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INNOVATIVE ANALYTICS SOLUTIONS

KerusCloud Use Example

Driving decision making with an adaptive clinical trial in the face of recruitment difficulties

Exploring alternative adaptive approaches to the study.

KerusCloud®

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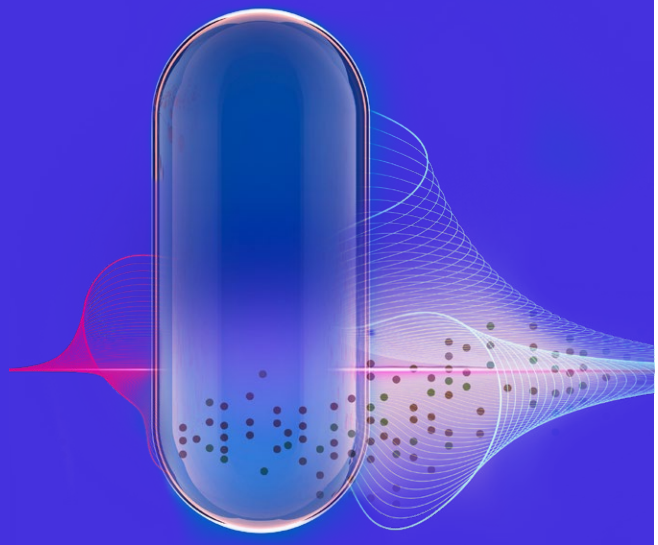

KerusCloud is a revolutionary simulation-guided study design tool that ensures clinical trials are designed effectively to collect the right data, in the right patients, in the right way. Its use supports evidence-based design decisions to extensively de-risk real clinical studies, reducing development time, costs and patient burden.

The Software

KerusCloud allows multiple study uncertainties to be explored simultaneously, in minutes, within a virtual environment. Study outcomes are visualised with an interactive heatmap where detailed results help identify the pros and cons of different design options. This allows the key drivers of study success to be pinpointed rapidly so that the best design and analysis approach can be selected, first time.

Diverse information and data types inform the simulations with sources including the scientific literature, disease registries, historical trials and real-world data. These data are captured in the platform as synthetic data sets, avoiding privacy constraints, and used to build virtual patient populations to answer 'what if' study scenarios questions.

KerusCloud's synthetic data driven simulations are uniquely informative. They best represent the complexity found in real studies by accurately mimicking the quirks found in real patient-level data, like missingness. Therefore, KerusCloud provides exceptional advanced analytical insights able to deliver the smarter studies needed to address today's complex clinical research challenges.

The Challenge

A sponsor biopharmaceutical company were experiencing **significant recruitment difficulties** for an ongoing clinical trial.

Challenge 1

This meant that it would be difficult to complete the original sample size.

Challenge 2

External evidence emerged during the conduct of the trial indicating the treatment effect was likely to be larger than assumed in the initial sample size calculation.

The sponsor wished to explore **alternative adaptive approaches** to the study which would **maintain integrity**, especially with regards to controlling for false positive rate (alpha) but enable the possibility of stopping the study early with fewer patients than initially planned, either for efficacy or for futility.

The Approach

KerusCloud study simulation software was used to explore different **group sequential designs compared to a fixed design with no interim analysis**, which would allow the team to stop early for futility or efficacy.

The team explored the following:

- **Different stopping rules for efficacy**

  Rule 1, Pocock: where the probability to stop for efficacy at the interim is higher (vs. O'Brien-Fleming). This makes it more difficult to meet success criteria at the final analysis if efficacy is not declared at the interim analysis (compared to the fixed design) i.e., "spend" more alpha at the interim.

  Rule 2, O'Brien-Fleming: where the probability to stop for efficacy at the interim is lower (vs. Pocock). This makes minimal difference to the probability of meeting success criteria at the final analysis (compared to the fixed design). i.e., "spend" less alpha at the interim.

- **Whether to include a futility stopping rule or not**
- **Different timing of the interim analysis**
  - 60% through recruitment
  - 75% through recruitment
- **Different assumed true treatment effect**
  - Null
  - Initially expected 10%
  - Updated expected 12%

The Results

KerusCloud was used to quantify the overall probability of success (PoS) and operating characteristics (OC) under different true treatment effect size assumptions, and under different design choices (timing of interim and stopping rules) (Table 1).

