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Delivering a quality CDISC compliant accelerated submission using an outsourced model

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ABSTRACT

Pharmaceutical companies are faced with the challenge of developing innovative treatments for patients and replacing older and expiring pipelines whilst containing research and development costs. Outsourcing models, whether functional outsourcing or full service outsourcing, are increasingly being relied upon to meet these challenges. This includes the outsourcing of the analysis and reporting of clinical trials and the creation of an electronic submission package to clinical research organizations (CRO). Sponsors are owners of drug compounds and are ultimately accountable for the quality of submission packages delivered to regulatory agencies. How to ensure submission quality in an outsourced model is a significant challenge facing all sponsors. To what extent should sponsors be reviewing the CRO's work and what level of checking is sufficient?

This paper uses a case study approach to examine a recent sponsor/CRO partnership in support of an accelerated oncology drug submission. High quality, CDISC compliant eCRT submission packages contributed to accelerated approval of less than 6 months under priority review by the US Food and Drug Administration (FDA). We will share our best practices and lessons learned from this submission experience.

INTRODUCTION

Lung cancer emerged as the most common cancer worldwide several decades ago with 660,000 new cases estimated in 1980. It remains the most common cancer in the world, both in term of new cases (1.8 million cases, 12.9% of total) and deaths (1.6 million deaths). It is responsible for nearly one cancer death in five.

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer accounting for about 85% to 90% of all cases of lung cancer. For those patients with NSCLC, mutations in the epidermal growth factor receptor (EGFR) can lead to uncontrolled cell growth and tumor formation. There are approved and established therapies for patients with NSCLC known to have activating mutations in EGFR but they are not curative and the majority of patients will progress within one year. There was therefore a high unmet medical need for a well-tolerated, effective, targeted anti-tumor therapy for patients with advanced NSCLC.

An AstraZeneca (AZ) drug compound was prioritized for an unprecedented development acceleration so that we could provide a new treatment option for patients with NSCLC. It achieved FDA Breakthrough Therapy designation and Fast Track status and the new drug application (NDA) was filed just over two years from first dose in man. By working with our CRO partners, we delivered a successful NDA submission, which included two pivotal phase II studies and eight CDISC compliant eCRT packages. The clinical submission was completed less than four months after data base lock (DBL) of the two pivotal phase II trials and the drug was approved by the FDA under priority review. It is one of the fastest development programs in the history of the pharmaceutical industry.

SUBMISSION CHALLENGES

For this submission, we followed a functional outsourcing model for the analysis and reporting of the six studies that were included in the submission, which included the two pivotal phase II studies as well as the pooling and submission work. These studies were delivered by a number of different CRO partners.

SUBMISSION LEVEL OUTSOURCING

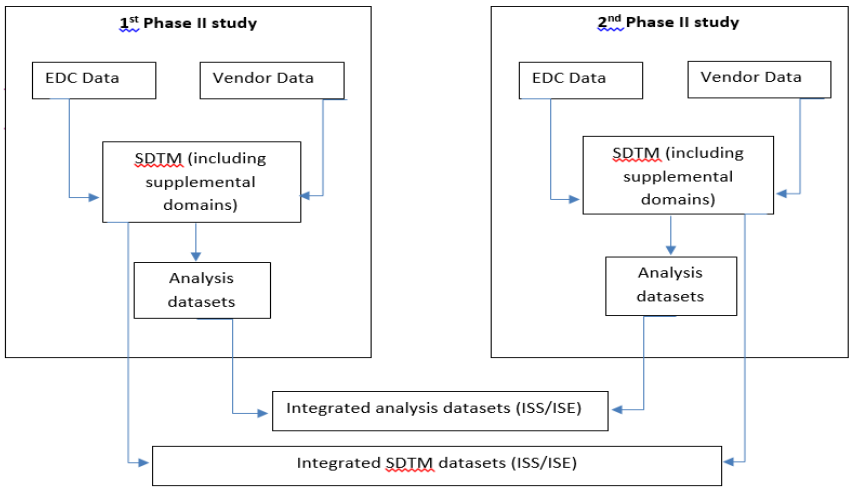
Whilst planning the submission work there were discussions about who would deliver the submission specific deliverables such as the pooled data for the integrated summary of safety (ISS) and integrated summary of efficacy (ISE) as well as eCRT packages for each study. One proposal was to do the work in-house but we decided that we would get the CRO delivering the pivotal studies to do this work. The key reasons for this being that it would not be dependent upon our own limited internal resource and also because the CRO would be more familiar with the data as they were delivering the studies. There were a number of key risks associated with this decision as this was the first project for the company to follow an outsourced model for submission deliverables and it was the first time the particular CRO had supported one of our company's submissions.

