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A CRO's Perspective on Successful Partnering to Deliver SDTM/SEND Contributions

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ABSTRACT

Is standardisation at the submission level driving complexity at the contributing CRO level? As the number of organisations contributing to a data package increase so does the complexity of the delivery. Here a CRO presents the challenges, successes and recommendations for other CROs and partners.

INTRODUCTION

As data standardisation has become integral to the submission process, the requirements of contract research organisations (CROs) has also shifted. CDISC guidelines are now making their impact felt far beyond the organisations responsible for the preparation and submission of data. The relationship between partnering organisations has also become ever more crucial to the successful delivery of SDTM and SEND format data.

The experiences of LGC, a CRO that acts as a test facility supporting the delivery of preclinical and clinical bioanalytical data, will be described. As an organisation working primarily downstream of test facilities and clinical parties there is often limited line of sight to the resulting data submission requirements. The challenges of working with multiple partners, together with suggested solutions for providing SDTM/SEND contributions to multiple Sponsor's or third-party organisations will be reviewed.

The effect of standardisation at the submission level will be examined in the context of driving complexity at the contributing CRO level. The task at LGC is compounded by multiple organisations and systems contributing source data often in a non-standardised manner, for integration into SDTM/SEND data. The opportunities taken to simplify processes to satisfy SDTM/SEND requirements will be described together with how these capabilities have been built at LGC. Associated learnings for similarly placed CROs that provide test facility services will also be shared.

The role of CDISC, PhUSE and other industry leaders, such as the European Bioanalytical Forum (EBF), in reducing complexity and supporting standardisation across the CRO and pharmaceutical industries will also be reviewed.

BACKGROUND

As a CRO with a focus on delivering bioanalytical services, LGC is in a novel position within the wider pharmaceutical industry. Only a proportion of the SDTM/SEND requirements directly affect the way that we work. As a service provider, it is our role to work with the customer to deliver the data that they require for their submission package. Primarily, these are standalone pharmacokinetic concentration (PC), pharmacokinetic parameter (PP), or surrogate laboratory results (LB) domains. Even though the data we provide is only a small section of the overall submission package, we need to ensure that we have an expert understanding of the CDISC guidance and have the processes in place so that we can deliver the product that is expected of us.

CHALLENGES

TIMINGS AND CONTRACTS

There are multiple stakeholders that feed into the set up and conduct of drug development programs, which in itself builds in complexity to the packages and relationships of the partners involved. LGC's position is novel in that it bridges the interface between the in-life or clinical organizations that generate bioanalytical samples, and the sponsoring or data management organization responsible for compiling

overall submission packages. This bridging position is often complicated by engagement with partners only after the in-life or clinical stages of a study have already been established. The result is often that source data received at LGC (such as demographics, sample collection dates and times), are not compatible with our own systems, or even the requirements for the output data packages. This presents both a 'top down' and 'bottom up' constraint on the way that we work.

As SEND/SDTM requirements have become mandatory for submissions, our partners requirements have changed correspondingly. The way in which we are required to present our own data has changed as a consequence, without our direct involvement in the creation of submission packages. Ideally, we would be able to tailor our data outputs easily, with minimal manipulations, to meet these changing requirements. Unfortunately, this is rarely the case and our internal processes have had to be quickly adapted to ensure that we meet our partner's expectations. Each program of work presents its own set of challenges and requires a different process to be used to reach the end result.

To address the complexity of these partnerships LGC have undertaken review and update of the contracts and agreements made with our partners. This includes providing clear outlines of the responsibilities of each of the contributing organizations. In itself this promotes early engagement with our partners on the exact data delivery requirements, a discussion which is too easily only considered at the point immediately prior to the transfer of data.

Beyond the overarching contract requirements, a customized data transfer specification (DTS) is also generated for each program of work. This is used to clarify any program or data specific factors and minimize any rework following production of the data files. To support this, SDTM and SEND data transfer specification templates have been built, which expand on the template drafted by the European Bioanalytical Forum (EBF) working group at the 2015 open meeting. The extent of the industry wide adoption of this draft template is not currently clear, with the final recommended template not yet published, but the benefits of standardizing these specifications are clearly aligned with the move to the standardization of data packages.

