Optimizing Clinical Trial Design through In Silico Modeling, Virtual Populations, and Mathematical Optimization

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QSP Modeling approaches combined with **mathematical optimization** methods allows to identify the **best-responding patients** to **increase the probability of trial success** before study launch

jk Trial simulation → **API Score optimization** → **API Responders identification (Baseline descriptors)** → **API Absolute benefit distribution** → **API EC filtering**

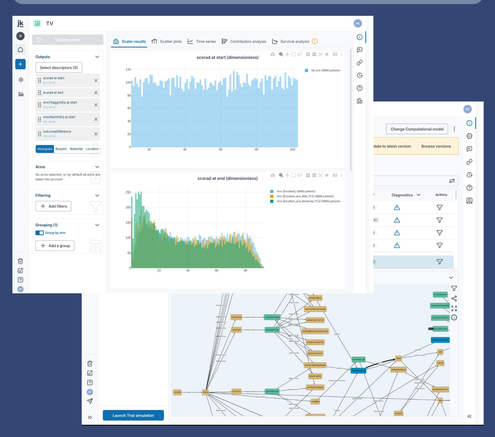


Figure 1: Simulation of a clinical trial on the **Jinkō platform**, where models, virtual populations, and results can be directly explored.

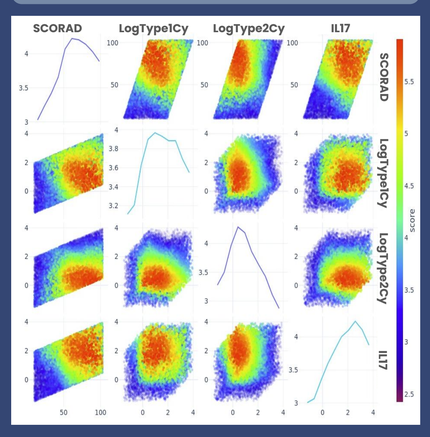


Figure 2: A score is computed for each of the initial trial patients. The patient with **highest score and its neighbors** define the best ECs

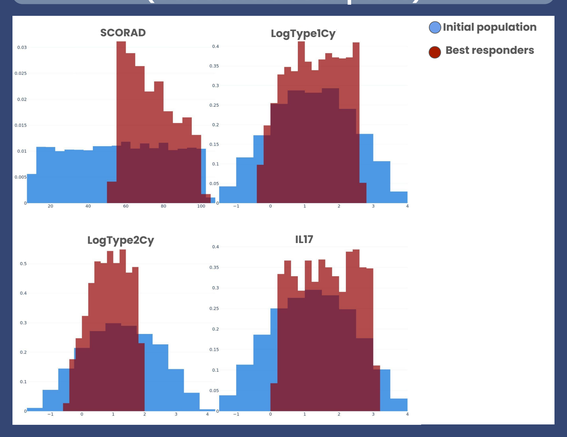
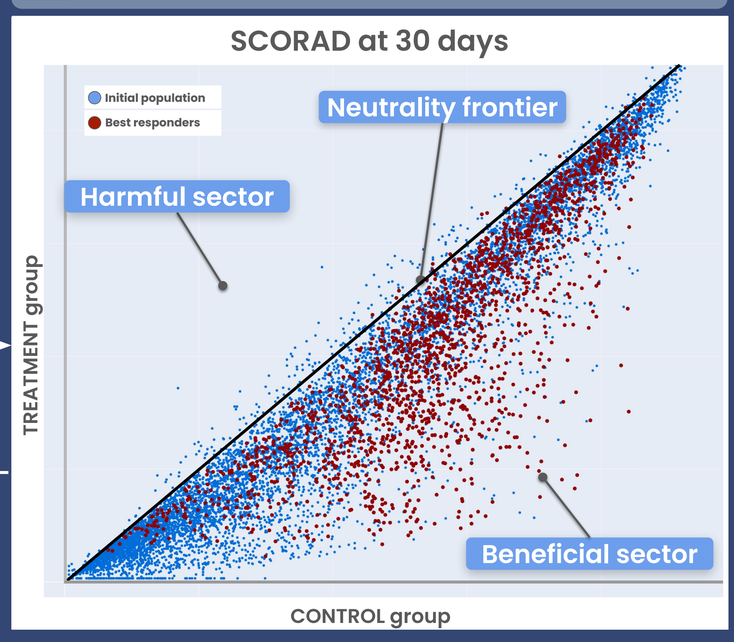


