

AstraZeneca and Quintiles Programming Groups – working collaboratively to successfully deliver a pivotal CRC phase III study

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ABSTRACT

The AstraZeneca (AZ) and Quintiles working relationship on the oncology project cediranib (RECENTIN™) began in 2005 with the remit to deliver 4 key studies in the colorectal (CRC) programme with one of these being a pivotal phase III study. The programmers from both companies worked collaboratively, bringing their own experiences and solutions to the team to ensure delivery was successful.

This paper will describe how the programming teams worked together; how the expectations were agreed at the beginning, what working model was employed and how this developed over the years. The challenges the team faced, as well as the lessons learnt along the way, and how these were implemented to improve the working relationship and deliverables, will also be discussed.

INTRODUCTION

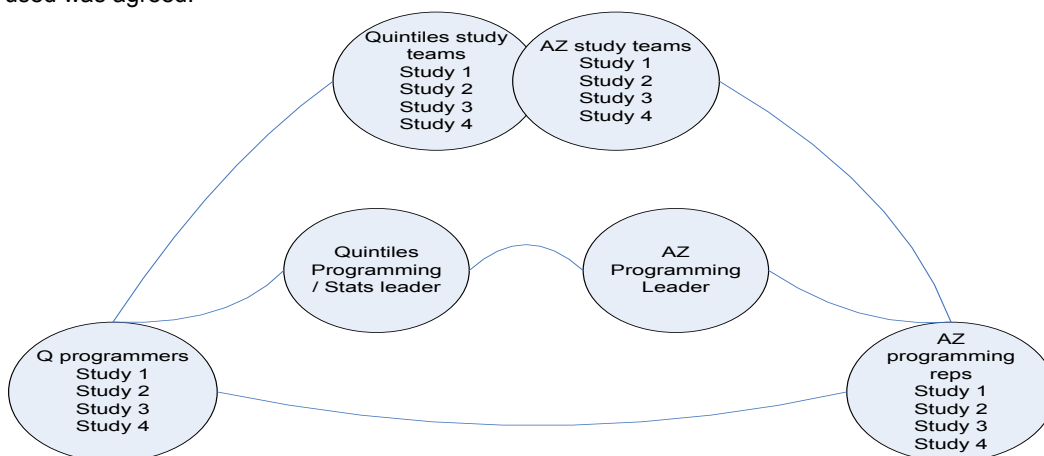
The AZ and Quintiles working relationship on the oncology project cediranib (RECENTIN™) began in 2005 with the remit to deliver 4 key studies in the CRC programme with one of these being a pivotal phase III study. The programmers from both companies worked collaboratively, bringing their own experiences and solutions to the team to ensure delivery was successful.

From the launch of the project, two different face-to-face kick-off meetings were held; a RECENTIN project meeting where all skill types from both AZ and Quintiles attended and a programming specific meeting. The aim of the project meeting was to discuss the scope of work across the project, the roles and responsibilities of AZ and Quintiles personnel, agree which standard operating procedures (SOPs) were to be followed, and how the project team would work together to deliver the 4 studies. The programming specific meeting went into further detailed agreements on topics such as communication channels and the standards to be used.

INITIAL EXPECTATION SETTING

ROLES, RESPONSIBILITIES AND MODEL USED

As part of the project initiation the roles and responsibilities of each member on the programming teams and the model to be used was agreed.



Given the need for regular communication of set-up activities, study progress and issues across the 4 studies, a direct project to project level link between AZ and Quintiles was established; any decisions or messages were then disseminated to the relevant study team programmer accordingly. This was seen, and proved to be, a more efficient approach than each study

programmer discussing the same issues. The Quintiles programmer, during the study development, would gain the full knowledge of the study, the study standards and the variable attributes whilst the AZ programming representative was put in place to answer questions on reporting database standards (RDb), standard safety domains and to co-ordinate programming activities internally. The AZ statisticians were the primary contacts for any questions relating to the Statistical Analysis Plan (SAP) and efficacy / Quality of Life (QoL) domains. This division of responsibilities provided clarity to the AZ study teams who were also working under a unique model; the project management, data management and programming aspects of the study were being performed by Quintiles whilst the statistics and medical writing were the responsibility of AZ. The defined structure of the programming teams ensured the AZ study team knew who to contact depending on the information they required.