These were **rapidly and reliably quantified** and then visualised in an interactive heatmap, which allowed both the interim and end of study results to be **explored for decision-making** (Figure 1). Where a treatment effect exists, the overall PoS for the fixed design was higher than for any of the adaptive designs, with the reduction of PoS being largest when there was both a futility and efficacy stopping rule at the interim (columns 4 and 5). The later the interim, the less that reduction in PoS (column 5 vs. column 4). Type 1 error is controlled at approximately 5% in each design (row 1).

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Interim analysis timing	Stopping rule for efficacy	Stopping rule for futility	Name (within KerusCloud project)
None	None	None	**Fixed**
60%	O'Brien-Fleming	None	**GSof60**
60%	Pocock	None	**GSp60**
60%	Pocock	Treatment effect p-value at interim>0.25	**GSp60fut**
75%	Pocock	Treatment effect p-value at interim>0.25	**GSp75fut**

Table 1. Design options explored using KerusCloud.

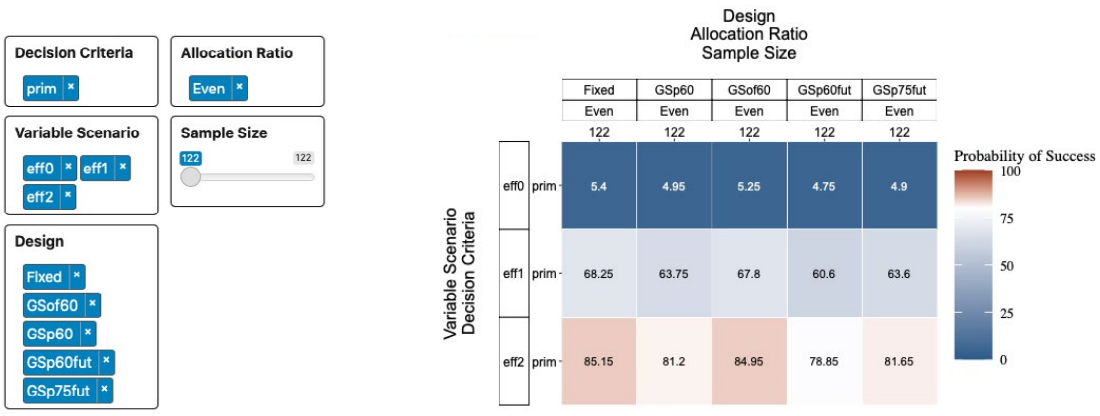


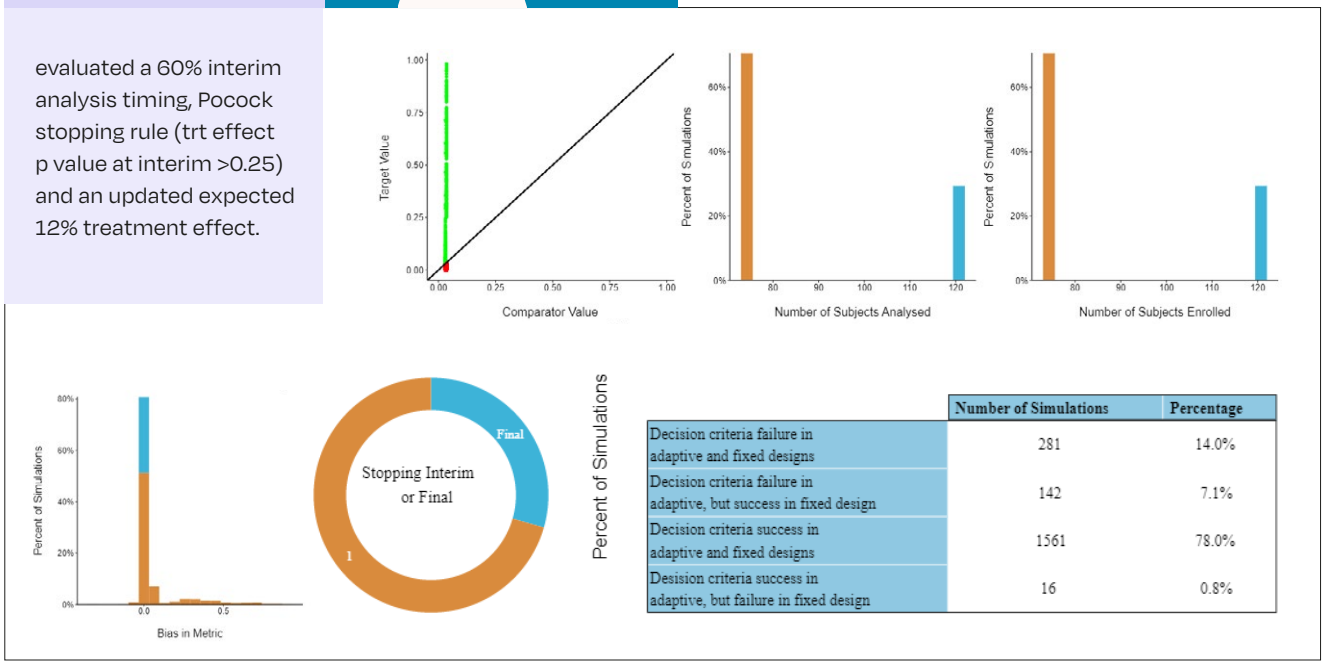
Figure 1. A KerusCloud heatmap showing the PoS values for different study scenarios, where dark blue indicates very low PoS and dark red indicates very high PoS.

In this instance, the overall PoS is **only part of the story**. The difficulty recruiting into the study was an external factor that made the sponsor comfortable with a limited decrease to the overall study PoS if there was a potential saving in the number of participants that needed to be recruited.

Figure 2 shows the operating characteristics of a particular design, showing in this case, the trial would stop for efficacy or futility over 70% of the time at the interim stage, which was a very desirable option for the sponsor. The trade-off is the 6.3% reduction in overall probability of success vs. the fixed design.

