New User FAQs

How does KerusCloud simulation differ from traditional approaches?

KerusCloud has been developed by Exploristics' statisticians to address the limitations of current study design tools which do not adequately support the designs of modern clinical trials that are generating increasingly complex clinical, demographic and biological data. Emerging approaches, like Precision Medicine, have led to studies seeking to answer multiple questions such as understanding the association of risk factors on treatment response and identifying subgroups of patients that derive benefits of treatment. However, the majority of traditional study design tools are too simplistic, assuming that only one factor influences variability in treatment response (eg. Treatment), and it is common practice to make fixed assumptions about the nature of the relationship between that factor and response. This traditional approach to designing studies is statistically crude and fundamentally flawed as it does not adequately account for the multiple sources of uncertainty in real studies.

In contrast, KerusCloud, is a versatile and flexible software platform that handles the many sources of uncertainty that now need to be considered when designing a clinical study. It is the only statistical software available that can evaluate multiple aspects of clinical trial design simultaneously as well as the only cloud-based simulation tool that harnesses the power of cloud computing to speed up simulation. This means that using KerusCloud ensures that the best combination of study design and analysis options can be assessed and selected for real studies in minutes, so that they can achieve statistically and clinically meaningful outcomes. No other commercial software can process and simulate the complexity of multiple correlated study variables and outcomes as KerusCloud does. Other software can simulate data and perform tests, but this is generally limited to either simulation of single variables or multiple independent variables which only crudely reflect real clinical studies. This unique ability to process multiple correlated variables and outcomes as well as subgroups and missing data means that studies simulated with KerusCloud are exceptionally realistic and informative as they closely mimic the complexity of biological, clinical and realworld data.

What does KerusCloud simulation offer beyond traditional study design approaches?

The power calculation formulae used in many traditional software tools rely on multiple critical assumptions that often do not hold: 1) that parameter estimates obtained from past samples are near perfect representations of the future population, 2) that large-sample mathematical formulae to reject a simple hypothesis of no difference can be applied in any situation, and 3) that data features (such as associations between variables or missing data) can be ignored or simplistically accounted for. In contrast, KerusCloud simulates future sample datasets such that all these factors are taken into account.

When parameter estimates are uncertain, such as when they come from smaller sample sizes or a slightly different population to that which will be studied, KerusCloud can account for this uncertainty through simulation. One option for the user is to assess a series of scenarios compatible with the available estimates. A second option is to incorporate the uncertainty by sampling parameters randomly from their "error range" or prior distribution. This propogates the uncertainty through the smilulation to provide more reliable predictions of the probability of success in your new sample composition.

Traditionally power-calculations focus on detecting a statistically significant difference, but cannot predict whether a 'significant' value is higher than a threshold of clinical utility or meets a benefit-risk criteria. KerusCloud can simultaneously evaluate multiple trial objectives which can allow the user to test whether a trial design is capable of attaining a combination of statistically AND clinically relevant criteria. In addition, because virtual populations are simulated at the patient-level, simulations in KerusCloud are reliable for any sample-size, even when traditional formulae would be inaccurate for small samples.

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Traditionally missing data is accounted for via a multiplier for dropout on the overall sample-size, while other features of clinical trial data such as partially missing data or correlation between variables are generally ignored at the design stage. KerusCloud simulates datasets with defined correlations to any number of other variables and variable types, and allows data features such as missingness to be related to other variables. By seamlessly incorporating these factors into the design and analysis KerusCloud quantifies the impact of these potentially critical factors on the probability of success.

Where does the data come from for KerusCloud simulations?

KerusCloud uses real data to create the synthetic data sets used for simulations. The real data comes from multiple sources, including the scientific literature, patient-level data and expert opinion. Patient-level data can be automatically imported into the platform via our proprietary Kerus Data importer (KDi) technology in the form of summary statistics from existing patient-level data sets. Many users of KerusCloud have access to their own internal patient databases. Alternatively, Exploristics sources its patient-level data from a range of databases and exclusive partnerships with data providers.

A common source of patient-level data comes from investigator-led observational studies. These studies are instrumental as they typically contain the risk factors and endpoints, measured over timeframes, that are relevant for clinical trials. These data can be augmented with publicly available statistics from the published literature and insights from experts and key opinion leaders (KOLs) in the relevant therapeutic field. All data sources are synthesised into an integrated database that captures the relevant knowledge and associated uncertainty using a range of data models. We have also created a data strategy team to proactively create a library of disease-specific databases that can be shared with KerusCloud users.