Elizabeth – “I had not experienced working to this type of model before and it was important to define what each person’s responsibilities were on the project and the lines of communication. During the early stages of the project this model worked very well and the project level link facilitated a comprehensive picture of the progress on each study”

New global RDb and table, figure and listing (TFL) output standards were introduced at AZ at the beginning of 2005 and these were adopted by the RECENTIN project team. The standards were to be used as the basis for all study deliverables by adapting them at the project level. The principles of the global standards and how they were to be used was discussed, and although there was little experience of the standards within the RECENTIN team at that time, it was agreed that they would be utilised on all the Quintiles delivered studies. It was then a key activity for both teams to become knowledgeable in the standards quickly so not to hold up activities.

Elizabeth – “This was an immediate challenge for both programming teams – not only were Quintiles unfamiliar with the project standards but the RECENTIN team were also getting to grips with the principles and the content. We worked very closely during the set-up phase of the first studies and often had lengthy discussions on complex variables and dataset structures to define an optimal standard”

During early telephone calls, it became clear that there would be a steep learning curve for both parties to get to know each other’s terminologies, acronyms and working standards. At the kick-off meeting, it was agreed that all of this information and the agreed programming approach would be centrally stored in a working document to be used by all programming team members throughout the study. This 30 page document covered the following key areas:

- Glossary of specific terms
- Deliverable format and requirements
- Required output format and the AZ publishing process
- Crucial programming documentation
- AZ programming standards and approaches

Paul – “The Quintiles team as a whole found this document to be invaluable all the way through the study. By setting out expectations of what AZ wanted to see at the start, we knew what was required and were able to plan how to deal with the logistics of adhering to AZ standards right from the beginning. By pre-emptively answering many of our questions about the structure of the deliverables in a clear manner, we were able to avoid firing back and forth numerous emails, and re-work was kept to a minimum. The document has been such a success that it has been passed on and adapted for other study teams in Quintiles who are working on more recent AZ studies, and has shown real benefit”

REPORTING STANDARDS

In 2005 the Quintiles Biostatistics department had recent experience of working on several standalone AZ oncology studies and had encountered differences between their standard programming strategy and the approach employed in-house at AZ.

As standard, Quintiles would generate a programming plan to give an over-arching view of the dependency of each dataset to the next, in a linear pattern. Where a variable is derived in dataset A and used again for derivations in dataset B, it is first quality controlled (QC) as part of the overall validation of dataset A and then passed through to B for validation as part of B. This approach suits the nature of a Contract Research Organisation (CRO) team, where several programmers are working at the same time on different data domains, and the timing of validation of the TFL outputs depends upon which datasets have already been validated. It avoids ‘bottlenecks’ where a few datasets are outstanding and only one or two programmers are able to work on them, as other programmers are able to begin on readying outputs for delivery at these times. The process for programming teams at AZ is to create a temporary subject level work dataset (RD_SUBJ), which can be called and referenced at any time for use in different dataset programs, and the dataset is not stored permanently until the last reporting dataset has been created. This approach is suitable when a low number of programmers are producing the study content over a longer period of time, as is typical at a pharmaceutical company.

The prior knowledge of the AZ process prompted early discussion on how the RECENTIN RDb standards would be adapted to reflect the way the datasets would be processed by Quintiles and it was agreed to amend the standards so that the Quintiles linear approach was put into practice, but was amended so that all AZ requirements were met as well. Furthermore, with the

introduction of new standards in the RECENTIN team, this provided a good opportunity for Quintiles to lend their expertise to aid development of the RDb standards for each of the studies.

During the course of the development of the RDb standards, new datasets/ variables or amendments to existing datasets/ variables were required. AZ programming advised on the principles for defining these, whilst Quintiles would collate their suggestions and queries to send to the AZ programming lead, who would liaise with the RECENTIN reporting standards team about incorporating programme-wide changes. As Quintiles were instrumental in shaping the RDb standards it helped nurture a collaborative environment and joint ownership of documentation from the beginning, and as a consequence the programmers gathered a stronger understanding of AZ-specific methods which was to have a positive pay-off later on in the study.

