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The Altascientist
SCIENTIFIC JOURNAL

ISSUE NO. 23

ROBUST SAMPLE MANAGEMENT FOR RELIABLE STUDY RESULTS

The proper handling of specimens (obtained from the trial participant) and samples (prepared for lab analysis), and their precise, timely treatment is crucial for reliable, robust data, and good decision making. When making a go/no-go decision for a new therapeutic, there must be certainty that the data which informs the decision is of the highest accuracy.

The quality of trial data depends on a rigorous sample management process that safeguards the integrity of samples at every step, from initial specimen collection through bioanalysis, to post-study storage. A CRO partner that conducts both preclinical and clinical studies, and supporting bioanalysis, ensures continuity of processes, knowledge sharing, and a centralized location for long-term storage of all your samples.

At both the bioanalytical site and the clinical site, meticulous workflows for safeguarding samples must be in place. Careful recording and storage of the samples, according to the study protocol and all relevant regulations and guidelines (e.g., GLP, GCP, ICH), is integral to the successful collection and analysis of trial data. Well-trained staff, managed by a dedicated Bioanalytical Principal Investigator with a clear mandate to safeguard the integrity of the data, is a valuable asset.

SAMPLE COLLECTION AND STORAGE CONDITIONS

Preclinical studies and clinical trials can involve many different sample types, in a variety of storage containers. The sample containers for storage below -80 °C are specially developed with materials that retain their integrity under such conditions — a plastic cap that can be refrigerated may not withstand temperatures below -80 °C. Likewise, the container for a different type of sample and temperature will have its own qualities, specific to the situation. The necessity for adding stabilizers, anticoagulants, or other preservatives, either after collection or before bioanalysis, also varies depending on the specifics of each trial. A comprehensive sample collection manual should be provided to the trial sites, detailing every requirement to ensure that all study personnel are fully proficient at maintaining specimen integrity. Flexibility to accommodate many variables with an equally rigorous workflow, and a readiness to learn and adopt the latest technologies, are key to a comprehensive sample management system that adapts to every sponsor's needs.

Clinical samples are generally stored in a controlled environment in one of five conditions:

- Room temperature (22 °C)
- Refrigerated at 4 °C
- Frozen at –20 °C
- Frozen at –80 °C
- Frozen in liquid nitrogen at –196 °C

Fresh blood samples are in a category of their own; they must be collected, transported, and analyzed within hours. Maintaining sample integrity during this time- and temperature-sensitive process is of the utmost importance. Fresh analysis of samples for flow cytometry is often critical, as highlighted by a 2019 article[1] published in the Journal of Immunological Methods.

Well-established workflows, appropriate SOPs, and dedicated staff contribute to the success of any fresh blood analysis. Clinical samples must be logged and shipped without delay. Laboratory scientists must be ready to start analysis as soon as the samples are released to their care. Close collaboration and excellent communication between the client, study personnel, bioanalytical experts, and sample management teams, are necessary to ensure the process concludes smoothly, within the allotted time frame.

