Exploring risks affecting clinical sample quality

Introduction

Biology aside, opinion on vital factors for the success of a clinical trial depends on the 'hat' worn by the person asked.

When asked the most important considerations, the trial sponsor will have such aspects as patient safety, clinical endpoints, patient recruitment, compliance, cost and timings, high up on their priority list. These are, of course, all vitally important, however, rarely is sample quality considered at all or, at the very least, will be found low down the list. Asking a laboratory analyst the same question is likely to generate a much more sample-centric response, highlighting such things as consistent processing methodologies between sites, accurate sample labelling and documentation and good quality samples. Being purely data focussed, the statistician will consider the power, probability of success and predicted patient variability. They look at the sample size required to confirm or reject a hypothesis. That sample size equates to a number of patients; however, it does not consider that some of the samples from that patient will not give a viable data point.

This paper examines the various risks to sample quality in a multi-site environment and ways in which the risks can be minimised. Views have been gathered from personnel active in the running of clinical trials from sponsors, clinics and analytical laboratories, as well as published literature.

Risks to sample quality

When comparing data from clinical samples, we make the assumption that all samples within the same trial are alike i.e. they were taken, processed and analysed in the same way. Considering that samples typically come from not only multiple clinics (sites) but also from different global regions, that may be a rather large assumption.

Sponsors typically collect more samples per subject during Phase 2 trials. The average number of sites used in multinational Phase 2b trials is 37 with numbers going as high as 400 (1). Taking each site as a variable and potentially even each person processing samples, it quickly becomes obvious that consistency is key to minimise the effect of those variables.

Preanalytical variables is a term used to define parameters which can affect the quality of a sample from the point of collection to analysis, with the variables and best practice recommendations being widely reported (2, 3) and understood in the bioanalytical sphere. Here, the variables affecting samples before collection have also been assessed. The fact that preanalytical variables have been reported for nearly 30 years but remain an issue at the time of writing, highlights the need to for clinical teams to incorporate bioanalytical expertise into early sample operational plans.

Risk to consistency can be broken down into four main areas: consumables, processing, sample tracking / storage and analysis. A summary of risk is shown in Table 1.

> "A clinical trial is only as good as the quality of its samples"

Table 1.

Factor	Requirement	Sources of risk	Potential effect of risk	Mitigation
Consumables	Same type and possibly batch are used across all sites	• Different manufacturer of blood tubes • Out of date blood tubes • Poor labelling	• Interference during analysis • Haemolysis or poor anticoagulation • Incorrect identification	• Centralised distribution of kits. • Centralised monitoring of kit expiry dates • High quality cryogenic labels pre-applied to consumables.
Processing	Consistent methodology across all sites	• Sample not frozen upright. • Incorrect volumes. • Method details not adhered to. • High staff turnover	• Sample leakage • Insufficient sample for analysis • Different resultant sample (non comparable)	• Clear instructions in laboratory manual. • Monitoring of compliance with instructions.
Sample Tracking / Storage	1. Accurate manifest matches samples shipped 2. Storage conditions as directed.	• Manifest not accurate. • Insufficient dry ice used. • Poor temperature control. • Transportation route delay.	• Loss of chain of custody. • Instability of samples	• Use of barcodes. • Centralised sample tracking. • Use of expert courier.
Analysis	1. Robust validated methodology. 2. Validation of clinic logistics.	• 'Cut down' validation used – is the data 'fit for purpose'?	• High batch failure. • Loss of sample data. • Unacceptable data for regulatory submission.	• Expert review of validation report. • In-study monitoring.

Consumables: Local vs Centralised Supplies

The simplest preanalytical variable to control is the consumables used to collect the samples.

Sample consumables are generally standard items found in any clinical laboratory, therefore, is it not easier and more cost effective to let each site source their own? At first glance, the answer is yes. However, on closer inspection of the impact of the consumables risk, we may well be more cautious. Perhaps a better question would be 'what cost do we assign to an incomplete data set'?

