

Case Study

Creating Go/No Go Decision-making Criteria for Early Stage Studies



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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 privately held biotechnology company was developing a novel therapeutic targeting fibrosis and inflammation. Following completion of a successful first-in-human Phase I study evaluating the investigative agent in healthy adult subjects and subjects with suspected non-alcoholic steatohepatitis (NASH) and liver fibrosis (Figure 1), the company wanted to explore safety and efficacy of its continued administration over 12 weeks while observing changes from baseline in metabolic, inflammatory and fibrosis biomarkers.

Regulatory guidelines usually require biopsy evidence of improvement for registration of a new treatment in NASH, however, the short duration and small sample size meant that a liver biopsy was not likely to be informative. Therefore, the company sought alternative sources of evidence to inform decisions on the development of the novel NASH agent at this early stage.

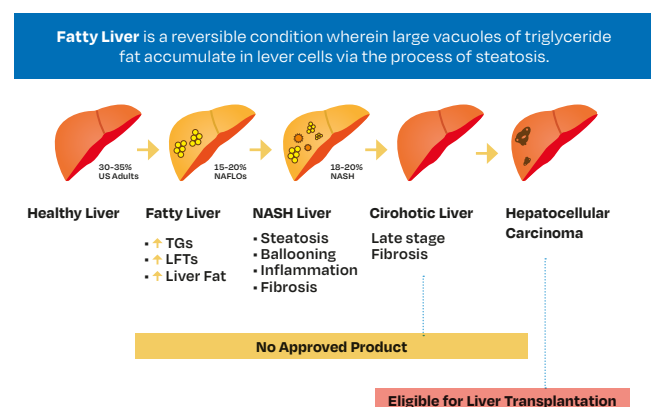


Figure 1. Liver disease progression, where fibrosis is categorised by severity of liver scarring

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The Approach

1. Creating a go/no go decision-making framework

Exploristics generated a formal go/no go decision-making quantitative framework based on a method from Lalonde et al., (1) and Frewer et al., (2). This method uses the upper and lower confidence intervals of a treatment effect to categorise the strength of evidence of the observed result into three decisions: Go; Consider; Stop. The boundary of these confidence intervals is compared to the lowest reference value (LRV) and a target value (TV), where LRV is the smallest clinically meaningful treatment effect and TV is the desired effect. These values are then used to construct a decision framework as shown in Figure 2.

The framework provided evidence to support three possible study outcomes:

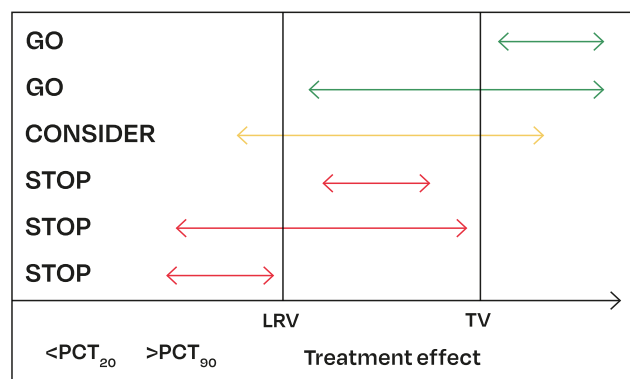
- + A go decision could be made where there is $\geq 80\%$ confidence that the true treatment effect is greater than the lower reference value ($\Delta > \text{LRV}$).
- + A stop decision could be made when there is $\leq 10\%$ confidence that the true treatment effect is greater than the target value ($\Delta > \text{TV}$).
- + A treatment effect that does not meet the Go or Stop criteria then falls into the consider zone where more data may be required.

2. Setting Up Decision-Making Criteria using KerusCloud

To set up a decision framework for the projected study the TV and LRV needed to be defined for relevant biomarkers and the pre-specified risks set. The sample size required for the study was obtained through simulation using KerusCloud. This required:

- + Key statistical information such as the statistical distributions and variation of the endpoints in the target patient population to be sourced via an extensive literature review for the metabolic, inflammatory and fibrosis biomarkers of interest.
- + Construction of a decision framework using the Lalonde method once the TV, LRV, risks, sample size and variability had been determined.

- + Evaluation of the framework's performance by obtaining the probability of being in each of the three zones (go, stop, consider) under different truths of the treatment effect, using KerusCloud's interactive heatmap (Figure 3).
- + Testing the framework with 20% and 50% of the data missing to mitigate for trial site closures due to the ongoing global COVID-19 pandemic.



Go if (green) $\text{PCT}_{20} > \text{LRV}$ and $\text{PCT}_{90} > \text{TV}$

Consider if (amber) $\text{PCT}_{20} \leq \text{LRV}$ and $\text{PCT}_{90} > \text{TV}$

Stop if (red) $\text{PCT}_{90} \leq \text{TV}$

Figure 2. Visualisation of the decision framework, where PCT_x denotes the x th percentile of the distribution of the treatment effect ($P(\Delta)$).

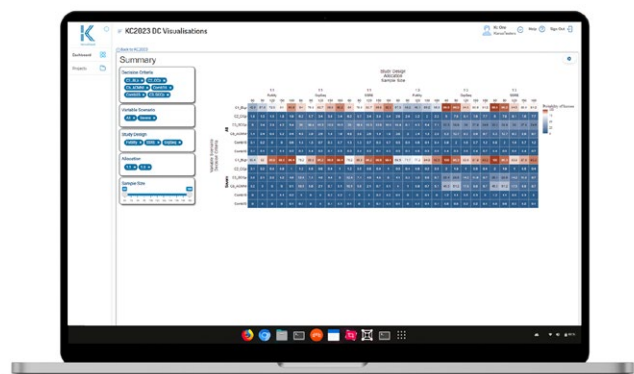


Figure 3. A typical results heatmap in KerusCloud



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The Results

KerusCloud:

- + Successfully incorporated the collated information into a decision-making framework to support decisions for the projected safety and efficacy study of the candidate NASH treatment.
- + The framework was shown to be robust in the event of a large proportion of missing data.

The Impact

Using KerusCloud:

- + The client obtained a clear decision-making framework for the projected study, **de-risking and accelerating the development path** for their investigative agent.
- + **Key exploratory biomarkers** for NASH were **integrated into the decision framework**.
- + **Mitigation for missing data gave the client an option to report on a smaller sample size** in the event of clinical trial site closures resulting from the COVID-19 pandemic.

References:

1. Lalonde, R. L., Kowalski, K. G., Hutmacher, M. M., Ewy, W., Nichols, D. J., Miligan, P. A., Corrigan, B. W., Lockwood, P. A., Marshall, S. A., Benincosa, L. J., Tensfeldt, T. G., Parivar, K., Amantea, M., Glue, P., Koide, H. and Miller, R. Model-based drug development. *Clinical Pharmacology and Therapeutics* 2007; 82:21-32.
2. Frewer, P., Mitchell, P., Watkins, C. and Matcham, J. Decision-making in early clinical drug development. *Pharmaceutical Statistics* 2016;15: 255-263.

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 case study 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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