SUBMISSION ACCELERATION

One of the key challenges that we faced was the acceleration in submission timelines and the importance of ensuring all the deliverables were completed to quality whilst meeting reduced timescales. AstraZeneca made the original decision for launch in January 2014 and the plans were to have the database locks of the two pivotal studies completed by July 2015 with a submission by the end of the year. These timelines were in place when the chosen CRO took on the analysis and reporting of the two pivotal studies. The timelines were subsequently reduced by nearly six months with a target date of June 2015 for the US and European submissions along with a Japanese submission in August 2015.

The plans for how to achieve the submission had to be developed very fast and by October 2014 we had a "locked down" submission plan. As a result of the accelerated timelines, innovative ways had to be found to speed up delivery. For example, an early blind data review of the outputs from the two pivotal studies was used to write draft Clinical study reports (CSR's) and high level documents.

A specific area that created a challenge for us with the reduced timelines to submission was the production of the pooled SDTM and reporting databases for the two phase II studies required for the integrated summary of safety (ISS) and integrated summary of efficacy (ISE). We originally planned to provide analysis data sets only for the pooled Phase II efficacy and safety data and the CRO had agreed to the reduced timelines based upon that assumption. However, we had feedback from the FDA that they wanted pooled SDTM data sets as well, and that these were required at the same time as the rest of the submission. The challenge then was how we could work with our CRO to come up with a solution that would allow us to meet these FDA requirements. The CRO had already completed the programming to create the pooled analysis data sets directly from the study analysis data sets, so we agreed that they could create the pooled SDTM separately whilst recognizing that this could result in minor discrepancies between the pooled data sets. The risk was managed by getting agreement from the CRO that they would check for any discrepancies and that these would be documented in the SDTM reviewer's guide.



MULTIPLE CRO PARTNERS FOR STUDY LEVEL SUPPORT

The analysis and reporting of the six studies that were included in the submission were not all done by one CRO. We had three different CRO partners delivering the studies, which were following four different outsourcing delivery models. One of the key challenges was project managing the work across all the studies and partners, many of which were delivering concurrently.

In order to support all the submission work we needed an in-house team of programmers who developed a detailed knowledge of all the studies and overall package. We had to adopt a flexible resourcing model, pulling in expertise from other projects when required and utilizing programmers from other projects who had expertise in specific areas. The in-house programming team grew from two programmers in May 2014 to a maximum of 13, just prior to the submission. The in-house statistical and medical writing teams also grew to support the submission.

PLANNING FOR A TIMELY AND QUALITY SUBMISSION

The in-house programming team retained accountability for the reporting and submission quality and needed to ensure that all the deliverables met quality standards whether the work was performed in-house or outsourced. We developed a comprehensive quality review plan that included the scope of work and quality assurance (QA)/quality control (QC) responsibilities. See below example:

Scope	Deliverable	QA Responsibilities	QC Responsibilities
Submission Level	• ISS/ISE analyses plans • Pooled data sets for ISS/ISE • TFLs and other outputs for ISS/ISE • CRT package for ISS / ISE	*AZ*	*CRO partner*
	• PK NONMEM data set	*AZ*	*AZ*
	• OSI data sets • OSI listings	*AZ*	*CRO partner*

For outsourced deliverables, the CRO was responsible for the QC and AstraZeneca performed QA review. As this was our first partnership for submission level work, we deemed key efficacy data sets as high risk and decided to double program those data sets in-house as an additional validation step for a 100% accuracy check.

The planning stage was also an opportunity to assess resource needs based on agreed upon deliverables, timeline and the amount of quality review required. Forward planning is needed for in-house resource to handle multiple reviews or competing demands with short turnaround time.

IMPLEMENTATION AND EXECUTION

There are many operational factors to consider to ensure successful partnering with CRO partners to deliver to time and quality.