As an example, blood tubes from different manufacturers may utilise the same anticoagulant, however, the manufacture process is likely to vary e.g, coated beads, powder and gel forming substances. Each manufacturer must register their individual tube as an in vitro diagnostic device (IVD) and is subject to the In Vitro Diagnostic Directive 98/79/EC. The directive ensures consistency of the IVD but does not relate that consistency to similar products from other manufactures. It, therefore, is clear that simply specifying e.g a 10 mL K_2EDTA blood tube is insufficient in our quest to standardise the way in which the blood is taken.

Most sponsors utilise centrally provided clinical kits to ensure consistency of supply.

Centralised Kits

When selecting vendors for kit supply, it is recommended that consideration is given to the kit design and potential for error in the clinic. For example, a plastic bag containing pharmacokinetic blood tubes and another containing loose labels which require sorting into time order then duplicates sorted and applied to the sample record is more prone to error than one in which blood tubes are pre-labelled and racked in time order with corresponding duplicate labels already applied to the sample record.

Picture the stressed research nurse having to collect samples from multiple patients and possibly multiple trials in the same day.

> "Easy to use, clear kits have a real impact on minimising errors in the clinic"

Labelling

The effect of quality labels on sample quality should never be overlooked. If the print becomes illegible when wet or the label falls off the tube when frozen, the sample will not be able to be accurately identified and will, therefore, be worthless. The amount of hand written information should also be minimised.

Processing

As with all aspects of a clinical trial, personnel experience and training is vital. Staff turnover is an obvious high risk, however, even experienced, long serving clinic staff will make errors if the laboratory manual and training instructions are poorly documented. It is unlikely that the clinic nursing staff in attendance at the Site Initiation Visit will be the same throughout the lifetime of the trial, therefore, laboratory manual training needs to be included in the ongoing Trial Training Plan, not just clinical aspects.

Laboratory manuals are known to be cumbersome documents with users having to flit between different sections to obtain the information they require. As a result, users often transcribe the information and leave the official manual filed in a cupboard. A clear, concise laboratory manual will go a long way to reducing variability and errors in the clinic, as well as stress level of clinic personnel. Make sure that your vendor is open to modifying processes or instructions where sites are finding difficulties.

What works for the central laboratory may not necessarily work for the clinic staff.

Regardless of complexity, it is essential that sites follow the Laboratory Manual. Early intervention to non-conforming sites can be achieved through in-study monitoring.

Even where all samples are set to be analysed at the end of a study, if any test is considered high risk to processing error e.g preparation of sputum for cellular differentiation, consideration should be given to the use of quality control test samples early on.

Sample Tracking and Storage

Sample tracking is one of the biggest challenges for any clinical or laboratory project manager. The foundation of robust sample tracking systems starts with the centrally produced kits used at the clinical site.

Most laboratories have Laboratory Information Management Systems (LIMS), however, clinics around the globe, may have limited resources, therefore, finding an electronic 'one size fits all' solution may not be the answer. Many vendors have tried to implement software to track the samples throughout the entire lifecycle, however, in practice, busy clinics are reluctant to have a different software package for each trial, preferring to stick to in-house systems.

