Choosing the Right Lab: Big is Not Always Beautiful

Many challenges have to be properly addressed in order to conduct a clinical study successfully: defining the right study design for a given drug candidate, selecting appropriate study centres with excellent access to the study population, and identifying a central lab which can manage all study-related tasks and which provides valid and reliable laboratory data with short turn-around times. This paper will discuss the different categories of laboratories involved in clinical labs and may be used as a brief guide to a good match between study design and laboratory services. The importance of laboratory data within clinical studies is often only fully recognised when clinical studies are being delayed or otherwise affected by the lack of reliable data. A few examples shall be used to illustrate the consequences of an improper choice of clinical laboratory: 1. Inclusion of patients can be significantly impaired when screening data are not available on the same or next day of the screening visit. 2. Data of pharmacodynamic endpoints can be misleading if non-validated methods have been used. 3. Several analytes are not stable in normal serum or plasma and need specific stabilisers or storage conditions. In cases where these requirements are not properly defined by the lab this may lead to analytical artifacts. However, due to the fact that design, geographic spread and read-out of clinical trials is very diverse, it is also recommended to consider different categories of lab partners for different trials.

The different lab categories can be discriminated according to the following scheme:

Type of laboratory	Laboratory facilities	Head-count	Focus	Quality systems	Documentation	Methods
International multisite central laboratories, often associated with global CROs	Wholly-owned sites on different continents	1000-2500	Clinical studies	CAP, ISO15189, GCP, compliance with EMA and FDA standards including GCLP	GCP/GCLP-compliant, archive with raw data, validated computer systems	Validated according to EMA/FDA guidelines
International central laboratories with qualified partner labs	Wholly-owned central lab and multiple regional independent partner labs	< 250	Clinical studies	CAP, ISO15189, GCP, compliance with EMA and FDA standards including GCLP	GCP/GCLP-compliant, archive with raw data, validated computer systems	Validated according to EMA/FDA guidelines
Independent central laboratories with international experience	Wholly-owned central lab	< 150	Clinical studies	CAP, ISO15189, GCP, compliance with EMA and FDA standards including GCLP	GCP/GCLP-compliant, archive with raw data, validated computer systems	Validated according to EMA/FDA guidelines
Bioanalytical laboratories	Wholly-owned speciality lab or subsidiary of CRO	20-300	Pharmaco-kinetic studies	GLP, compliance with EMA and FDA standards	GLP/GCLP-compliant, archive with raw data, validated computer systems	LC/MS-MS methods validated according to EMA/FDA guidelines
Local reference laboratories or hospital laboratories	Independent lab or lab belonging to a laboratory chain	20-250	Standard medical care	CLIA or ISO15189	Standard result reports	Verified according to standards sufficient for patient care

The evaluation of advantages and disadvantages of the different lab types has to be discussed in the context of the needs that have to be addressed for a given clinical study. Large international Phase III studies with more than 2000 patients conducted on different continents clearly benefit from the global infrastructure of an international multisite laboratory. The same is also true for studies conducted in China, where national regulations restrict the export of clinical trial samples and where generallyonly international multisite laboratories arerepresented with established lab facilities. Large multisite central laboratories that are associated with a global CRO are also often chosen when the overall study management is in the responsibility of the CRO they belong to. Finally, international multisite central laboratories are often involved in clinical studies of different phases due to preferred provider agreements with global pharmaceutical companies. The global infrastructure of international multisite laboratories offers the benefit of potentially uniform procedures and harmonised SOPs. However, one should also take into account that these international multisite central laboratories have been generally built by the acquisition of national or regional laboratories with their own infrastructure. Therefore, the different subsidiaries do not necessarily have uniform methods and SOPs. This aspect should be challenged when choosing the right partner.

Source: MLM Medical Labs'

International central labs with independent qualified partner labs can offer a valuable alternative, especially when it comes to multi-centre Phase II studies or Phase III studies with up to 2000 patients. These laboratories often work with strong qualified partners and therefore provide a great deal of experience that will facilitate the conduct of the clinical trial. The involvement of partner laboratories that are in direct reach of the clinical study sites can reduce logistic costs and avoid delays due to customs clearance. Furthermore the arrangement with partner labs offers the advantage that management attention is focused on the optimal conduct of clinical studies – provided that reliable and efficient partners have been chosen – and is not diluted by running a global organisation with all financial and regulatory implications.