Figure 3: The **sub-population of best responders** is found when applying the **best ECs** to the initial population



	Virtual population	**Best responders**
Population size	10000	1842
Sample size per arm	184	30 **(-84%)**
Treatment efficacy	8.6	13.8 **(+61%)**
Patients in harmful sector	275 (2.75%)	12 (**0.65%**)

Figure 4: Clinical outcome of interest: SCORAD at the end of treatment **in treated group against control group**. Initial population in blue and best responders in red

BACKGROUND

Randomized controlled trials (RCTs) are designed to estimate treatment effects in a defined population. However, restrictive **eligibility criteria (ECs)** may reduce generalizability and increase the risk of false-negative results. **Optimizing ECs** is therefore essential to **improve trial efficiency and statistical power**. We present an integrated in silico framework that combines mechanistic disease modeling, virtual populations, and mathematical optimization to systematically refine ECs—ultimately enhancing treatment effect size, power, and overall trial performance.

METHODS

To illustrate the framework, using **Jinkō platform**[1] we simulated, a synthetic two-arm trial using a large virtual patient cohort suffering from **atopic dermatitis (AD)**. The underlying quantitative systems pharmacology model[2] describes the skin barrier integrity interactions with the immune system and includes treatment models, accounting for the cutaneous administration and mechanisms of action of emollients and topical corticosteroids (TCSs). This QSP model was calibrated with quantitative relationships in skin biomarkers, clinical data for standard of care (SoC) treatment efficacy. The latter was defined as the difference in SCORAD index between patients treated only with an emollient, considered here as control, and patients treated with an emollient combined with a mild TCS.

4 descriptors were chosen among all baseline characteristics measurable in real-life clinical practice for the design of the eligibility criteria by first running a sensitivity analysis study.
The aim of the algorithm is to find ECs such that the associated sub-population has a **large efficacy mean and a low efficacy variance**. The efficacy is computed using bootstrapping with a sample size equal to the initial trial required sample size. This means the sub-population defined by ECs must be of a size greater than subsample_size, defined as the required sample size times a user-defined multiplicative factor (typically equal 10).

The search for optimal ECs consists in finding the patient with highest score. For each patient i, the score s_i is defined as a weighted sum of the mean and variance of the efficacy for the sub-population of subsample_size neighbors around patient i:

$$s_i = w_m \langle \mathrm{eff} \rangle_i + w_s \sigma_{\mathrm{eff,i}}$$

The mean and variance of the efficacy are computed with a nearest neighbor regressor, using the Chebyshev distance to emulate the application of eligibility criteria.

RESULTS

The application of the optimization approach to the simulation outputs allowed to successfully optimize the clinical trial design by defining ECs in order to maximize the differences in terms of outcome metric between the control and the treated arm, therefore maximizing the measured efficacy and reducing its variability.
The use of optimized ECs significantly increased the treatment-associated efficacy while decreasing the required sample size:

- **Efficacy** increased by **+61%**
- **Sample size** reduced by **-84%**
- Proportion of patients observing a **harmful effect** of the treatment **divided by 3**

CONCLUSION

Combining QSP modeling with virtual populations and mathematical optimization provides a **powerful strategy for improving clinical trial design**[3]. This approach enables the identification of patient subgroups that are most likely to respond to treatment, reducing sample size while enhancing trial efficiency and success. Aligned with Model-Informed Drug Development (MIDD) principles, these in silico methods have demonstrated potential to **shorten development timelines and reduce trial costs**. Ongoing work will focus on validating the framework against real-world RCT outcomes and extending it to optimize additional design parameters, including treatment duration, dosing, and scheduling.

REFERENCES

[1] Jinkō: www.jinko.ai
[2] *A quantitative systems pharmacology workflow toward optimal design and biomarker stratification of atopic dermatitis clinical trials*. Go, Natacha et al., Journal of Allergy and Clinical Immunology (2024)
[3] *Impact of Model-Informed Drug Development on Drug Development Cycle Times and Clinical Trial Cost*. Clin Pharmacol Ther, Musuamba et al. (2023)