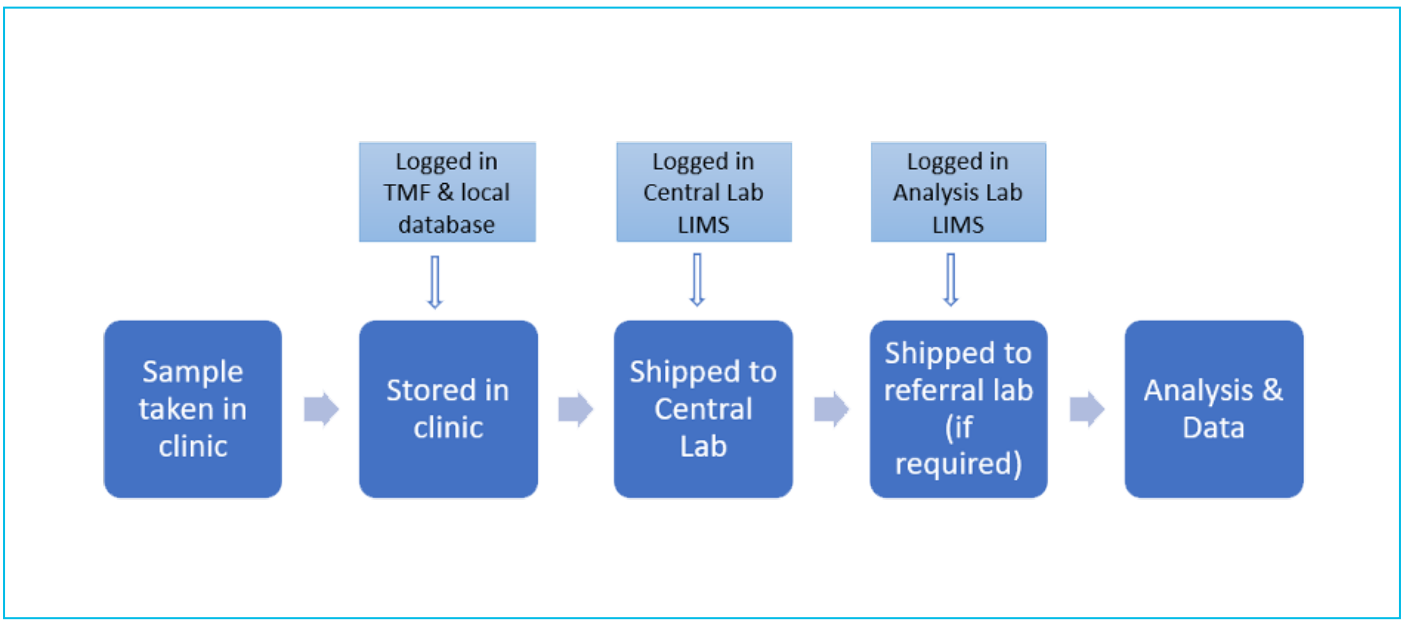
Figure 1 shows a schematic of the typical sample flow when utilising a Central Laboratory (CL). Samples become 'visible' at the CL, when they are received, reconciled with the paperwork and logged onto the LIMS.

The main risk in this process is good old human error. Barcodes can significantly help in risk reduction, however, be mindful that barcodes may not be compatible at all stages in the process e.g the clinical site storage facility database.

During early phase trials, it is not unusual for rapid turnaround analysis to be requested, as data may be required to make clinical decisions or trial progression. In these cases, the trial sponsor may require samples shipping direct to a referral (external) laboratory. This creates further tracking challenges so ensure that your logistics vendor has robust processes in place to fulfil tracking and reconciliation requirements.

Tracking does not only involve the facility location but also the storage location (freezer, ambient etc), shelf or even box position and the storage temperature. An auditor may well want to see records of any individual sample to demonstrate that the sample has been tracked throughout its lifecycle and has been stored under the conditions which it has demonstrated stability.

Figure 1: Typical central laboratory workflow



Analysis

When considering if an analytical validation is sufficiently robust, you must first consider what the data is to be used for. Acceptable requirements may be quite different for data which is to inform clinical decision making than for data which is purely exploratory and not to be used in a regulatory drug submission. The United States Food and Drug Administration states that the level of validation should be appropriate for the intended purpose of the study (4).

For the purpose of this paper, it is assumed that the analytical validation is robust, therefore will not be discussed. Rather, the risks in the whole process, which may have impact on the analysis, have been considered.

Sample preparation at the clinical site and the associated logistics is generally not part of the analytical validation, in yet, particularly for biological assays, may well be vital in demonstrating that the bench-based validation is valid.

Some areas to consider are:

- Is sample processing at site likely to affect the resultant sample for analysis? Remember that the clinic personnel may not be a highly trained analyst.
- Mitigation steps for delayed, time-sensitive samples.
- Controlled temperature shipping requirements. 'Ambient' in the back of a courier van in the height of summer or an airplane hold may not be the ambient (18-25° C) generally found in a laboratory.

Conclusion

The risks which have the potential to impact clinical sample quality have been explored. All risks should be fully explored as early in the trial planning stage as possible to maximise the sample quality and consideration of risk mitigation incorporated.

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