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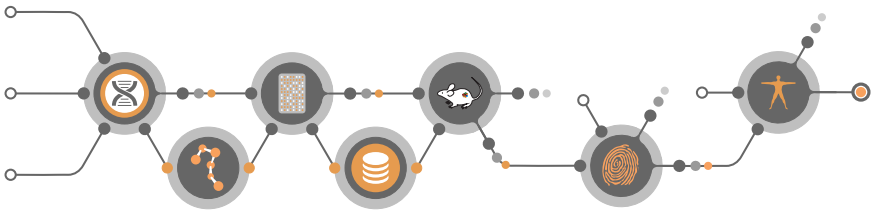

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studylog®
Animal Study Management Software

Utilizing Studylog® to Efficiently Run HuTrials™

Oncology App Note

Crown Bioscience's preclinical Translational Technology Platforms de-risk transitioning your therapy into the clinic.

The development of new oncology agents is currently being impaired by a high failure rate in late-phase clinical trials. While many agents show promising preclinical response, there is a lack of translation of this efficacy into the clinic, with only 5% of anticancer agents being licensed after successful Phase III trials[1]. The majority of failures are related to efficacy rather than toxicity, and this high attrition rate suggests that the translational tools currently being used to predict clinical response are not optimal.

Background on HuTrials

To increase efficiency in translational oncology, methods are needed which can aid in human trial design, and in the identification and validation of biomarkers and genetic signatures of a potential responder population in a cost-effective manner. Preclinical Phase-II like mouse clinical trials, also known as human surrogate trials, "avatar" trials, or HuTrials are proving to be just such an approach (discussed in detail in our Translational Oncology Application Note).

Within a HuTrial, highly predictive patient-derived xenograft (PDX) models, which preserve both the genomic integrity and heterogeneity of the disease of each patient, are used as patient avatars. Once enrolled in the HuTrial, each PDX subject reflects the pathology of its original patient, and the cohort of patient avatars represent a diversity of the human oncology patient population. The main functional utilities for HuTrials include drug positioning or repositioning, screening for lead candidates, facilitating human trial design and co-clinical trials, and discovery and/or validation of genetic signatures predictive of response and predictive biomarkers. Leveraging these biomarkers and signatures to select patients for efficacy based, late-phase clinical trials provides the greatest likelihood of success of an agent in the clinic, and a potential reduction in the attrition rate for novel oncology therapies.

The Challenges of HuTrials

The implementation of a HuTrial is more complex than a standard PDX study. HuTrials aim to represent as much of the oncology patient population as possible; therefore, requiring a large library of validated and genomically/genetically annotated PDX models.

On average HuTrials utilize 30 to 100 models, with multiple treatment arms per model, which utilizes a large number of animals at any one time. The ability to run multiple HuTrials simultaneously requires a large capacity, and an efficient organization and control within the preclinical unit.

The design of a HuTrial should mimic that of a complex, late-phase human clinical trial including multi-site enrollment and acceptance of all-comers. Multi-site enrollment requires facilities world-wide to be centrally managed and to be able to work from one standardized protocol. The acceptance of all-comers means that animals can be enrolled at any time during the study, which requires effective study management to ensure model treatments and measurements are performed, and that samples are taken, at the correct time point for every study participant. Randomization of animals in a similar method to clinical trials is also required.

Piggy-backing studies which utilize the same model can increase the speed of HuTrials and reduce their costs. For example, two or more studies using the same model can share one vehicle treatment arm, significantly reducing the cost of each study. This requires an efficient system of study management to ensure study data is collected and separated correctly, to ensure anonymity for each study.

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Analysis and reporting of HuTrials also needs to be similar to human clinical studies, with endpoints such as objective response and survival provided, to allow ease of comparison of preclinical and clinical data. Clients need to be able to access data, and share protocols and results in the simplest and least time consuming method possible, to ensure the efficiency of their studies.

Running Multiple, Parallel HuTrial Studies Requires a Large Study Capacity

Crown Bioscience pride ourselves on the ability to rapidly initiate HuTrials, in maintaining the operational capacity to screen multiple models simultaneously, and to perform any given HuTrial in months instead of years.