Design option *(PoS)* | *eff2* | *78.85* | *Gsp60fut*

evaluated a 60% interim analysis timing, Pocock stopping rule (trt effect p value at interim >0.25) and an updated expected 12% treatment effect.



	Number of Simulations	Percentage
Decision criteria failure in adaptive and fixed designs	281	14.0%
Decision criteria failure in adaptive, but success in fixed design	142	7.1%
Decision criteria success in adaptive and fixed designs	1561	78.0%
Desision criteria success in adaptive, but failure in fixed design	16	0.8%

Figure 2. Advanced characteristics of a design option from the heatmap displayed in Figure 1. The drill down graphical and tabular outputs for this design option show the number of participants included in the analysis, success/failure compared to the fixed design and any bias in the observed metric versus the fixed design that came about from examining the data earlier than planned.

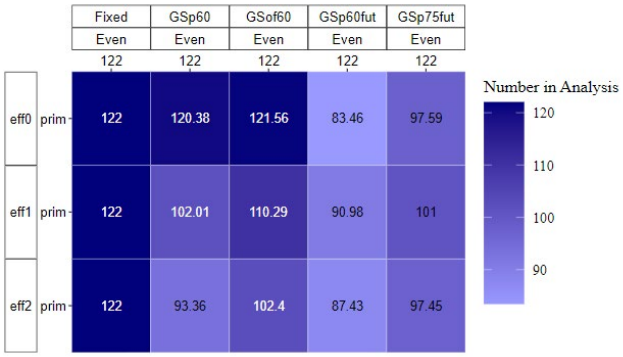


Figure 3. Mean number of participants analysed in each design type under consideration, where dark purple indicates a larger sample size and light purple indicates a smaller sample size.

The mean number of participants (across all simulations) in each design can be visualised by **KerusCloud** (Figure 3).

The analyses showed that choosing the Pocock spending function led to a smaller average sample size than the O'Brien Fleming, but the reduction in overall study PoS was higher.

The results also show that if the drug is not working (null scenario), the average sample size when using a futility rule is substantially lower than when a futility analysis is not included at the interim analysis (row 1 columns 4 and 5 vs. columns 1, 2 and 3).

