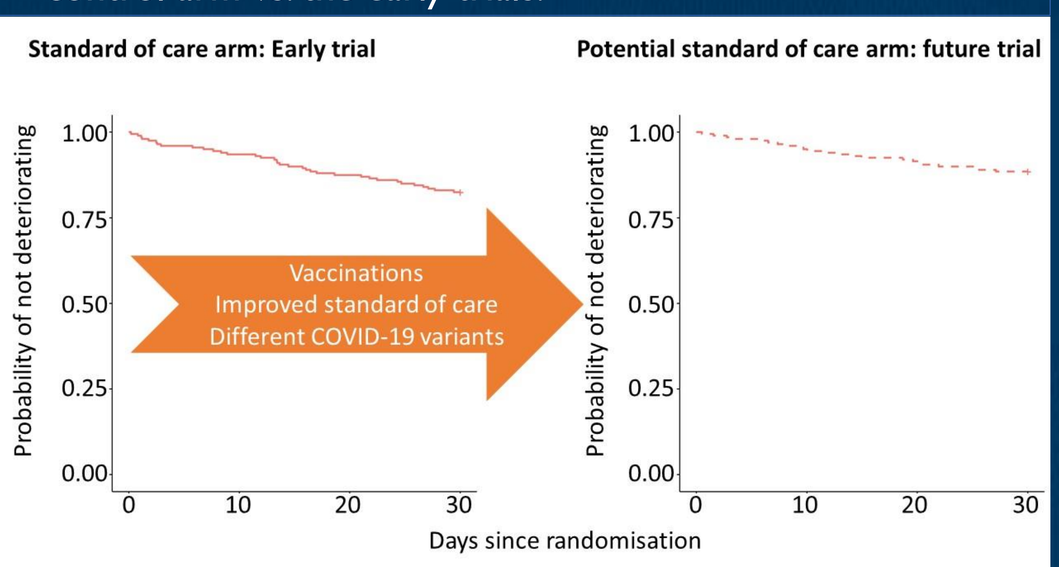
Power calculations for time-to-event outcomes using simulation in the presence of improved standard of care in the COVID-19 pandemic.

J.R.J. Inshaw[1], A. Nickless[1], N. Madeleine[2], S. McPherson[2], B. Ferrari[2], A. Jackson[2], S.R. Miller[1]