Our rapid initiation of HuTrials is due to the large number of PDX models that we keep in constant passage. Crown Bioscience have developed the largest commercially available collection of over 1,100 PDX models from both Asian and Caucasian backgrounds, covering over 20 different cancer indications, and multiple subtypes within one indication. All models undergo stringent validation and quality control before they become part of the HuPrime® and HuKemia™ collections which are "fit for efficacy studies". Many of the fit for efficacy models are in constant passage, and can be combined with newly developing models (which may not yet have a full data package to be "fit for efficacy") in HuTrials if required.

Our ability to run multiple studies simultaneously (for the same client or for different companies) is based on our large scale operational capacity. Crown Bioscience are the largest user of immunocompromised mice in China, and our global capacity is >30,000 mice at any given time. This ensures availability for a large number of HuTrials to be performed every year in a streamlined manner.

Multi-center HuTrials Similar to Human Clinical Trials can be Performed

Human late-phase clinical trials enroll patients from multiple study centers around the world, ensuring faster accrual of study subjects and study completion.

A wider geographic diversity of patients is also provided, although this may lead to differences in response across a study population.

HuTrials which are run at multiple sites have the same patient enrollment benefits. Crown Bioscience can run HuTrials across our two sites in China (Beijing and Taicang), with subjects also enrolled at our research sites based in the UK and US. This allows model enrollment across the globe, and free research capacity to be used wherever available, increasing the speed of study completion. HuTrial sites can suit the geographic needs of the client and of our models e.g. models which are currently available only within one country (or which are newly developed within a specific country) can be included within a multi-center HuTrial initiated elsewhere without delay. HuTrials can incorporate both Asian and Caucasian models, specifically to study model differences or to include as wide a diversity as possible.

Whether a single-site or multi-center HuTrial is established, each study is centrally managed using a single protocol, similar to the organization of multi-center human clinical trials. This allows all models and endpoints to be trialed and analyzed in an identical fashion for easy comparison of results. Crown Bioscience also have a comprehensive supporting service capability, functioning like a clinical trial central lab, to enable pharmacokinetic/pharmacodynamic (PD) analysis, including histopathological, immunological, bioanalytical, and PD biomarker analysis of trial data. These key logistical components enable HuTrials to be run in an efficiently managed, and therefore highly cost-effective, manner.

Utilization of Studylog to Efficiently Run HuTrials

With the complexity and challenges laid out by HuTrials, Crown Bioscience require a software partner who can meet our rigorous day-to-day research needs.

Studylog is an animal study workflow suite, which has both desktop and web-based applications to expedite research studies[(2)]. Crown Bioscience use Studylog to optimize our HuTrial workflow and integrity to the highest level possible, through a range of efficient software functions such as ease of client communication, centralized management, flexible study design, and integrated analysis of results.

Studylog Facilitates Easy Client Communication

Studylog allows rapid and easy communication with clients during study set up and through study data collection.

Over half of the top 20 global big pharma companies use Studylog, which expedites protocol sharing. For example, a pharmaceutical company can create a protocol using Studylog, then export this protocol to Crown Bioscience for our use. We can then easily export raw data to our clients as required, giving them snapshots of the ongoing study results. This allows our clients to review the study and potentially add in additional hypotheses or questions to answer as the study continues. This can reduce the overall number of studies that a client needs to run, and so reduce costs, by incorporating

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more information per study. At the end of the study, our client also has all of the Studylog recorded data in-house, as if the study was performed internally, to be able to access and data mine in the future. For clients without in-house Studylog, we can also easily export raw data reports as required, which do not need Studylog for interpretation, and which can also guide ongoing study alterations.

Studylog Allows Efficient Centralized Management of Multi-center HuTrials

Study management across multiple Crown Bioscience sites is also made as efficient as possible using Studylog.

Each of the Crown Bioscience sites have independent Studylog databases, which can be synchronized to allow multi-site studies to run and collect data using the same protocol. This allows the inclusion of models from sites around the world in the same study, and the best utilization of our free HuTrial capacity around the globe. Security features across the software give study specific rights to staff at different sites as needed, so that a centrally managed protocol and related study design can only be altered by designated Study Directors. A messaging function allows real-time communication between Studylog users working on the same HuTrial, to ensure that any queries or requests are answered across continents in the timeliest fashion possible.

HuTrials can be Designed to Closely Match Human Clinical Trials in Studylog

Late-phase human clinical trials enroll patients with specific disease characteristics on a patient-by-patient basis.