Together, these results allowed a **multidisciplinary team** to:

- **quantify and debate** the merits of different design options.
- make an **informed decision** which also described elements in the study design which were **uncertain**.
- decide where they wanted to spend the "alpha" and **understand the implications** for the overall study in looking at the data part way through for decision-making.

The Impact

Simulation with KerusCloud provided key insights for the team when making decisions around the required sample size to support the design of this clinical trial, highlighting the benefits of simulation to fully explore the risks for a study.

- **The recommendation of an interim analysis using established adaptive design methodology ensured:**
  - **if the conclusion from the interim analysis was to continue recruiting, then the sponsor could do so with the confidence that this was necessary to obtain the appropriate PoS**
  - **an understanding of what the most likely outcome from this interim analysis would be, so that appropriate plans could be put into place**
- **These insights allowed the sponsor to quantify the reduction in PoS they would incur if they decided to introduce an adaptive interim analysis. They were able to identify the adaptive design that gave them the right balance with regards to benefit (smaller average sample size) and risk (probability of making an incorrect decision at interim or final analysis).**
- **Unique to KerusCloud, the PoS was calculated using simulated clinical trials, which mimic real-life data as accurately as possible, going beyond theoretical sample size calculations and providing a more accurate PoS.**
- **Ultimately, the results provided the team with options for a de-risked study, with the potential to save time, costs and patients.**

Why Exploristics?

Expertise In Early Development

The development of investigational drugs is a complex and expensive process with many risks. For over ten years our teams have been supporting and de-risking clinical development with their in-depth statistics and modelling expertise. Our study planning, statistical analysis and programming services add value to early stage development programmes by ensuring they deliver the robust evidence needed for incisive, informed decision-making.

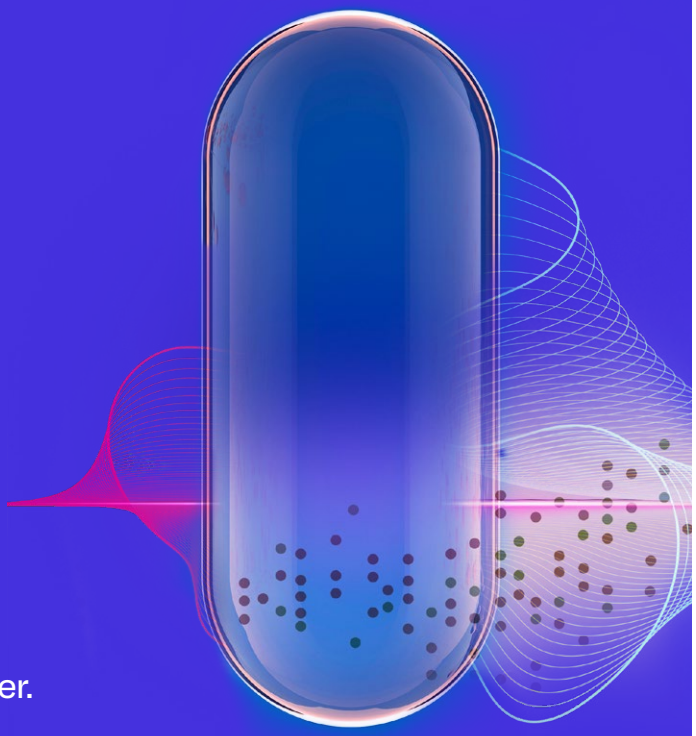
With many of our development solutions built around our unique **KerusCloud** platform, we can provide exceptional, bespoke, end-to-end biostatistics support from strategic decision-making and protocol development to analysis, reporting and stakeholder engagement.

Robust Evidence Packages

The unique offering of our comprehensive biostatistics services in combination with **KerusCloud** ensures that Exploristics can help to generate strong evidence packages to support regulatory engagement or investment, accelerating development timelines and increasing the value of pipelines.

Let's talk!

If you'd like to discuss this use case example further or learn more on how our **technology enabled services** can support your development project, please contact our VP of Sales & Marketing, Abbas Shivji, at **abbas.shivji@exploristics.com** or **book a call**.



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