1: Exploristics Ltd, Belfast, UK
2: BerGenBio, Bergen, Norway

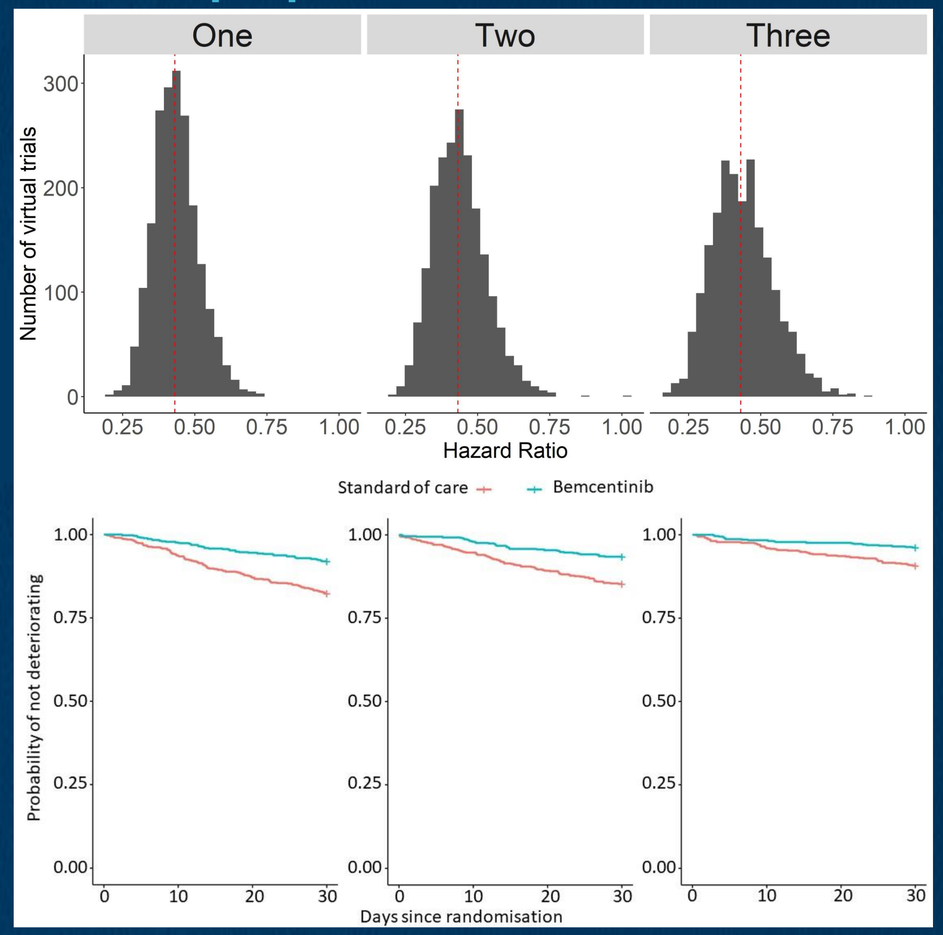
Problem

- Early COVID-19 trials took place prior to the approval of therapies to treat the disease.
- A variety of factors could change the response for the control arm vs. the early trials.



- Failure to account for this potential change in the control arm may result in low probability of success in future trials.

Virtual populations

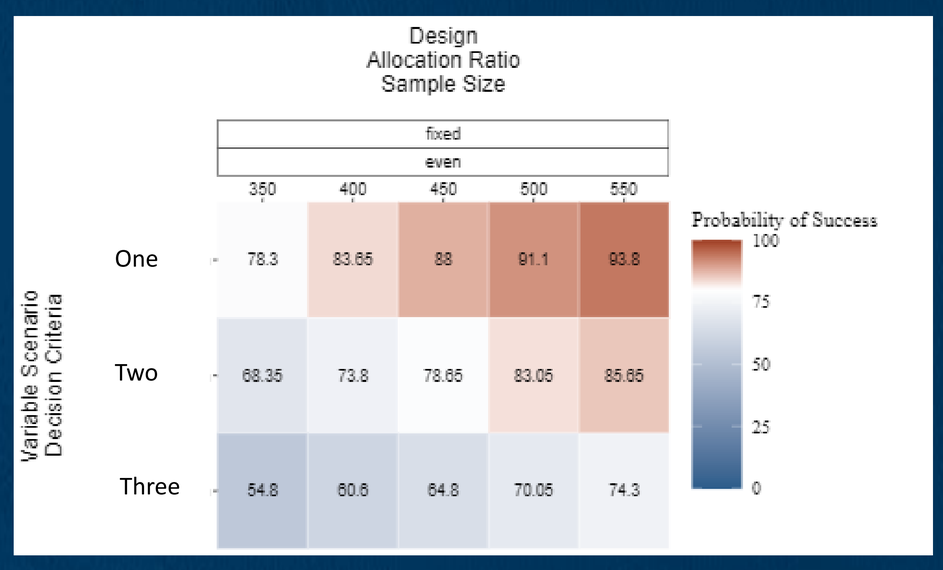


Aims and approach

- To design a phase IIb study, examining the effect of Bemcentinib on hospitalised COVID-19 patients.
- Endpoint considered was the time to deterioration of 1 point in the WHO ordinal scale over 30 days follow-up.
- We simulated data using *KerusCloud* to mimic a range of possible scenarios. 2000 trials per scenario.
- We held the treatment effect constant at that observed from meta-analysis of two completed phase IIa studies, with a hazard ratio = 0.431, participants less likely to deteriorate on Bemcentinib vs. standard of care.
- Event times for both arms were approximated using Weibull distributions[1], censoring distribution as a uniform at 30 days.
- "Success" defined as log-rank p-value <0.05.

Scenario	Event rate	Description
One	18%	Assuming no change in event rate from early phase trials to future trial.
Two	Patients 0-20%: 18% Patients 20-40%: 16% Patients 40-60%: 14% Patients 60-80%: 12% Patients 80-100%: 10%	Assuming diminishing event rate throughout the course of the future trial.
Three	10%	Assuming lowest event rate throughout the course of the future trial.

Probabilities of success



Conclusions

- Even if the treatment effect size remains consistent between an early trial and the future trial, a change in control arm response can have a large impact on study probability of success.
- If not considered, the probability of success recruiting approximately 350 participants in the future trial would appear to be close to 80%, but if the event rate was notably lower than in the original trial were true (scenario three), it could be closer to 50%.
- Simulation allows quantification of the probability of success under complex scenarios (e.g. scenario two, with diminishing event rate over time) in a way traditional power calculations cannot do.

References

[1]. Marks, N.B. Estimation of Weibull parameters from common percentiles. *Journal of applied statistics*, doi: 10.1080/02664760420003051 22

Acknowledgements

- We are grateful to all trial participants.

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