What are the recommendations for correlation starting values in a simulation?

Using literature searches for correlations between variables may give some indication of correlation values, although these may sometimes be imprecise. The advantage of KerusCloud is the ability to experiment with a range of values to suit your needs. By building in uncertainty, a more robust trial can be designed to account for the limitations of current knowledge.

What are the system requirements for KerusCloud?

As a cloud-based platform, there are no specific hardware requirements. To use KerusCloud you will need an internet connection (recommended ≥1.5MBps and ≤50ms latency), a screen with sufficient resolution (recommended at least 1366x768 pixels) and a Chromium or Mozilla-based browser such as Chrome or Firefox.

What statistical methods are available in KerusCloud?

User guide bundles are available with KerusCloud which give an overview of the statistical methods incorporated into the software, as well as the terms included in the application. The statistical methods within KerusCloud are constantly updated to keep abreast of new statistical innovations. This builds on an extensive library of standard statistical analyses; methods such as ANOVA, T-tests, tests for categorical data, and non-parametric analyses.

What does the KerusCloud workflow look like?

KerusCloud has a simple set of dashboards and a natural workflow which makes it easy to use. The User Dashboard displays each project being evaluated helping to keep track on progress. Individual projects can then be viewed on the Project Dashboard. Here, the user can easily navigate a series of intuitive point and click Wizards to rapidly build, evaluate and manage a trial project that may contain multiple study configurations to test including:

- **Virtual Population**
  variables, advanced options, correlations, scenarios
- **Design**
  sample-sizes and treatment allocations
- **Analysis**
  analyses and summaries
- **Decision Criteria**
  comparisons, thresholds and combinations

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The user defines the statistical tests to run, and which criteria define a success. Thousands of Monte Carlo simulations are then conducted to evaluate the performance of the design, analysis and decision options. Typically, these take minutes to run. KerusCloud simulates the data, performs the tests and evaluates objectives and returns a simple graphical output summarising the likelihood of success for each objective in each trial configuration.

Further information on the KerusCloud dashboard is available on the Exploristics website at https:// exploristics. com/keruscloud-platform-overview/.

What does the output from KerusCloud look like?

The end result of a KerusCloud simulation run is an interactive heatmap, which summarises the probability of achieving each of a set of relevant success criteria and a range of different scenarios.

For every combination of variables the probability of demonstrating a benefit of treatment has been quantified, with values above the target (success) coloured orange and those below (failure) in blue. You can subset the heatmap using the drop-down boxes at the top, alter the probability of success threshold with the slider or highlight a row to generate a bar-graph showing the probability of success as a function of sample-size.

These interactive graphics enable results to be simply visualised and explored more extensively, facilitating the identification, extraction and interpretation of important results and features in the data. Key insights can be shared more easily within and across project teams so that researchers can identify factors critical to success, quantify the cost/benefit of available options and take action to mitigate risks resulting in an optimised plan.

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Can simulated data be exported for analysis in another programme?

Yes, simulated data is easily exported in a ZIP file containing all the Virtual Population simulation data in multiple comma-separated value (.csv) files with a manifest file for ease of management and reference.

Can my project be accessed/ retrieved at a later date?

Yes, each user has an associated workspace where they can define their custom study designs. The study designs, analyses, decision criteria and simulated results are stored securely within the workspace and are available to edit and view each time they log in to the KerusCloud platform.

How does KerusCloud handle so many large simulations?

KerusCloud has increased processing power with up to 96 parallel cores for a single simulation and an intelligent process management system which boosts processing power as needed, so even the most complex simulations can be run in minutes and the results reviewed in real time. The software is hosted on Amazon Web Services (AWS), where the Kerus statistics engine benefits from the scalability and performance of the cloud. This allows KerusCloud to produce results within minutes, even for large and computationally intensive simulations.

How secure are my data, simulations and results within KerusCloud?

KerusCloud offers best in class security with unparalleled cloud security measures and multi-factor authentication for complete control over access rights. In addition, it is a cloud-based application that harnesses the security already provided by Amazon Web Services (AWS). KerusCloud is deployed in a “Virtual Private Cloud” on AWS which is logically isolated from all other virtual networks. Here, KerusCloud data is protected by multiple layers of security so that only the owner of what is stored can gain access. Importantly, Exploristics does not hold any patientlevel data in the cloud as the information is extracted for use in KerusCloud in the form of summary statistics.