The atmosphere of a partnership where both sides were able to offer ideas and shape the study subsequently found its ways into other areas as the study reporting progressed. There was an underlying recognition that there was a shared common goal and as long as the outcome was the same, different ideas of how to achieve it were welcomed. For example, when Quintiles asked to introduce macros outside of the standard AZ suite which would help the programming effort run more smoothly, deviation from the set process was permitted and documented. This allowed some flexibility in how the programming was developed and valued the varied experiences of programmers on the team.

PROCESSES

Discussions on which company's processes were to be used for the different aspects of the studies were discussed at the kick-off meeting. It was agreed that Quintiles would adopt the AZ process of issuing a dummy set of outputs during the development of the reporting requirements and issuing the Draft TFL documents to the study teams 3 to 4 weeks prior to the database lock (DBL).

Elizabeth – "This was a new process that had recently been introduced at AZ and one which had not been fully implemented on any AZ study previously therefore there was a risk that the process would not be optimal. The study team viewed all options but decided to accept this risk"

In addition, during the kick-off discussions, Quintiles presented their process for the validation of programs. This involved a 3 step process; 'ready for QC', where the program author would check their work against the appropriate documents and templates, an independently programmed QC check written by another programmer, and a senior level review where a senior department member independent of the study team would review and sign-off the work. This detailed description of the validation process helped the AZ Programming team to plan the study deliverables and when making ad-hoc requests helped determine what level of validation would be the most appropriate. For example, during the preparation of the Clinical Study Report (CSR), the AZ study team requested reviews of the RECIST data at set time points; the understanding of the validation process allowed the team to have an informed opinion of the level of validation required versus the cost associated with the deliverable.

Processes and standards used from each company

AstraZeneca	Quintiles
Reporting dataset standards (RDb)	Dataset processing
Table, figure & listing output standards (TFL)	Liaising with DM and 3 rd party for data
Programming standards	Programming standards
Program naming conventions & TFL output numbering	Adaptive use macro suite
System for transferring data and documents	Use of Q&A tracker and regular meetings
Dummy run and Draft SAS process	Validation process

As there were 4 studies ranging from phase I through to phase III being delivered by Quintiles, the RECENTIN team were eager to gain efficiencies, passing the experience and knowledge of the RECENTIN standards from study to study. The food effect study was unique in its design and, although the reporting concepts were the same, the data structures were set up to reflect this. Of the 3 remaining studies, two were phase II, whilst HZIII was an adaptive phase II / III design, and these 3 were particularly similar in terms of the study design and data structure. It was identified early on that the studies would prosper if there was a flow of knowledge across all of the studies.

SECURE TRANSFER OF DATA

With the delivery of 4 studies, and the amount of data and outputs that would be generated, a reliable and secure data transfer method was required. It was essential that the method could deal with large volumes of individual datasets, accommodate

multiple users and be flexible in terms of frequency of transfers and types of files being transferred. On the advice of the AZ Information Systems (IS) team, Cyclone file transfer was implemented and after a few initial technical glitches the method proved to be both secure and straightforward to use.

PROJECT MANAGEMENT

COMMUNICATION AND ISSUE RESOLUTION

It was agreed in the early stages of the study programme that regular meetings between the Quintiles and AZ statistics and programming leads would be organised with a set agenda for each meeting. These meetings were intended to be a forum for some of the more complex statistical and programming questions which arose over time, to be discussed. The meeting format, where everyone was focussed on the subject under discussion, suited particular topics more so than multiple lengthy email exchanges which, from past experience, could often take longer and lead to ambiguities and misunderstandings.

Additionally, at certain stages during the study, when deadlines were not imminent, a Question and Answer (Q&A) tracker was introduced, by Quintiles, to log questions and answers. This was a working document to be maintained by the statisticians and programmers at both companies so that key decisions were stored centrally. The Q&A tracker was a particularly good tool when the study was being developed and no deliverables were pending as it allowed a few days turnaround from both sides to investigate and answer questions. In using the Q&A tracker, AZ ensured a consensus view from the statistician, physician and programmer was reached where necessary. This upfront agreement ensured that issues were not re-visited when outputs were reviewed and led to time savings and higher quality outputs. Nearer the time of critical timepoints however, email became the preferred method for these types of questions due to the quicker response times.