SYSTEMS AND PROCESSES

With the drive towards standardized data formats, which is generally accepted as beneficial for the sharing and integration of data from multiple sources, we have inherently lost a degree of flexibility in how data is provided. An unmodified spreadsheet, often created directly from laboratory information management systems (LIMS) or data processing software, is no longer sufficient.

Specialized software is required, along with the additional validation, maintenance and data integrity considerations that go alongside this. As is standard across the industry, SAS© software is employed at LGC to provide extensive data transformation capabilities and to support the provision of datasets in submission ready formats (SAS transport files, .xpt). Additional capacity and expertise has been built using the skills of the in-house pharmacokinetics (PK) team. Here the generation of the pharmacokinetic parameter (PP) domains has been integrated into PK parameter generating process itself, using Phoenix® WinNonlin® workflows to provide an end to end solution for this specific domain.

One particular constraint that has been faced is the inflexibility of many LIMS and the significant investment required to evaluate and deploy the SDTM/SEND supporting alternatives. Crucial to understanding the potential returns of this investment is to understand the potential efficiency and throughput gains of these systems. A significant review of capacity, resource and contractual requirements is underway, along with a growth in the data management team dedicated to supporting our partner's data delivery requirements.

TRAINING AND EXPERTISE BUILD

CDISC guidance is openly available, but as with all guidance, it is open to interpretation. Our partners may have a different interpretation to our own, and from experience there are significant differences in the requirements of different partners based on these same guidelines. LGC's approach to ensuring our outputs are consistent with SDTM/SEND requirements has been to develop our own in-house understanding with the support of external experts. Bespoke training tailored to our exact requirements has provided us with the confidence to challenge contradicting interpretations with a view to ensuring the

acceptance of the final data submission package. By establishing a well-developed baseline understanding has supported the delivery of data files with a 'right first time' approach, avoiding trial and error and supporting the positive working relationships with our partners. This has also meant that subsequent data revisions arising from a partner's changing interpretation of the guidelines have been restricted. The avoidance of re-work is critical in supporting efficient service delivery to LGC as a commercial organization.

The use of specialized data managers aligned to specific internal customers and external partners has provided us with the benefit of a consistent approach to data generation. However, successful data delivery is only possible with ongoing support for final delivery throughout the duration of the program of work. This involves engagement and education of our own program managers who are often the first point of contact with our partners. A program manager does not necessarily need to understand the details of the data management process or CDISC guidelines, but they need to have an overall awareness of the expectations and an understanding of how operational decisions may impact data delivery. Investment in the awareness training of all staff is underway to build on the learnings from current partnerships. This in-house training will develop with the development of the CDISC guidelines and the changing requirements of our partners.

PARTNER ENGAGEMENT AND UNDERSTANDING

Requirements for SEND have been in the pipeline for the past two years with the requirement becoming mandatory for all submissions as of November 2017. Unfortunately, transition to the use of this data format has been slow to translate to the service requests from our partners. Proportions of our partners are proactive in their approach and have developed their own systems and processes to support the receipt and transfer of SEND/SDTM data. The exceptions however are consulting us for guidance beyond our responsibilities for the bioanalytical data packages, or are not yet aware of their own future requirements.

From our position of providing restricted data domains we are able to offer advice to our partners on how to interpret and implement these guidelines, but are conscious that any further reaching implications for the overall submission package are beyond our expertise. Helping our partners to understand each of our exact responsibilities can sometimes prove to be challenging. The timing of our involvement, most often once the in-life or clinical phases are initiated is often too late to resolve potential issues, and requiring mitigating steps in follow up.

Related to the timing of our involvement with studies, frequently the data transfer requirements have already been established between our partners and the organizations responsible for the overall data submission package. Any inconsistencies in interpretation of the implementation guides, or details driven by the specific study/trial design are often too late to influence. In these situations our approach has been to ensure that any associated implications for our own data contributions are well understood by our partners allowing them to plan and prepare for any follow up requirements prior to submission.

TEMPLATING AND SOURCE DATA VARIABILITY

An early observation on the changing requirements for how we provide data to our partners has been around the incorporation of information that is provided us from external sources. This includes in-life sampling times, collection date and times and subject demographics. LGC do not widely offer central laboratory services and are usually reliant on the accuracy of demographic data provided by external sources.

