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FDA review principles applied on CRO oversight

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ABSTRACT

A common setup in a Sponsor/CRO relationship is that the CRO delivers SDTMs, ADaMs and TLFs for clinical studies to a pharmaceutical company. Often statistical analysts from the pharmaceutical company have to use these CRO deliverables to create integrated submissions to regulatory agencies. One big challenge with such an arrangement occurs when data or reporting issues are realized at a late stage in the development cycle. This can jeopardize the relationship between the CRO and the sponsor and often leads to a blame culture and requires resource intensive solutions to resolve. This paper will describe how the Sponsor/CRO relationship can be managed effectively by learning from the relationship between FDA and Sponsor. It will be described how the sponsor can apply FDA review principles when reviewing CRO deliverables. In addition to more efficient and diligent processes, these principles require additional skills, which should be considered in the professional development process.

INTRODUCTION

Outsourcing the tasks to produce the statistical work package from clinical data science functions like data management, statistical programming or biostatistics, is one of the many key elements to develop a new compound. Pharmaceutical or biotech companies cannot or do not want to build up the internal headcount required to produce all the required deliveries on their own and reach out to contract research organizations (CROs) to produce pieces of all the necessary deliveries needed for a successful agency submission. Often these pieces are all deliveries for one or several complete clinical studies for a new compound and might include the production of the CRF/eCRF, CRF data, SDTMs, ADaMs, tables, listings and figures, and even the clinical study report.

In many cases the collaboration between a CRO and a sponsor is challenging. When expectations from the perspective of the CRO or sponsor are not met, it often results in a blame game between both parties involved.The successful management of outsourced clinical studies requires a sponsor to think about three important principles: the relationship to the external partners, the CRO oversight, and lastly the impact of outsourced studies to data knowledge generation.

A successful relationship between a sponsor and a CRO needs to be established in the first instance. This requires a clear exchange of expectations and a well-defined ownership and accountability for both involved parties. One might think about the clear definition of deliverables and delivery standards, as well as a clear adherence to delivery timelines. A well-defined ownership should also include a clear definition of responsibilities, processes and technology platforms.

It is a common misunderstanding that in case companies decide to outsource entire work packages to CROs, internal staff is not involved in these studies at all. While a complete hands-off approach does not work, a detailed quality check, which might include the recreation of all deliveries, does not work either. The first case might lead to unexpected surprises at the time of submissions. The second case is actually persiflage of the idea to outsource the study and repeat most of the work again. Defining a proper oversight model that clearly identifies how internal staff is supporting outsourced studies is critical. This model will then need to be forecasted in resourcing and budget plans.

Another critically important piece is the development and maintenance of internal data knowledge in those cases where external partners generate data. There is a general concern often stated by internal staff, that if data has not been produced by themselves, they cannot implement these data into integrated analysis data pools. Leveraging the interaction between the sponsor and the CRO can increase internal data knowledge though, if the CRO oversight includes review methods which do not solely focus on quality checks.

In case these three important topics are not considered and addressed adequately, the collaboration between the sponsor and the CRO can easily lead to a lot of frustration for both involved parties. Sponsor staff tends to blame the

CRO staff that they do not delivered as hoped, and CRO staff might be frustrated as they produced and delivered to their best knowledge. These blame games usually end up in lose-lose situations for both parties and in the process generate a lot of additional effort.

So the magic question is, how can someone build a successful collaboration between sponsors and CROs with a vested interest for both parties?

In order to answer this question, we should take a look at a collaboration, which seems to work well for most of the pharmaceutical and biotech companies. This is the relationship to the FDA or other regulatory agencies. Successful drug approvals are living proof that this relationship works. Recent standardization efforts driven mainly by the FDA and the corresponding guidelines [1], help tremendously to improve the relationship. Open and transparent communications at events such as the PhUSE annual conferences, and even more collaboration at events like the FDA/PhUSE Computational Science Symposium are designed to present a clear understanding of expectations.

In the following sections we will have a more detailed look at how the FDA uses the biometrical work packages from pharmaceutical companies and try to translate this FDA-Sponsor relationship into ideas on the Sponsor-CRO relationship. This will address the three above-mentioned important topics on relationship, oversight and data knowledge.

THE FDA DATA REVIEW

The FDA is very transparent and open to communicate how they process data submitted by sponsors. They are looking for an active dialogue at conferences like the PhUSE annual conferences or at the FDA/PhUSE Computational Science Symposium. At the PhUSE annual conferences in 2011 in Brighton [2] and the annual conference in 2012 in Budapest [3], former FDA Clinical Reviewer Dr. Chuck Cooper gave an insight into how FDA reviews data. At the PhUSE annual conference 2014 in London, Dr. Lilliam Rosario (Director of the Office of Computational Sciences) introduced the JumpStart program [4]. Key learnings from these keynote presentations were about the FDA data review approach.