Paul – “The communication methods we used across the 4 years varied, but consideration was always given as to what would work best. For instance, when the specifications and programs were originally being developed there were inevitably a good number of questions which could be of high complexity, but low urgency, and so sending a Q&A tracker back and forth via email over the course of a week or two served the purpose of these questions best. Nearer to delivery time points however, there were often a lower number of questions which were less complex, but more urgent, so a phone call or TC was the ideal forum for these”

As HZIII continued into phase III, both Quintiles and AZ ensured continuity of key staff as the HZI and HZIII lead programmers led the programming effort from Quintiles, and the AZ programming lead continued in the same role. Similarly, where possible, programmers who had worked on phase II deliverables helped out with phase III. This continuity across an adaptive design ensured that knowledge and lessons from phase II were maintained for the phase III component of the study.

DELIVERABLES AND PROGRAM DEVELOPMENT

In order to meet the remit of efficiency during phase II, Quintiles resourced the RECENTIN programme internally by having a core team of 5 team members who were fully resourced, and 6 partially resourced team members. Due to the close similarities between the phase II studies, where possible the programming workload was resourced so that team members took responsibility for specific domains. As datasets or outputs were produced and as program maintenance was required in one study, the programmer would have the responsibility to copy changes across and tailor the program from study to study as applicable. This ensured that domain knowledge from one study was consistently applied across the programme.

Paul – “During Phase II of the RECENTIN programme, there were occasions where we had deliverables for 3 studies during the same month, and as consistency across trials was imperative for the end of phase II decision, it was important to us to assign domain experts who were able to familiarise themselves, take decisions and generate the content across all 3 studies. We ensured that all team members were keenly aware of the nuanced differences between the studies so that assets were not re-used incorrectly. This approach was a success as we were able to meet the challenging timelines and homogenise the programming methodology for the entire programme”

All the phase II outputs delivered during Feb 2008 led to the positive decision to move forward into the phase III programme. As HZIII continued into phase III at the beginning of March 2008, Quintiles were responsible for producing Independent Data Monitoring Committee (IDMC) deliverables and reports detailing the interim number of progression free survival (PFS) events every other month. These reports aided AZ in the modelling of the date of the 850th event, at which point the pivotal PFS analysis was to be performed. In addition to these scheduled interim deliveries, Quintiles were also asked to produce ad-hoc listings of RECIST data for internal AZ review. In total during phase III alone, 28 deliveries were sent over the course of 2 years and the majority of these were based on interim data which had not undergone full cleaning. As recruitment ramped up during phase III, and the number of patients increased from 226 to 1800, it was apparent that the validation approach across these deliveries needed to be efficient without affecting the quality of each individual delivery.

A standalone program to identify data issues was put in place with the aim of identifying all data issues not resolved at the time of each transfer, and to aid the audit trail for validation. The principle behind this program was that for every new interim run, data issues which were spotted were derived programmatically before being reported to a batch submitted log. With each extra run, this program was the first program to be run and aided the QC programmer as a first port of call for any observations