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How secure is KerusCloud as a platform?

KerusCloud is an extremely secure software platform. It has been extensively audited by Vertical Structure, an independent cyber security advisory company specialising in providing human focused security and penetration testing services for web applications, cloud infrastructure and mobile applications. The objective of the auditing process is to identify weaknesses and points of entry within the Kerus Cloud UI source, identify potential areas of intrusion, including configuration issues and application vulnerabilities. Static Analysis was carried out in August 2019 and Penetration Testing in December 2019. Exploristics continues to work with third party cybersecurity experts for the purpose of penetration testing to ensure that our platform remains secure against cyber attacks.

How robust is KerusCloud?

KerusCloud is a very robust software capable of assessing many parameters in the simulation of data as well as performing statistical validity and quality control checks at each stage of the input, simulation and analysis of your theoretical trials. Development follows a strict workflow containing quality control steps, including code review, creation of test scripts and testing. All testing has agreed acceptance criteria. We run daily smoke-tests to ensure integration of features does not cause regression of existing functionality. Aside from testing within the development team, we also allow beta-users to test the software prior to general release.

To support the user, embedded within KerusCloud is a range of checks that prevent implausible options from being selected. KerusCloud performs checks on each variable input to ensure it conforms to set limitations e.g. standard deviation must be greater than 0. This offers protection against users providing erroneous inputs.

Is there a limit to the number of variables I can include in my study design?

No, in KerusCloud you may define the size and complexity of your study without limitation on the number of variables included.

Are there options for testing multiple scenarios in a single simulation run?

KerusCloud has the option to create multiple scenarios for 1) variable parameter values, 2) correlations and 3) other advanced data features within a single project. The specified values for each scenario (or combination of scenarios) are then simulated in series, effectively allowing a researcher to simulate multiple trials but reducing the need to enter other study information repetitively.

What happens if I set a distribution for variable parameter or correlation value in KerusCloud?

If variable parameter values or correlations are entered as distribution-based, KerusCloud randomly draws values from this distribution and uses these drawn values as the parameter values in the simulated datasets. This is effectively a Bayesian approach, with the distribution providing the prior for the parameter, and the resulting probability of success an “assurance”.

Can you simulate longitudinal data in KerusCloud?

Yes, it is possible to generate correlated longitudinal data but the analysis options do not currently include any related analyses. This is included in our ongoing product Roadmap for KerusCloud.

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What are my options for solving analysis questions using KerusCloud?

KerusCloud provides several ways to address analysis questions. Most importantly, uniquely it can assess variations on analysis questions in parallel using multiple analysis and objective options to allow the user to compare possible results from each variant to discover

Is KerusCloud capable of doing model building?

At the design stage KerusCloud allows creation of derived variables to specify the relationship between variables in the virtual population explicitly. KerusCloud is not yet able to do model-building within the Analysis stage, although regression analysis models are on the product roadmap. Until these are implemented, the export functionality allows the virtual population to be analysed outside of KerusCloud.

Can you use KerusCloud for Go/No Go decision frameworks?

Yes, KerusCloud allows the creation of multiple decision criteria based on clinically-defined thresholds such as minimum value or target value for effect. The operating characteristics of these rules can be evaluated for all your different scenarios.

What kind of studies can I use KerusCloud for?

KerusCloud can be used to optimise a wide range of study types. Completed case studies include:

- **Early Phase Development** Evaluating probability of success for study design and analysis options to support efficient generation of clinical evidence for early stage research
- **Enabling Early Approval** Developing a robust evidence package for regulatory interactions accelerating drug approval
- **Identifying Best Strategy** Selecting the best overall strategy for drug development by comparing development paths
- **Composite Biomarker** Building and validating a composite biomarker model
- **Bayesian Extrapolation** Evaluating a Bayesian adaptive study design
- **Real-World Evidence** Simulating patient level outcome data to inform clinical trial design based on RWE, clinical trial and literature data
- **Precision Medicine** Implementing Precision Medicine strategies
- **Best Endpoint** Identifying the optimal endpoint or patient subgroup to demonstrate a response to treatment

To view case studies, please go to https://exploristics.com/case-studies/

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