PROJECT MANAGEMENT OF STUDY AND SUBMISSION DELIVERABLES

A high level plan for the submission that encompassed all the individual study deliverables was developed and maintained in-house by the clinical team. The CRO partners then used this plan to develop their own project plans, which included details of each specific deliverable.

DEVELOPMENT OF QUALITY REVIEW CHECKLISTS

We developed quality review checklists that itemized the detailed checks to be carried out, checking compliance with the CDISC/AZ standards as well as the quality of the deliverables.

The checklists developed were:

- SDTM data set checklist
- ADaM/reporting data set checklist
- TFL checklist
- eCRT package checklist

The checklists were applied to all the submission studies. Differences found during review were corrected by the CRO partners prior to data pooling. Below is an example of our SDTM checklist:

SDTM data - *structural checks*
Run the domain specific validation program, customize where necessary
Open data set and scan through for issues visually with mapping
Confirm mapping matches AZ standards.
Check no unmapped RAW variables exist
Check all variables in the data set are present in the spec
Check for truncations
Check trial design data sets against protocols - Check protocol for trial summary information - Ensure all expected visit numbers, visits and visit days are accounted for in TV - Check rules in TA and TE are complete - Check values in TI match protocol/CRF and are complete
Review CRO log files for errors/warnings
Check issues in OpenCDISC reports

DEVELOPMENT OF STANDARD REVIEW PROGRAMS

As QA reviews were repeated at various stages of deliveries and performed across multiple studies, we developed in-house standard SAS® review programs to automate as many checks as possible to:

- reduce the amount of time and resource taken to perform data set review
- maintain consistency of review across data sets and studies

Below is an example of review program code that checks the adverse event (AE) domain:

```
*** General check 1: Confirm sort order is as per spec;
%gen1(dset=ae, sortby=STUDYID USUBJID AEDECOD AESTDTC AEENDTC);

*** General check 2: Check that required and expected variables are present.;
%gen2(dset=AE);

*** General check 3: Check QNAM/QLABEL matches standards.;
%gen3(dset=AE);

*** General check 4: Check Day 0 does not exist.;
%gen4(dset=AE,var=AESTDY);

%gen4(dset=AE,var=AEENDY);

*****************************;
*** Dataset specific checks ***;
*****************************;

*** AE check 1: Confirm number of records between raw and SDTM;
%ae1(dset=RAWPSC.AE);

*** AE check 2: Check AEREL matches standards;
%ae2;

*** AE check 3: Check QVAL mapping matches standards;
%ae3;

 *** AE check 4: Check variables are upper case where expected;
%ae4;
```

Overall, standard data review programs automated about 60% of checklist items and greatly increased the efficiency and consistency of our QA reviews.

COMMUNICATION WITH THE CRO PARTNERS

It's really important to ensure open and clear lines of communication with the CROs. For this project, we implemented 3 levels of regular touchpoints with the CRO delivering the two pivotal studies and submission work:

- Tollgate meeting – led by AZ Biometrics Team Lead
  This meeting was focused on critical delivery issues; team members were expected to rapidly convene at any given time within 24-hour notice
- Steering committee meeting – led by AZ Clinical Information Science Director (CISD)
  This meeting was focused on timelines and forward planning
- Operations call – led by AZ programming lead
  This meeting was focused on operational tasks related to programming (e.g. applying data cutoff, protocol deviations, etc.)

Frequency of these meetings were dependent on delivery need. They were more frequent (e.g. weekly) as teams worked toward database lock and final deliverables and less frequent post submission.

ENSURE FINAL eCRT QUALITY

Initially, the programming group worked with regulatory/publishing to determine the M5 folder structure for submission. After the eCRT packages passed programming review, they were delivered to publishing. Publishing made all the electronic components ready on the publishing backbone. Programming then checked all eCRT files and OSI files in module 5 clinical study reports folder (M5). It was not content checking at this stage, but checking whether the files were in the expected M5 folder and the number/size of each data set were the same as those on the programming side. PDF file size may be different because of file compression done by publishing tool.

This is an important final quality check and the last step before electronic submission.

OSI DELIVERABLES

As part of pre-NDA/pre-BLA meeting, the Office of Scientific Investigations (OSI) usually makes an information request for the sponsor to provide information according to the FDA OSI guidance. This information will help OSI make site inspection decisions.

