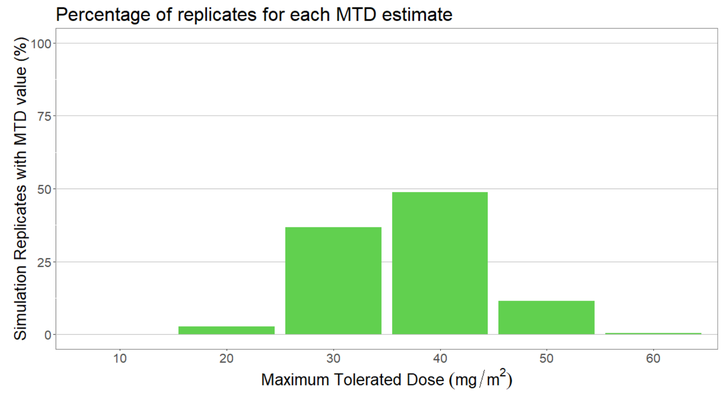
RESULTS

Our FIH trial simulator was successfully tested through modeling of published exposure-response data of neutropenia grades from a FIH study of a thymidylate synthase inhibitor [3]. The dose-exposure relationship was described by fitting a linear model on the log-transformed area under the concentration-time curve (AUC) data. An ordinal logistic regression model was used to relate AUC to neutropenia grades. A 3+3 design study with dose levels as those evaluated in the real clinical study [3] was simulated. Of 1000 study replicates, the most common MTD estimate was 40 mg/m^2 (n = 488), which was the MTD estimated from the original dose-escalation study [3]. Thus, simulation results are in good agreement with observed study results.

Simulation settings

- Number of replicates: **1000**
- Dose levels (mg/m^2): **10, 20, 30, 40 , 50, 60**

Dose (mg/m^2)	Average number of subjects
10	3.05
20	3.42
30	4.27
40	4.19
50	3.51
60	3.00



Dose (mg/m^2)	10	20	30	40	50	60
n (%)	0 (0)	26 (2.6)	368 (36.8)	488 (48.8)	114 (11.4)	4 (0.4)

CONCLUSION

This example illustrates the application of InSilicoTrials' platform to perform in silico dose-finding oncology studies. Our cloud-based technology empowers users to perform *in silico* clinical trials using an intuitive user interface. Users may explore alternative dose escalation schemes, as well as the impact of variability and sample size on the probability of establishing a MTD, and to compare candidate drugs with different anticipated safety profiles.

REFERENCES

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[3] D. A. Rinaldi et al., "Initial phase I evaluation of the novel thymidylate synthase inhibitor, LY231514, using the modified continual reassessment method for dose escalation," J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol., vol. 13, no. 11, pp. 2842–2850, Nov. 1995, doi: 10.1200/JCO.1995.13.11.2842.

DISCOVER

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