The FDA developed a structured approach how to process and review data to meet the tight review timelines. The published guideline on electronic data submissions in November 2013 [1] is an important piece in this structured approach. Basically this approach can be explained by the following figure, which describes the staggered process on FDA's data review:

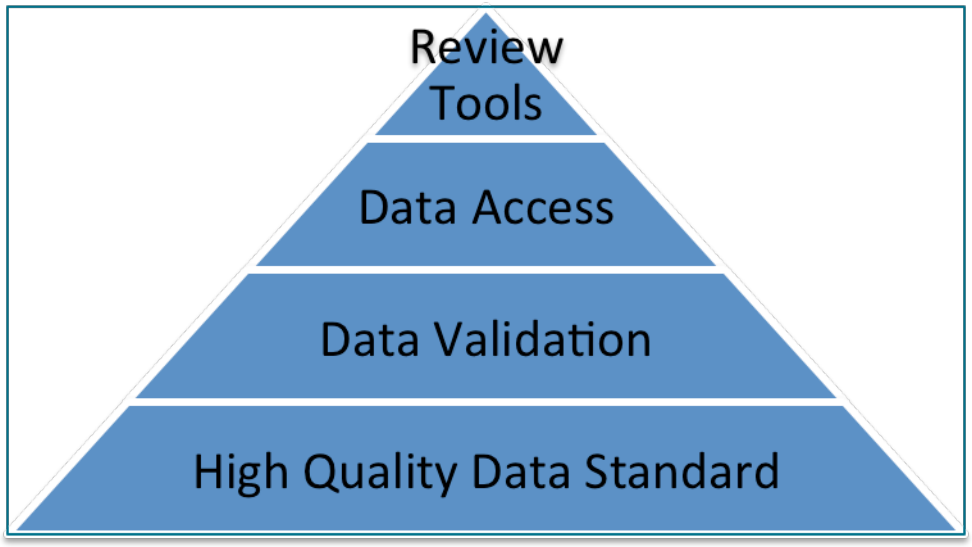

Figure 1 - The FDA structured data review

HIGH QUALITY DATA STANDARD

The foundation of the structured data review by the FDA is a high quality data standard. The FDA continuously develops internal expertise on data standards such as CDISC and communicates this to sponsors prior to data submission and ideally early in the IND phase. They clearly direct sponsors to critical resources like the data standards catalogue, common issues documents and relevant agency guidelines, which then refer to standard organizations such as CDISC or PhUSE. A standard, agency compliant delivery package from a sponsor following the guidelines and the FDA data standard catalogue should include:

- Study data submitted in CDISC SDTM format in version 3.1.2 or higher

- SDTM metadata definition in define.xml
- Human readable study data reviewers guide (SDRG), which also addresses existing data issues
- Analysis data submitted in CDISC ADaM format
- ADaM metadata definition in define.xml
- Human readable analysis data reviewers guide (ADRG), which also addresses existing data issues
- Tables, listings and figures created based on the SDTM and ADaM datasets
- Documentation might also include programs to create datasets or produce statistical outputs

DATA VALIDATION

The second step in the staggered review approach is to validate submitted data. Several formal checks are performed to ensure that submitted data adhered to the defined standards and can be reviewed by the clinical reviewers with various tools. The specifications are openly shared with the industry. The OpenCDISC tool [8] is one example of formal checks applied to ensure adherence to standards and data traceability.

DATA ACCESS

The third step is the data access for the FDA clinical reviewers. Submitted data is uploaded to clinical data repositories, which can be accessed by reviewers. The checks performed in the previous step ensure that this third step can be performed. Once the data is uploaded, various reviewers to perform their pieces of data review can access it.

REVIEW TOOLS

In the fourth and last step, reviewers access the data with various tools like JReview or SAS/JMP Clinical. Reviews might follow a standard review catalogue (e.g. the JReview Standard Review Catalog) and also include customized macro libraries like MAED or FIRRS. All these review tools provide the reviewers with various forms of analyses needed to assess the content of the submitted data. This analysis also includes comparison of data to data in the FDA clinical data repository. The assessment of the reviewers then requires a balanced combination of strong analytical and medical data knowledge to interpret all the results. At the end, all of the assessments from the agency data review are consolidated in a review report, which is then communicated to the sponsor.