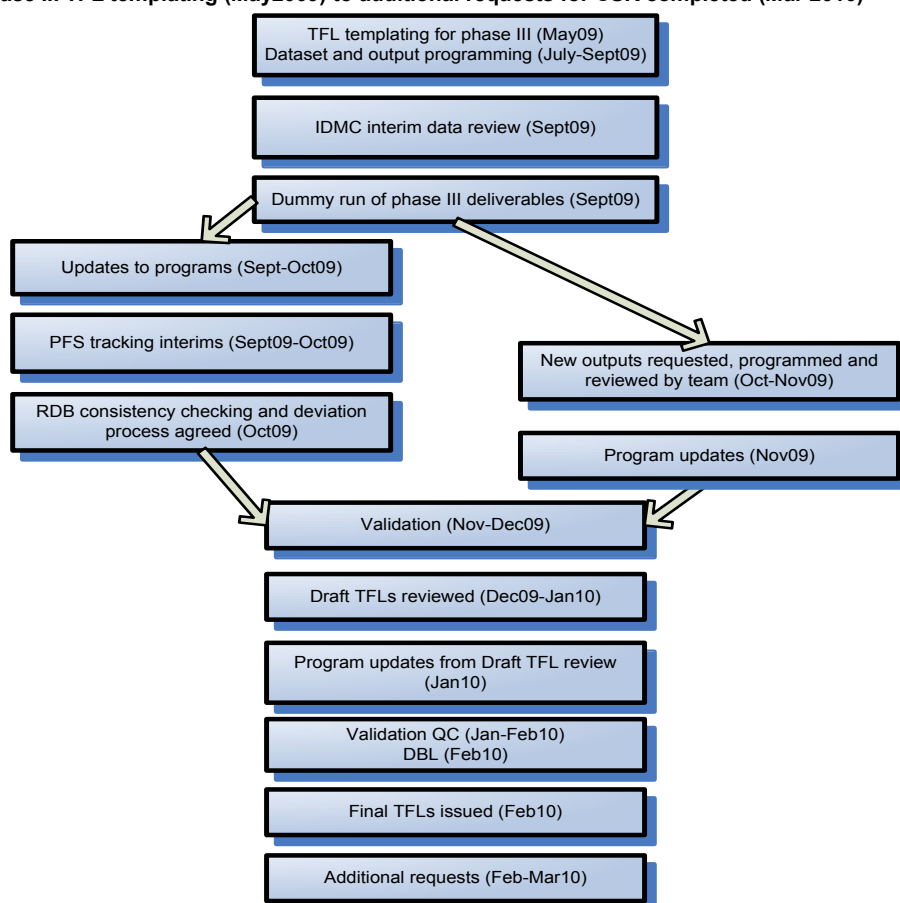
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spotted as QC issues without an obvious cause. As the program would have checks for all previous types of data issues encountered, any new data issues caused by an already encountered source, would be flagged. As the study continued and more and more data issues were observed and reported to the log this way, the QC workload was reduced as this iterative process was identifying a higher proportion of issues, thus bypassing the need for more detailed investigations. The log thus acted as an audit trail, so if the issue was previously queried in the dataset and not resolved at a subsequent transfer, the issue as previously documented could be referenced. An additional benefit of this approach was that any questions raised by AZ in relation to specific data points were often resolved immediately by running this data issues generation program.

Another consistency check put in place across the multiple deliveries was to ensure that cross checking of patients and outputs across repeated blinded deliverables could take place. As the dummy randomisation scheme used for phase II was re-run every time new patients were enrolled, it wasn't possible to track frequency totals for treatment groups from one delivery to the next. At the start of phase III it was decided that to aid validation across the deliverables, the process for generating the dummy randomisation scheme would change from phase II, so that only patients who had been randomized since the last data transfer would be assigned a dummy code, and all older patients would retain their previous dummy treatment codes. This helped to track changes between the various previous deliverables and allowed an additional continuity check.

As well as the deliveries during phase III, Quintiles programming also helped the Data Management (DM) Group by programming edit checks for the laboratory and RECIST data to aid the cleaning. The lab program has since been utilised on other AZ studies within Quintiles.

Deliverables from phase III TFL templating (May2009) to additional requests for CSR completed (Mar 2010)



RE-USE OF PROGRAMS AND INTEGRATION

Following the phase II decision to continue the programme into phase III, it was identified that previously produced programs from across the 4 studies could form the basis of the study content for phase III. Once Quintiles were aware of the requested TFL outputs, a library of all programs used for creation of outputs from the completed phase II RECENTIN studies were interactively run on current data, and assessed for their suitability in comparison to the TFL templates for the phase III deliverable.

All dataset and output programs were assessed to determine whether the request for phase III contained content similar enough such that re-using them would be a quicker solution than starting programs from scratch. These programs were

flagged and any changes required to match the phase III templates were also documented for the programming team to reference. Although this was a relatively lengthy task, the time spent at the start of phase III yielded many benefits as it cut the overall programming time required and ensured that previously agreed decisions were carried through.

An additional step was introduced to ensure the AZ statistical programs could be incorporated into the rest of the Final TFL outputs and run with no errors at Quintiles. This ensured valuable time at the delivery stage wasn't compromised. Another part of the testing process was to ensure that the reporting dataset creation programs and output programs would run without errors when they were returned to AZ. As different operating systems were used in the 2 companies, Quintiles created a set-up program which mirrored the options used in the AZ system. Once this set-up program had been removed, the programs were imported into the AZ system and run. This step was incorporated into each study so that, if required, AZ could re-run the programs at a later date with a new cut of data.