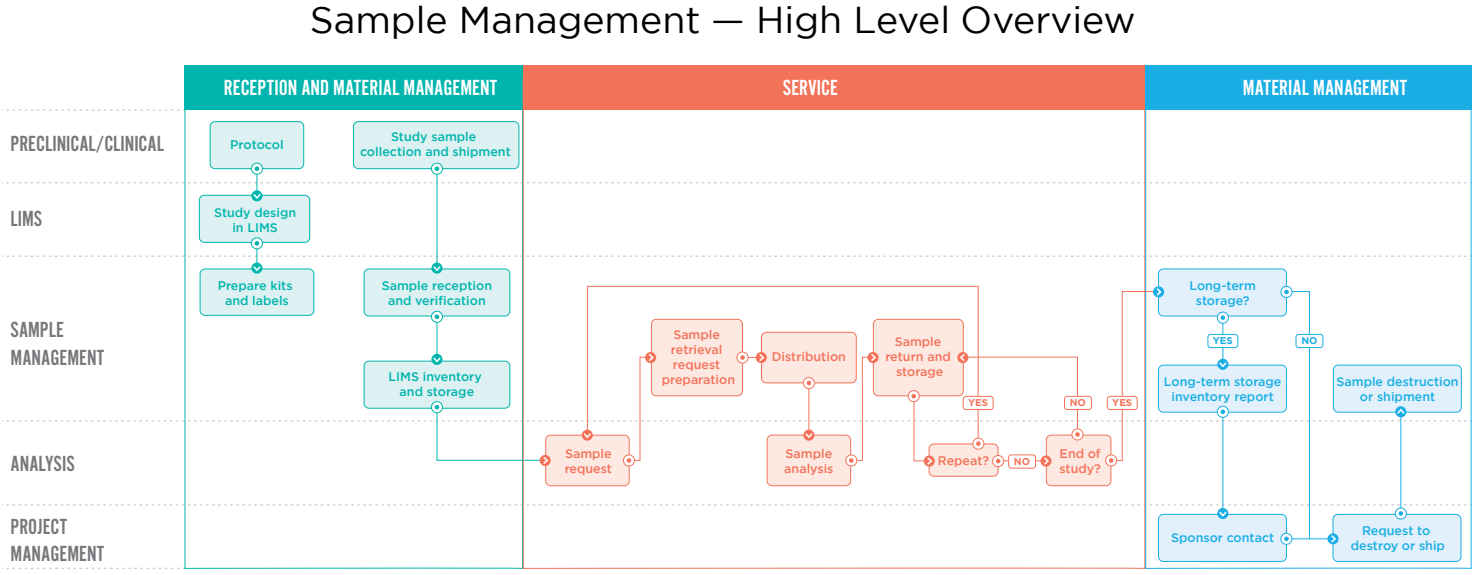
STANDARDIZED WORKFLOWS FOR RISK MANAGEMENT AND CHAIN OF CUSTODY MAINTENANCE

Consistent, standardized workflows implemented across studies minimize any potential risk to sample integrity and reduce the chance of chain of custody breaks. Use of an electronic data capture (EDC) system at the clinical site ensures complete data entry, and decreases mislabelling or erroneous identification of clinical samples.

A comprehensive, state-of-the-art EDC system tracks all relevant information for each specimen collected, ensuring all samples are accounted for as they move from collection to transport, to lab analysis, and finally to storage. At the bioanalytical laboratory, a laboratory informatics management system (LIMS) is used to ensure chain of custody and traceability. The barcode assigned to the tube and container is used throughout the process by both the EDC and the LIMS for stringent chain of custody maintenance, ensuring that no errors are introduced due to a logistical breakdown in the tracking of the samples.

Sample management and bioanalytical workflows should accommodate the different requirements for preclinical and clinical samples, cell and gene therapies, and small and large molecules. Method development and bioanalytical expertise in LC-MS/MS, ligand binding cell-based assays, flow cytometry, and PCR, allow for a broad collaboration across different products in development.

STANDARD SAMPLE MANAGEMENT PROCESS



STABILITY TESTING

Stability is defined as "the capability of a sample material to retain the initial property of a measure and for a period of time within specified limits when the sample is stored under defined conditions"[2]. Stability testing is crucial to understanding the environmental conditions under which samples will remain viable. Time, temperature, humidity, evaporation, agitation, and light are some of the elements that may have an impact on the shelf-life stability of samples. Determining and then maintaining the ideal conditions for samples is a crucial element of a sample management process.

For each study conducted, stability criteria are defined up front. A reference molecule is tested over a given period, under prescribed conditions, to determine the stability of that molecule in a defined matrix. The clinical samples are then monitored throughout the study to ensure they have been maintained in the appropriate conditions, as determined during stability testing.

Both short-term and long-term stability are important. As a drug progresses through different clinical phases, it is important for a sponsor, as well as the manufacturing partner, to understand the stability of their product under different conditions, such as how well a molecule handles -80 °C conditions over a period of days to years, and the number of acceptable freeze-thaw cycles. The variety of different storage requirements for COVID-19 vaccines are an excellent example of how stability testing affects not only the clinical trials, but the eventual manufacturing and distribution of drug products.

LABORATORY MANAGEMENT

At the bioanalytical site, clinical samples are entered into a LIMS according to the labelling and documentation provided by the clinical site. Clinical sites that use an EDC will assign a barcode to each sample tube, and the LIMS will use that same barcode. Manually prepared (non-EDC) documentation will be entered into the LIMS accordingly. Any discrepancy between the information on the tubes relative to the physical documentation, or the number of samples collected versus the number received at the laboratory, is immediately identified and resolved, including complete documentation of necessary corrections, as required by GLP guidelines.[3]

Samples are then stored under the assigned conditions (or analyzed immediately in the case of workflows designed for fresh specimens). Using a LIMS, all movement of samples is tracked so there is a thorough recording and audit trail of cumulative time out of storage, freeze/thaw cycles, time thawed, and chain of custody. Once a sample has surpassed the limit of its stable period (previously determined during stability testing and as defined by the cumulative total amount of time out of storage), it is revalidated to determine its condition, or not used for additional analysis.