The OSI request consists of three main parts referred to as Parts I, II, and III.
Part I: Tabular listings of site information
Part II: Subject data listings by site (10 listing titles)
Part III: Summary level clinical site data set (clinsite.xpt, define.pdf)

The AZ lung cancer drug was a fast track product and FDA decided they would accept a rolling submission. In a rolling submission, the OSI package is often submitted ahead of the clinical submission so site inspections can be started as soon as possible by FDA. The fact that OSI was to be submitted prior to the clinical submission presented particular challenges as OSI files are based on final CSR reporting data sets. Therefore, OSI could not be considered final until the reporting data sets were final. We worked with the CRO to consider this timing and dependency in the project plan so that OSI files were ready as soon as final reporting data were generated and passed validation and review.

The clinical team is often involved in Part I of OSI generation and the programming team in Part II/III of OSI. Proper quality control steps need to be taken to crosscheck similar information presented in different parts of OSI package to ensure consistency prior to submission.

ACTIVITIES POST-SUBMISSION

Programming support does not end with the submission. There are post-submission activities that require programming resource and planning.

PROVIDING SAS PROGRAMS TO THE FDA

In preparing for the submission, we had communicated with the FDA that the "SAS programs are available upon request", which the FDA had accepted. One week after NDA filing with the FDA, we received an information request from the FDA to submit executable SAS programs as soon as possible.

Even though we had stated our intention to make SAS programs available upon request in the pre-NDA meeting and the FDA accepted it, we had not anticipated the request could come so soon. Substantial resources were mobilized to prepare over 2000 SAS programs from three studies plus pooling for submission within a week of FDA's information request. Amendments were made as needed to ensure that that SAS programs would run in a SAS PC environment. The SAS programs were converted to text files (*.txt) and reviewer's guides prepared for each study to itemize each program and its purpose as well as the steps needed to execute the programs.

The key challenge that we had was converting the programs to run on SAS PC whilst ensuring they replicated the same results. The phase I study had been analyzed in our own company analysis and reporting system and we had to extract the programs from this system along with the utility macros they used, create a windows set-up file and adapt the programs to run in the new environment. The pivotal studies had all been created on the CRO analysis and reporting system so these also required a large number of amendments to get them to run. In total, approximately 290 hours were spent on preparing all the programs for the FDA, but with a flexible team who were prepared to work additional hours we were able to send the programs to the FDA within eight calendar days of receiving the request.

RESPONDING TO REGULATORY QUESTIONS

The main post-submission activity that we planned for months in advance was responding to regulatory questions from initially the FDA and European Medicines Agency (EMEA) and later the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) as well as requests from other countries. The decision had been taken that we would do the regulatory response work in-house, rather than outsourcing it to our CRO partners. This decision was made because of the unpredictable nature of the work (we would not be able to necessarily provide clear specifications of exactly what was required upfront to the CROs) and the need to be able to respond very quickly to requests. Two months prior to the submission a team was formed. The team consisted of six people, including statisticians and programmers under the leadership of a Clinical Information Science Director (CISD), who managed the requests that came through and provided a key link between the clinical and regulatory groups. We also had a programming team lead.

A key part of being able to respond quickly and efficiently to regulatory questions is having a team of Programmers who are familiar with the data and SAS programs available from the studies. By having the team in place prior to the submission, they were able build up this knowledge providing support for publication work and preparing outputs that would answer questions we were anticipated to receive from the regulators. In order to ensure we could effectively utilize knowledge from our CROs, two of the programmers who had worked on one of the studies were contracted to work directly on the team for seven months.

The programming team members were based in the UK and US. This meant that late requests (e.g. UK time, late afternoon) could be successfully completed overnight (UK time) by the US team and were then ready to deliver first thing the next day. This worked exceptionally well. The team members were willing to work flexibly and hence were able to assist with new urgent work at a moment's notice. In order to ensure quality outputs the work was double programmed along with an additional review by the programming team lead, prior to forwarding to the clinical team.

LESSONS LEARNED

This section summarizes some of the key lessons learned whilst working on this submission from a programming perspective.

COMMUNICATION WITH THE CRO PARTNERS

With such an accelerated submission, it is imperative to maintain clear communication channels at all times between the sponsor and the CRO, checking and re-checking understanding of deliverables/scope/priority/timelines.