Our experience has been that external parties that provide this source data work in their own way, using different templates and formats. This is true even within the same organizations operating from different locations or within different operational functions. A simple but illustrative example is taken from electronic sample shipping manifests, received from external central laboratories, responsible for the handling and storage of samples directly from clinical sites. It is not unusual for LGC to receive manifests from the same providing organization that use different variable names, in different variable orders, with different nomenclature for the same program of work. This leads to additional complexity when incorporating this source data into our own data domains.

Such small differences in source data can have a significant impact on final data provision; requiring considerable customization of data handling for each externally sourced data file. In the case of large clinical studies with numerous sample deliveries and associated manifests, this is particularly true. The overall result has meant that LGC have been unable to extensively implement data handling templates with a one size fits all approach and rely on the input of skilled data managers.

LGC have approached our partners with the request to ensure that externally sourced files are received with consistent content and formats; this is not always possible for reasons beyond our sponsoring partner's control. In these cases a mutual level of service provision has been agreed to ensure that where LGC faces significant challenges to the provision of SDTM/SEND data, concessions are possible, such as providing the domains without demographic data.

As a radical alternative, consideration was made for LGC adhere to a strict template format that does not make concession to the formatting or content of source data. In practice, this is not practicable for LGC, or acceptable to our partners. Similarly, consideration was made to requesting in advance of LGC's contribution access to the associated laboratory results (LB) domain. The advantage of which would be access to a standardized version of the demographic information required in associated PC/PP domains etc. Again, this is not practical considering the required timings for the cleaning of demographic data and the provision of LGC's domain contributions to our partners.

A form of standardization and templating has been achieved at LGC through the use of a reporting laboratory information management system (LIMS). Inherently flexibility is built into many LIMS in order for the systems to be able to support the variability in preclinical and clinical study designs. Rather than supporting standardization this presents challenges by allowing variability in how each program is set up, depending on the preference of the user. The establishment of comprehensive standard operating procedures and the use of project/study specific requirements through a partner agreed data transfer specification (DTS) document has supported a holistic approach to service provision.

TIMELINES

A further challenge that is presented at LGC is meeting partner timelines for the delivery of data and making sure that expectations are met. LGC are at the beginning of their journey and new processes may often take longer than expected from a more experienced CRO. However we are in a position where we have a good relationship with our partners, using an open and co-operative working environment to achieve the shared goal of delivering data in preparation for FDA submission.

SUCCESSES

A CASE STUDY

Building on an already established partnering relationship, a program of work was commissioned at LGC to retrospectively deliver SEND format pharmacokinetic concentration (PC) and pharmacokinetic parameter (PP) domain data. This provided the opportunity to develop SEND expertise in-house at LGC from a starting position of understanding the operations of the Sponsor organization and having an already well developed working relationship.

The resulting mutual understanding lent itself to creating a safe test bed for the establishment of new processes and systems. However, this was offset by the disadvantages of not being able to integrate SEND requirements into the setup of the study phase. Delivery was also simplified as it was removed from the operational pressures of delivering an analytical project (such as resolving methodology issues or analytical run failures).

A master data transfer specification document was employed to cover the overarching program of work. Study phase specific information such as test names/parameter names (TEST/TESTCD) specimen material (SPEC), units of measure (ORRESU) etc were appended as separate documents, preventing duplication of the main pharmacokinetic concentration variables and reducing document review times. This provided a consistency in approach at LGC, and visibility of the overall program of work for our partner.

Ultimately SEND format contributions were delivered with success, but with limited learnings available on how to set up and optimize bioanalytical studies as a partnering CRO.

LEARNINGS AND RECOMMENDATIONS

The above examples and scenarios lead us to recognize partnering as a significant area of development and focus for successful SDTM/SEND delivery. Based on LGC's experience in establishing SDTM/SEND capabilities and working with our partners to build success into these processes, the following recommendations are made.

SELECTING PARTNER ORGANISATIONS

A useful framework for the considerations to be made when selecting partners has been compiled by PhUSE[1]. The points made are relevant to both the contracting groups who are the target reader group and their partnering CROs, who should be aware of the criteria that they are being evaluated against. When selecting partnering organizations and setting up data delivery agreements, care should also be taken to avoid alternative interpretations of guidelines and contractual agreements. This is particularly significant when working with new partners.