CUSTOMIZED PROCESSES

Sample management includes standardized processes with flexibility to adapt to different situations, including capabilities for handling hazardous materials, such as cytotoxic or biocontainment Level 2 or 3 (CL2, CL3) samples. Highly trained personnel working with the latest personal protective equipment appropriate to the situation, is a key element of ensuring the health and safety of all individuals involved, from study participants to clinic medical staff and laboratory scientists.

Given the risks inherent in working with these types of samples, processes must deliver the highest degree of safe, meticulous, and careful handling, including specific cleaning procedures for equipment, such as benchtops, barcode readers, and instruments.

Fresh blood samples require a distinct, equally conscientious, and perfectly coordinated process to ensure that the samples are collected, recorded, transported, and received by the laboratory, to be analyzed within hours. Frozen samples can be stored for days or weeks before analysis takes place, whereas no such time allowance exists for fresh samples. Dedicated personnel, excellent communication, clearly established roles and responsibilities, and a strong logistical expertise are key elements of a successful fresh sample process.

MANAGEMENT OF BIOANALYTICAL MATRICES

A comprehensive sample management program includes capabilities to handle a wide variety of matrices, with robust method development and validation expertise. For every study, method development, validation, stability testing and sample analysis should be performed in an appropriate matrix relative to that which is used for the study. A bioanalytical laboratory must have exhaustive procurement procedures and an in-house inventory of matrices available.

Matrices can be ordered as they are needed, which may result in supply chain delays if the selected matrix cannot be procured to support study timelines. A secure approach is to maintain an inventory of matrices at the lab site, such that there are no delays in method development and validation that would negatively impact a study timeline.

POST-STUDY SAMPLE MANAGEMENT

At the end of a study, ensuring data reproducibility is part of the standard procedure for bioanalysis intended for PK and TK assessments, generally by retesting a subset of 10% of the total sample pool. Once reproducibility is demonstrated and reports generated, samples are either archived, placed into long-term storage, returned to the sponsor, or destroyed.

Long-term storage of study samples in a secure, stable, temperature-controlled environment is a definite advantage for sponsors. It is particularly helpful in cases where samples may need to be re-tested, or have additional analyses conducted, whether as a regulatory agency request, or a sponsor's need for additional testing.

ALTASCIENCES' CAPABILITIES

Altasciences has laboratories in the U.S. and Canada and multiple preclinical and clinical sites, including designated Containment Level 2 areas for work with Risk Group 2 pathogens. Because of our work with NHPs, our preclinical site have BSL-2 designation for various species. We offer rapid turnaround on interim analyses so sponsors can quickly make go/no-go decisions based on accurate data, with bioanalytical analysts available 24/7 if needed. We have decades of experience with BA/BE studies and can offer rapid throughput on these routine samples.

Our bioanalytical scientists work with the latest technologies to provide bioanalytical services from discovery to preclinical and clinical pharmacology, in accordance with GLP and current FDA/EMA guidelines for both small and large molecules. Each bioanalytical validation and bioanalytical phase for sample analysis has an assigned Bioanalytical Principal Investigator. We have dedicated laboratory space for LC-MS/MS, ligand binding, and flow cytometry, supported by an expansion of our large molecule laboratory in 2021.

We have experience with a wide spectrum of biological matrices in both animal species and humans, including but not limited to serum, plasma, blood, urine, feces, tissues, cerebrospinal fluid, and vitreous humor. Our capabilities include adapted systems for collection, analysis, and storage of microsamples (Mitra® VAMS®) and dried blood spots, for preclinical and clinical programs.

Study personnel maintain open and constant communication with key stakeholders for data sharing and project progression/adjustments.

Altasciences is committed to the delivery of comprehensive, compliant, and robust sample processes, from specimen collection to bioanalysis, and on to long-term storage or destruction.

ALTASCIENCES' RESOURCES

Webinars

Sample Collection Kits and Lab Manual

Bioanalytical Project Management

Transitioning Novel Scientific Workflows to Routine Bioanalysis

Critical Sample Handling Processes for Clinical and Preclinical Studies

Fact Sheet

Clinical Sample Collection Kits and Management Support

Video

Custom Sample Collection Kits

REFERENCE

1 Guder WG, Fiedler M, daFonseca Wollheim F, et al. The quality of diagnostic samples. 4th completely revised ed. Oxford: BD Diagnostics, 2005.

2 Diks AM, Bonroy C, Teodosio C, et al. Impact of blood storage and sample handling on quality of high dimensional flow cytometric data in multicenter clinical research, 2019. https://www.sciencedirect.com/science/article/pii/S0022175919301140. Accessed April 5, 2022.

3 Organisation for Economic Co-operation and Development (OECD). https://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm. Accessed April 28, 2022.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements.

Altasciences helps sponsors get better drugs to the people who need them, faster.