Any of these four steps could produce findings, which prevents a seamless review by the FDA. The FDA openly shares these common findings of their review to help sponsors improve their data submissions. For example the posters [5,6,7] presented at the PhUSE CSS in March 2015 summarize various common issues found in data submissions. Traceability of the end-to-end clinical data workflow (i.e. from data entry into CRF/eCRF or other source data, to SDTMs and ADaMs to tables, listings and figures) and data consistencies are key principles that need to be considered by a sponsor.

APPLICATION OF FDA REVIEW TECHNIQUES TO SPONSOR/CRO RELATIONSHIP

In the following section we will now try to apply the methods from the FDA/Sponsor relationship, which were described in the previous section, to the Sponsor/CRO relationship.

HIGH QUALITY DATA STANDARDS IN THE SPONSOR/CRO MODEL

The first step of the structure data review approach “High Quality Data Standards” requires a lot of attention in the Sponsor/CRO relationship. A well-defined and precise sponsor standard, which is properly communicated, will help to avoid frustrations and confusions when it comes to data review by the sponsor.

Similar to the FDA, a sponsor should define standards for deliveries for a clinical study. These should be the same as expected from the FDA and communicated in the data standards catalogue. However, the standards communicated by the FDA still leave some room for sponsor interpretation. For example, the CDISC implementation guides for SDTM and ADaM data still leave some room for interpretation and allow sponsor specific definitions. A sponsor has to close these interpretation gaps. An example for a sponsor specific SDTM and ADaM interpretation guide has been presented by Mabe [8]. The layout of such an interpretation guide should be very similar to the CDISC implementation guide and would clearly define and document the expectations from the sponsor.

Closing the interpretation gaps is of critical importance especially if a sponsor collaborates with multiple CROs. In order to achieve data consistency, a sponsor should provide CDISC sponsor interpretation guides to CROs, which exactly describe the expectations by the sponsor. As interpretation guides and data standards might evolve over time, these interpretation guides have to be version controlled similar to the CDISC implementation guides. A sponsor interpretation guide might consist of a certain set of global rules (e.g. definition of safety) and project specific approaches (e.g. derivation of therapeutic area specific variables) to ensure transparency or results.

Another critical example, which requires special attention in the Sponsor/CRO collaboration, is the handling of metadata and codelists using controlled terminology. Especially CDISC extensible codelists require special attention if a sponsor collaborates with multiple CROs. The sponsor should establish a process, which requires CROs to ask a sponsor for permission to extend codelists in a controlled manner.

Overall the critical resources a sponsor needs to provide to the CRO and the final deliverables from a CRO could be defined as followed:

Critical Resources provided by Sponsor	CRO deliverables
• Documents like the protocol, the SAP, DMC charters (if not also outsourced) • Version of CDISC SDTM Implementation Guide (or reference) • Corresponding version of Sponsor CDISC SDTM Interpretation Guide • Version of SDRG (or reference) • Version of CDISC ADaM Implementation Guide (or reference) • Corresponding version of Sponsor CDISC ADaM Interpretation Guide (including project specific standards*) • Version of ADRF (or reference) • Detailed descriptions of CRO work product deliveries (eg. TLF output requirements, side margins, layout descriptions, bookmarks, etc.)	• CRF datasets, other external source data and annotated CRF • SDTM and ADaM datasets (including corresponding metadata) • define.xml for SDTM and ADaM • OpenCDISC reports for SDTM and ADaM • completed SDRG and ADRG (incl. justification of existing data issues mentioned in OpenCDISC reports) • submission ready TLF output
*: project specific standards might even include the provision of sponsor defined macros for global or project specific derivations or algorithms	

Table 1 – Potential deliveries from Sponsor and CROs in an outsourced clinical study

Table 1 above describes a potential scenario for a delivery of a submission relevant clinical study. In essence, the sponsor should ask the CRO to provide exactly the same deliveries, which the FDA would ask for at a time of submission, but with a little bit more sponsor specific details. For studies, which are not submission relevant, the sponsor might chose a risk based approach and might ask for less to reduce costs in the outsourcing model and to have a more effective focused review of critical data and topline results.

A clear, efficient and routine communication between the sponsor and the CRO is very important. Sponsors seek a close communication to the FDA to present their submission packages and want to fully understand special requirements for each submission. Why should the sponsor communicate less with a CRO? Often there is a misunderstanding that the CRO exactly knows what the sponsor expects. A CRO works with multiple sponsors though and expectations might vary between various sponsors. All assumptions and expectations need to be clarified and documented. The initial investment of time and resources to set clear expectations is a small price to pay for benefiting the bigger picture and to avoid the finger pointint in the end. The sponsor will get the expected results and the CRO will provide customer satisfaction supporting their own business model.