Elizabeth – "This proved to be an effective way to work; by having all system options in one program and removing this program from the suite, we were able to seamlessly run the programs in-house"

THE CHALLENGES

PHASE III STANDARDS DEVELOPMENT

During the planning for the CRC submission there was a strong steer from the submission delivery team for the 2 pivotal CRC studies (HZ), of which Quintiles were delivering one (HZIII) and AZ the other (HZII), to be delivered to the same reporting output specification to aid clinical interpretation. In order for this to be achieved it was imperative that both study teams worked closely and developed the RDb standards and the tables, figures and listings together. From the start of the phase III TFL template development both study teams contributed to the specifications and ensured a consensus view was taken from both a medical and statistical sense. Throughout the review of the dummy set of TFLs and the Draft TFL documents for HZIII, which was the earliest of the two studies that would be delivered, both study teams were required to review the outputs to ensure the content was optimal for both HZ studies as there would be no opportunity to revisit HZIII at a later date once the outputs had been finalised.

Moreover, although the initial development of the study RDb standards had been the sole responsibility of each study team programmer it was necessary to bring the standards for both HZII and HZIII in line. This was no easy feat; the 2 studies had used the global standards as their basis but during early development some derivations had been interpreted slightly differently on the 2 studies. The rationale for ensuring RDb consistency was introduced by AZ following the dummy run of the TFLs and both programming teams understood the need to acquire this consistency. Quintiles bought into what AZ were trying to achieve for the submission and agreed to have a two day face-to-face meeting to go through each key variable definition, which worked well. The original idea for this process was to ensure consistencies between the studies, but the act of discussing face to face also acted as a validation step for both studies to ensure interpretation of the standards and SAP was correct. This saved time at later reviews as both study team programmers knew exactly how each key variable was to be created and this had been incorporated into both studies, therefore assumptions were consistent. These inconsistencies may not have been spotted until a later review or at all. Both studies were updated depending on the findings. Following the consistency meeting, both programming teams worked together and ensured any issues identified were communicated across both teams.

There were several external sources of data e.g. project level reference ranges, used in the RECENTIN project to ensure consistency across the studies and to improve efficiency. Any updates that were made to the master copies of these data were distributed to all study teams including the Quintiles studies. This ensured further consistency across the HZ studies.

Elizabeth – "It was essential that the Quintiles Programming group were on board with what the RECENTIN submission team were trying to accomplish with the CRC submission; I discussed the rationale for consistency across the 2 phase III studies and Paul and his team bought into what we wanted to achieve"

Paul – "By spending time with AZ programmers going through the standards in detail, not only were we able to ensure consistencies, we also improved the confidence in the standard of the specifications. So instead of thinking of this as a change of scope, we amended our validation plan accordingly to take account of this thorough review"

DRAFT TFL REVIEW

Prior to the Quintiles led Draft TFL review meeting AZ consolidated all comments from the two study teams and gained consensus on any conflicting comments prior to forwarding to Quintiles. This ensured Quintiles had a consistent message about what updates or additions were required. This pre-meeting consolidation meant that valuable time in the meetings was spent on only the critical items. Additional time savings were also realised by the HZII study team as they were able to incorporate all relevant changes from HZIII review into the Draft TFL outputs prior to them being issued.

Elizabeth – "Any steps that could improve efficiency at critical times were introduced. By bringing both teams together to agree content we managed to achieve time savings on both studies"

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To speed up the comment review process at the time of each Draft TFL deliverable, any queries relating solely to questions on the data were documented separately by AZ. This allowed the Quintiles programming team to concentrate on checking or making amendments to their programs at a critical time whilst permitting the DM team to progress the queries that had been raised on the data.

AZ statisticians programmed the key primary endpoints on the study at a time of critical delivery, following the Draft TFL review when timelines were tight. Queries were raised and Quintiles responded to these at the same time as making Draft TFL review updates. Although this was a beneficial activity and generated discussions on complex key primary endpoint derivations which sometimes resulted in changes being incorporated into the efficacy programs, this step would have been better as a planned activity programmed at an earlier stage using a complete set of clean data.