To match this, HuTrials function with a rolling enrollment of models, based on parameters such as when a specific tumor volume is reached. This results in day-to-day complexities as each model can be at a different stage in the study, potentially with all models in the same group requiring different assessment on the same day. Studylog has a powerful study manager system, with schedules for measurement and sample collection set up for each animal as they are enrolled, independently of the other animals in the same group. The study design is also flexible, with the management system allowing changes to be made during the study as required by clients, with a full audit trail built in to capture all changes. At the end of the study, data from each group are aligned to allow easy analysis of results. This rolling enrollment and a robust scheduling manager also allows piggy-backing of trials utilizing common models, which reduces costs across studies. The study manager establishes a clear separation of models from differing HuTrials, ensuring that results are only contained within their appropriate study and final report.

Randomization methods in Studylog are also designed to allow our HuTrial to match a client clinical trial as required. There are five randomization methods included, with stratified sampling and multi-task (multi-parameter randomization) matching clinical methods used. Similar to human clinical trials, these methods allow differing treatment groups to be randomized to be biologically similar which allows accurate comparison of data across groups within the trial.

Studylog Increases Throughput of Large, Parallel HuTrials through Efficiency of Data Acquisition

When running multiple, large HuTrials at once, a system is needed to keep track of every assessment required for each individual animal on a day-by-day basis.

The scheduling manager described above has multiple functions to improve the efficiency and completeness of data acquisition throughout the studies, which is essential with hundreds of animals to monitor daily.

Full background information can be included in Studylog for each animal including origin, body weight, animal health, and a number of other parameters, which allows each animal to be tracked from enrollment throughout the study. Preparation sections for test agents allow easy formulation and rapid calculations of doses to be delivered for each animal, which is useful when multiple different arms and treatments are being studied in parallel. Studylog also streamlines data collection, providing daily alerts on which measurements such as body weight and tumor volume need to be collected for each animal. This streamlined data collection is vital for the speed and efficiency of our HuTrials, and also for the humane treatment of animals. For example, if a body weight falls too low or a tumor grows too large, then an alert for that specific animal will also be received. This is more efficient than manual calculation of these factors for hundreds of animals each day. All of the data collected is saved directly to a central database, with data integrity being an important part of Studylog design, and all data available for regulatory needs.

At the end of the HuTrial, sample collection stages can also be programmed to give instructions on exactly which samples are needed on which days, with sample preparation

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details similar to human clinical trials included e.g. centrifuge speeds, sample storage. This ensures that sample collection always occurs at the correct date and time for each animal even following rolling enrollment into the study, and that clients receive all of the assessments and samples that they require.

Studylog Allows Rapid Final Reporting in a Format to Suit the Client's Needs

When HuTrials are completed, reporting final results quickly and completely to a client is essential, and this is also expedited through Studylog.

In order to mimic human clinical trials, each separate model is regarded as a patient and the data from models is grouped together for analysis. Studylog incorporates both internal and external graphical and statistical software to allow fully comprehensive reports to be produced, which can include endpoints similar to human clinical trials such as survival curves. The software contains templates for over 30 different report types, which reflect best practices within the industry, and which we can customize to meet individual client requirements as needed.

Coming Soon from Studylog

Crown Bioscience are at the forefront of oncology innovation and require a software partner who is continually evolving and incorporating features to enhance our studies.

Studylog will soon be releasing a client web interface, which will allow clients to directly access their data at any time they require, anywhere around the world. Connecting clients directly to their results in real time will improve communication and discussion of results, and improve efficiency of study design changes.

Conclusions

Crown Bioscience HuTrials, also known as Preclinical Phase-II like mouse clinical trials, human surrogate, or "avatar" trials, are increasing efficiency in translational oncology, through aiding in human trial design, and identifying and validating biomarkers and gene signatures of potential responder populations in a cost-effective manner.

The ability to run large, parallel, multi-center HuTrials requires a large capacity and a highly efficient system of HuTrial design and implementation.
Studylog software provides just such a tool, optimizing our HuTrial workflow and integrity to the highest level possible through a range of efficient software functions, such as ease of centralized management, flexible study design, and easy analysis of results. Studylog allows us to be more reactive to HuTrial data in real time, to interact easier with clients, and to increase the efficiency of data capture and study throughput for each and every HuTrial we perform.
Crown Bioscience can be contacted at busdev@crownbio.com for any further questions or information required on HuTrials, or for information on other Crown Bioscience products and services.
For more information on Studylog software, please contact Studylog Systems at info@studylog.com, by phone at +1.650.290.7540, or via the web at www.studylog.com.

References

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