ENSURING QUALITY DELIVERABLES

- Apply consistent data review checks to all submission studies to ensure all data followed the same standards and for ease of pooling
- Emphasize to the CRO partners and internal stakeholders that data set quality, including CDISC compliance is as important as the quality of the tables, figures and listings
- Programming should do a final quality check of the electronic components of the submission on the publishing backbone in the M5 folder structure

SAS PROGRAM SUBMISSION

- It is best to clarify program submission requirements in the pre-NDA meeting. Even though this decision may not be to submit SAS programs with the initial NDA package, the programming team needs to be prepared to provide programs to the FDA at very short notice
- The FDA prefers standalone SAS programs that are less macro dependent, use simple procedures, and are easy to follow

REGULATORY RESPONSE WORK

- Ensure that the programmers appointed to the team have good solid SAS skills, good industry knowledge and good therapeutic area knowledge. This is not the environment to assign less skilled programmers
- Appoint a programming lead who manages the workload and carries out an additional review of the deliverables prior to them being handed over
- Ideally have Programmers based in different time zones to enable late requests to be efficiently managed

KEY POINTS TO CONSIDER WHEN PREPARING FOR AN ACCELERATED SUBMISSION

This section summarizes the important factors that one needs to take into account when planning to deliver the programming components of an accelerated submission using an outsourced model.

SPONSOR AND CRO WORKING AS ONE TEAM

The sponsor and CRO partnership can be effective when both are willing to work as one team. The common goal is to deliver submission ready data packages to time and quality. Only when working towards this same objective, the sponsor and the CRO can truly consider each other as equal partners and collaborate. It takes time to build a good working relationship, especially if it was first collaboration experience between the two companies. What's more important is the willingness of teams from both the sponsor and the CRO to adapt to each other's working style, keep open communication and adjust quickly to changing reporting and timeline demands. It is also important to stay flexible and creative to meet the challenges along the way.

MAINTAIN IN-HOUSE PROGRAMMING CAPABILITY

Using an outsourcing model, the amount of in-house resources may be under-estimated.

Many assume that "the CRO is doing everything". In fact, there are pieces of submission work that may not be covered by the existing CRO contract, such as PK modeling or population PK analysis. There are also ad-hoc requests that the CRO would not want to accommodate due to time/resource constraints.

Sometimes it can take too long to secure a contract with a CRO for a specific type of work. Regulatory response work, which demands strong internal coordination and shorter turnaround time, may not be best suited for outsourcing. There are also resource needs for in-house quality review.

It is very important to maintain good in-house programming capability even with an outsourcing model to retain expertise and meet the demand, which can spike suddenly if the CRO is not able to handle the work due to requirement changes or capacity issues.

PUBLISHING SUPPORT

Electronic submission guidance by the FDA is available on the FDA website. The sponsor may also have specific guidance available to ensure success of an electronic submission. Publishing is generally the last step before electronic submission. If publishing guidelines are not followed, submission component will not be able to pass publishing validation. Any re-work at this juncture could put submission timelines in jeopardy.

It is very important to ensure eCRT components not only contains quality data and are CDISC compliant but also publishing ready. CRO partners need to be made aware of sponsor publishing requirements ahead of CRT preparation. It is advisable to have the CRO send a test CRT package for publishing and resolve any remaining issues with the CRO before signing off on final delivery.

IT SUPPORT

All programmers should know how to raise an IT issue and raise priority levels when needed. The worst thing that can happen during critical delivery period is system breakdown when you need it the most. In an accelerated submission environment facing tight timelines any IT issues can put delivery at risk. To prevent IT issues from happening or minimizing the impact, it is a programming responsibility to communicate business critical needs and timelines so IT can plan for peak period demand and support.

CONCLUSION

Outsourcing is common practice nowadays by pharmaceutical companies for the analysis and reporting of clinical trials. Project/submission level outsourcing carries greater risks than study level outsourcing alone. Sponsors who are ultimately accountable for submission quality should develop a robust quality assurance plan and tools to ensure CDISC and submission standards are met. The Sponsor/CRO partnership in an outsourced model can work well to support an accelerated drug submission with proper planning, regular touchpoints, impeccable execution, and that a thorough quality review process is in place.

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