International Phase II and Phase III studies can also be supported by independent central laboratories with international experience. These laboratories often provide a broad portfolio of standard and speciality parameters as well as all flanking services like kit-building, logistics and data management. Therefore such independent laboratories are especially of interest for clinical studies from Phase I-III

that rely on non-standard biomarkers as clinical endpoints, and which are challenging with respect to method development, logistics or project management. In order to illustrate the potential of independent central laboratories, two case studies are presented here:

Case study # 1. An independent laboratory was chosen by a global pharmaceutical company as central lab for an international study in the area of metabolic disease. The study was conducted in the US, and Central and Eastern Europe. Total ketone bodies, beta-hydroxybutyrate and acetoacetate were selected as biomarkers, among others. Unfortunately the stability of acetoacetate is very limited: serum samples are stable for only three days at -30°C. The laboratory started a new stability testing and demonstrated that stability could be increased to six days by storing these samples at -80°C. This allowed the sending of samples in bundled shipments on dry ice, dramatically reduced shipment costs, and led to reliable analytical results due to extended stability and immediate testing after arrival. One reason among others for the involvement of the independent central laboratory was that this laboratory was interested to establish and validate the assay of beta-hydroxybutyrate and acetoacetate in contrast to other labs, including international multisite central laboratories.

Case study # 2. According to EMA guidelines, almost all new drugs licensed through the centralised procedure have to come with a pediatric implementation plan for clinical studies with infants. There are multiple challenges for pediatric studies. One is the limited volume of blood drawn and the need to restrict the number of blood draws per visit to the absolute minimum. An independent central laboratory has been selected by a large global sponsor as a central lab for a global pediatric study. One of the most important reasons for this choice was the fact that this lab was able to present a concept for analysing all desired parameters with very low blood consumption and a reduced number of blood draws per visit, which facilitates the recruitment of subjects in this ethically very sensible study collective. An international multisite central laboratory has offered a different approach involving different lab sites in different countries which would have done only a few of the numerous biomarkers of interest. This would have automatically resulted in multiple blood draws and a larger sampling volume which was not acceptable for the sponsor. The independent central laboratory offered the advantage that all analyses were conducted at only one laboratory site with a small sample volume.

Independent central laboratories are often privately-held companies and provide the advantage of flat hierarchies and a generally low turnover of personnel, which translates into fast and direct communication with the clients with a stable team of project managers as key contacts. The low turnover guarantees a constant and seamless communication between client and laboratory staff when multiple projects are being conducted for the same client. In addition, these laboratories often do not rely on larger preferred provider arrangements and have to generate their revenues from multiple clients with smaller projects. Therefore they are very flexible and willing to adjust to the requirements of the sponsor. It has been observed that this business attitude is often very attractive for smaller and mid-size biotech and pharmaceutical companies that are less interesting targets for international multisite central laboratories, since these clients do not offer the revenue potential of global pharmaceutical companies.

Finally, local reference or hospital laboratories are still being used for clinical studies. However, in 2012 the EMA issued new regulations on the use of clinical laboratories in clinical trials[1]. The EMA reflection paper defines several criteria for laboratories involved in clinical trials, which can be regarded as a merger of the standards of good laboratory practice (GLP) and of ISO15189 or CAP requirements. The criteria requested by the EMA can also be summarised under the quality standard good clinical laboratory practice (GCLP). The EMA reflection paper requires a high degree of organisation of the clinical laboratory, regular GCP training, defined procedures for study-related processes, a stringent and audit-safe documentation of all laboratory activities, and a fully-developed quality management system. These requirements are difficult to meet by hospital and reference laboratories that primarily focus on patient care. Therefore it can be expected that this type of laboratory will play an increasingly marginal role in upcoming years, whereas central labs will be the predominant providers of laboratory data for clinical studies.

When choosing the right lab for a given study, the different types of central labs discussed here should be carefully evaluated. Especially in the case of large multinational Phase III trials, international multisite central laboratories offer clear advantages. However, in the case of Phase I studies and mid-size Phase II or III studies clients can take advantage of the high flexibility, service attitude and experience of independent central laboratories or international central laboratories with qualified partner labs.

Reference

1. *Reflection paper for laboratories that perform the analysis or evaluation of clinical samples (EMA/INS/GCP/532137/2010*

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