For example, appropriate training in the submission requirements is an essential element for the successful delivery of SDTM/SEND contributions, but it is not the only factor: appropriate standard operating procedures, acquired experience, and other personal qualities are also relevant to successful partnering. This competency applies both to partnering organizations responsible for compiling SDTM/SEND contributions and to Sponsor contacts responsible for the commissioning or operational delivery of the study.

DATA DELIVERY AGREEMENTS

It is recommended to appoint and engage early with responsible parties, ideally at the study concept or set up stage. To drive success, it is fundamental that Sponsors and contributing CROs have a clear understanding of their own specific data delivery requirements. This should be tailored and specific to the study at hand, with a detailed understanding of study requirements beyond the outline of the implementation guides. Clear and accurate contracts outlining these requirements have a clear place and benefit to the partners involved.

The scope of data delivery agreements should include both the receipt of source data (such as sample demographics) and the resulting data to be delivered to the Sponsor or third-party. The standardization of source data delivery is currently an under developed area that is considered to require further industry focus, as below.

APPROACH TO DATA DELIVERY

Recognition is needed across all parties that late changes to requirements will have an impact at the partnering organization level, which may not be anticipated and may lead to unexpected implications for data delivery.

From an understanding of a study's data delivery requirements, it is recommended that formal data delivery requirements are considered in the context of the use of the data. For example, fit for purpose data formats may be more appropriate if visibility of data is required at interim time points. This may allow for the faster provision of data from partner organizations, particularly if demographic data is unlikely to be available at the time, or is subject to change. This can simplify and streamline interim data deliveries pending compilation of SDTM/SEND contributions in preparation for submission.

STANDARDISATION OF SOURCE DATA

Complexity at the contributing CRO level is strongly related to the non-standardization of source data, such as sample demographics, provided by central laboratories and test sites. In addition to data delivery agreements, agreements should be reached with partnering organizations on the format of received source data. This may in turn be facilitated by agreeing the timing of the incorporation of this data into SDTM/SEND contributions – only following source data and cleaning by the providing organization.

This is endorsed as a significant area of consideration for partnering CROs and industry leading groups. The recommendation is made for organizations such as the European Bioanalytical Forum (EBF), PhUSE and CDISC to extend their current focus from data submission deliverables, to include working towards a common exchange format and process for sample demographic data.

COMMUNICATIONS

Underpinning the above recommendations are the principles of good communication which should be combined with clear, consistent messaging across all involved partners (from central laboratories, test sites, third party data management providers and submission partners). Details of any required communication plans may be included as part of data transfer specification set up to promote this.

All parties should recognize that involved organizations are performing at various levels of implementation of the standards, but that the long-term objective of satisfying the submission standards is a shared one. Open communication regarding each organizations implementation plan and status should be considered at the partnering agreement stage.

It is also relevant to consider that technologies and data management platforms are evolving rapidly to support CDISC guidelines but may not be accessible or compatible with other systems fundamental to the generation of data. Significant and bespoke customization along with a related time and resource burden may be the most impactful consequence felt at contributing CROs.

CONCLUSION

It is recognized that as organizations transition to integrate SDTM and SEND requirements into their own organizations, complexity is inherently increased at the contributing CRO level. The recommendations made above are intended to facilitate partnering with contributing CRO organizations and improve the understanding of the challenges faced at sponsoring organizations.

Of particular importance is the engagement of CRO contributors with support organizations such as the European Bioanalytical Forum, PhUSE and CDISC to improve the efficiency of sharing sample demographic data across organizations. This also requires a wider buy-in into this process across all partnering, central laboratory/test site and third-party organizations.

A process of clear and open communication, with transparency of the services and capabilities offered is fundamental to the success of a partnering relationship. Competency combined with experience, an ability to innovate and adapt to changing requirements are key characteristic that should be adopted by all parties for success. These may require time and commitment to establish but in turn, lead to long term benefits for all involved parties.

REFERENCES

1. SEND Implementation Wiki – SEND between Organizations – Available at http://www.phusewiki.org/wiki/index.php?title=SEND_Implementation_Wiki_-_SEND_between_Organizations

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