DATA VALIDATION IN THE SPONSOR/CRO MODEL

Once data sponsor has completed the first step to define his data standards model as described in the section above, the sponsor will be in the position to validate the delivered data from the CRO. Similar to the staggered approach by the FDA, the sponsor should then validate the adherence of the CRO to the defined data model

The sponsor should perform a formal data structure check as the tool OpenCDISC provides. As a first step to accept the CRO delivery, it should then be checked if all data issues are adequately addressed by the CRO. This should be a confirmed requirement and an adequate report should be provided to the sponsor with the assessment. Without this, the sponsor should ask for this to be done prior to reviewing.

The sponsor should also include formal checks if the CRO adhered to sponsor specific standards as described in the SDTM and ADaM interpretation guides. As these are sponsor specific rules, the sponsor should prepare standard checks to check the formal correctness of the submitted data.

Formal data structure checks might also include formal checks of project specific standards. A sponsor could for example try to apply a set of standard checks to check if the CRO adhered to the project specific response criteria. Violations against these formal project requirements should be reported back to the CRO and these issues need to

be fixed or addressed to ensure data consistency.

The sponsor should be able to validate the data in a timely manner. Ideally standard reports are produced by common and sponsor specific standard tools (eg. set of SAS checks, etc.). This standard report could then be provided to the CRO and should also be stored by the sponsor together with the submitted data to document the review and support later post processing. Both, common and sponsor specific tools could of course be shared with the CROs to establish transparency and a streamlined review of common items to build efficiencies. This open sharing of review techniques will help the CRO to better understand the sponsor requirements.

For these formal checks, the sponsor should have detailed checklist prepared. Checklists should include for example checks for completeness of deliverables as contracted (see Table 1).

It is important to perform these formal data checks as a first step before trying to perform more detailed and analytical data review. Formal checks against well-defined rules are easy to implement, document and could also be communicated to the CRO. A sponsor must not stop here though as data can be formally correct, but could contain unreasonable content or results.

DATA ACCESS IN THE SPONSOR/CRO MODEL

As described in the FDA review section, the FDA loads the submitted data into the clinical data repository. This allows the FDA reviewers to access the data and compare it to existing data in the similar drug classes. Translated to the sponsor/CRO model this means that each sponsor should have a clinical data repository as well. There should be a well-defined area where data should be stored. Sponsor reviewers should have access to existing data pools for comparison. The sponsor reviewer should be able to access this data with any tool they want to use for review.

Data access also means well-documented data. If either the data repository or the submitted data is not adequately described, a sponsor reviewer will not be able to perform an adequate data review.

In the previous section, the steps to validate the submitted data have been described. If this step was completed successfully, the data should meet the formal requirements for post processing by the sponsor. The sponsor should then be able to utilize this data and perform the next steps in the structured data review.

REVIEW TOOLS IN THE SPONSOR/CRO MODEL

The validation of adherence to the data model as described in the previous section and the data access are requirements to perform the next step, which is the analytical review. The formal checks validate that the data structure allows upload to data pools and that various sponsor reviewers are able to assess the content quality of the delivery with their preferred tools. The check for the content quality requires analytical skills as this review is focused on data understanding and analysis. While formal tools can be used to detect formal data issues, it requires analytical skills to find troubleshooting data, identifying common data issues or detect issues, which might be compound specific and therefore require compound knowledge. This analytical review should be focused on the interpretation of the data and will help on the one hand to ensure a good content quality of the CRO deliverable. On the other hand it will also help to increase the sponsor internal data understanding of data, which will require further post processing (e.g. integrated summary of safety/efficacy or publication support).

Similar to the FDA, the sponsor could perform various standard analytical checks and compare it to already existing data. The sponsor could create simple summary statistics about baseline characteristics, patient disposition, adverse events or other safety data, and efficacy data. Outlier analysis (e.g. by means of boxplots or frequency tables) is also a useful tool to get further insight into the content of a datasets across the study. A lot of these analyses are of course present in the tables, listings and figures provided by the CRO, but in order to check for consistency against previous datasets, it is valuable to perform a set of standard analyses. The focus here should not be on the recreation of CRO deliverables, although this might be useful for some analysis of critical importance. The focus should rather be on compound specific analysis, which could be seen as a sort of compound characteristic. For example, a compound has a certain pharmacokinetic profile, which is described by certain pharmacokinetic variables. Also the safety and efficacy profile should be similar in each study. A set of compound specific standard analysis could describe these compound specific characteristics based on the study deliverables from the CRO.

Once a set of standard analyses is available for a new delivery, the sponsor should then compare it against existing standard analyses from data pools of the same compound and assess the differences. It should be checked if the specific compound characteristics can also be observed in the submitted study. Differences could be explained by the protocol design of a new study, but they could also lead to important content questions about the submitted data. However, the sponsor reviewer should have a very close look at the analyses results to fully understand the delivered data. If the sponsor reviewer cannot explain observed differences, he could ask the CRO for investigation and explanation.

In addition to the standard summary statistics and outlier analysis, the sponsor should also look for exactly the same critical data, as the FDA will do when they receive the data. The FDA is especially interested in death cases, serious

adverse events and patients who early terminate their study participation. Therefore it is reasonable that the sponsor examines these cases as well. The sponsor should prepare individual patient profiles for deaths, serious adverse events and early terminations and should try to understand if all data for a single subject is consistent. Do all data for a single patient exactly explain what happened? If that is not the case, there might be data issues, which have to be clarified by the CRO if they are not described in the SDRG or ADRG. The sponsor should really play with the delivered data and dig deeply into the database to familiarize. This helps to build up the data knowledge and also to learn more about the specific study. Usually these steps are done during the data management review or medical review. But there might be suspicious data found that could have resulted more for an issue with data transformation. In this step, the sponsor might find data issues, which need to be explained by the CRO and are therefore important for the oversight. Even if the CRO did everything correctly, the knowledge of these existing issues is valuable and of importance for later data post processing.

These analytical review techniques require a good understanding of existing and submitted data. While often a statistical programmer is focused on producing dataset and outputs for a study, this analytical review requires different skills than pure programming skills. As described in my paper “Managing the Change – Evolving from Statistical Programmers to Clinical Data Scientists” [XX], a statistical programmer should have the right skills though to perform these analyses. It could be another step towards a better data understanding and becoming a clinical data scientist.

A last and very important step after the formal and analytical review is the adequate documentation of all findings. Similar to the assessment report by the FDA, the sponsor should describe the findings of the formal and analytical review. On the one hand this is important for further clarification needed by the CRO, on the other hand is also very important for further data processing. The sponsor might want to further process the data in a couple of years and might want to utilize the data for integrated analysis purposes. For the later usage of the data it is important to know the critical cases of a study, since these might require special focus. A thorough documentation is very helpful especially for these cases.

ADVANTAGES OF APPLYING FDA REVIEW TECHNIQUES IN A SPONSOR/CRO SETTING

The structured review techniques in the sections above might first appear time consuming and create a lot of work. One fundamental misunderstanding when outsourcing clinical studies though is that it can be done resource neutral. Especially in the setup phase of a new Sponsor/CRO partnership, additional efforts need to be taken to establish a good relationship and clear agreements and expectations between the sponsor and CRO.

While the above-mentioned review techniques might increase the delivery quality, it is of course also important for the sponsor to openly communicate the review techniques to the CRO. An open and transparent communication will help the CRO to even better understand the expectations from the sponsor and vice versa.

These review techniques also help the internal staff to gain knowledge about the data through their analytical data review. In case the sponsor reviewer is a statistical programmer, it will help to acquire new skills and help the development towards a clinical data scientist, who has a thorough understanding of analytics and a very good compound knowledge.

The sponsor will also learn about the critical patients and can proactively address questions, which might come up by the regulatory agency once the sponsor submits the data. This will help the sponsor to prepare for the integrated analyses of safety and efficacy.

Even if the described review techniques require time and resources they represent an added value for the CRO/Sponsor relationship and also for the data quality. Therefore they are of strategic relevance and should not be underestimated.

CONCLUSION

There is a lot we can learn from the relationship between the FDA and a Sponsor, which can be applied to improve the relationship between the Sponsor and a CRO. A good relationship starts with a clear exchange of expectations. A sponsor needs to fully understand what the FDA expects in order to meet these expectations. The same is also true for the CRO, which needs to fully understand what the sponsor expects. Clear communication and well-defined standards is the key component. A structured CRO oversight model is the second step towards a successful collaboration. The structured data review by the FDA can easily be translated to a sponsor review and helps both the sponsor and the CRO. The sponsor will receive the expected high quality results and the CRO can execute their tasks in a timely and transparent manner. The mutual benefit within the scope of a study could lead to future business and customer focused deliverables. Another important outcome of this structured data review is also the generation of data knowledge and insight. This last step is very important in a effective collaboration with the CRO, as this allows the sponsor to learn for later agency submissions.*f*

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