As a result of issuing the dummy set of TFLs for review and the Draft TFLs prior to DBL, the dummy run underwent a thorough study team review at an early stage to ensure the outputs and content were fit for purpose which aided the Draft TFL review. This resulted in reduced requests for changes at a critical time and allowed the Final TFL document consisting of around 460 outputs to be delivered in less than 3 weeks following the DBL.

ADDITIONAL UNPLANNED REQUESTS

At a late stage in the development of the outputs for the CSR, when the scope of the delivery had been agreed and planned, a new set of around 100 unexpected TFL outputs were requested. This request came to both HZ teams as a result of recently released competitor information and was seen as a necessary component for the forthcoming CRC submission. The AZ Programming lead contacted the Quintiles lead with the new requirements as early as this was known and went through the rationale for this request. Accommodating these unexpected additions was a challenge for Quintiles, and during Q4 2009 the Biostatistics department was heavily resourced across a wide range of studies, so would have been very strained to guarantee fitting all of these outputs in to the requested timelines. After several internal meetings, it was decided that the internal validation process would prioritise the production and validation of the new outputs and older outputs for which there had not been previous comments were then to be fully validated afterwards, in concurrence with the AZ draft review.

Paul – “By being transparent with AZ in relation to our processes, and by arranging more regular progress calls we were able to keep expectations from both sides realistic over the coming weeks. Happily, in the end the Quintiles programming team pulled together really well and we were able to get everything done, including full validation on all outputs in time for the draft review”

FLEXIBILITY POST DBL AND CO-LOCATION OF STUDY TEAM MEMBERS

AZ statisticians requested a step to be added to the normal process in that Quintiles would provide unvalidated reporting datasets 2 days following the DBL date. This step was incorporated effortlessly and had no impact on the subsequent timelines Quintiles were working to which allowed the statisticians to start work on their efficacy programs. The QC programs were run to ensure the datasets matched. This step was planned in, and other team members were given other tasks, such as data checking, or validating the unblinding process to make sure that the impact of this was minimised.

Due to the sensitive nature of the study data all personnel working on the HZIII study were co-located in a separate building on site at AZ which allowed confidential discussions on the data to occur freely. Once the data was unblinded the team planned for potential additional programming requests dependent on what the data showed, the scope of these ad-hoc requests being unknown. It was felt essential that the Quintiles programming team be part of the on site team to have those in-depth discussions on data interpretation and additional programming.

Quintiles assigned the lead programmer to work on site at Alderley Park, whilst the statistical team lead and the rest of the team were based in the office in Bracknell. As the work was of an ad-hoc nature, 5 of the HZIII team members were resourced so that they could be available to help with urgent requests coming from the interpretation discussions at short notice.

The lead programmer was able to attend the interpretation meetings and offer feedback on the programming structure to the AZ team, whilst holding discussions and passing on requests to the team based at Quintiles, who were in a position to produce a large amount of ad-hoc requests in a short space of time. These additional outputs were also prioritized and delivered in batches.

LESSONS LEARNT

From the outset it had been agreed that Quintiles would drive the development of the TFL templates for each study in conjunction with the AZ study team. The team recognized that from experience of the first study, the finalisation of the templates was a lengthy process as most of the outstanding decisions were completed over email due to availability of key personnel. A change to the process was necessary and it was agreed that the initial TFL template development would be completed by AZ for future studies ensuring all the key skills were involved in the development. The templates would then be handed over to Quintiles for any minor updates e.g. addition of footnotes, required during program development.

As well as delivering the reports for the CSR for the 4 studies, Quintiles programming were also involved in supplying datasets and programs to the IDMC. The planning of the IDMC started at an early stage, with agreeing the members that were to make up the committee, when the first meeting was to take place and the TFL outputs required. A valuable lesson learnt from the first IDMC was that, although from a programming perspective the requirements had been agreed with the IDMC members, the data going into the outputs was not as complete or as clean as was expected. For each subsequent IDMC it was imperative to include DM personnel in the planning so that expectations on data completeness could be managed.

At times during busy delivery periods, requests for datasets and outputs from Quintiles were requested from several skill areas at AZ. It was agreed that all future requests would be centrally coordinated and communicated to make the process more efficient.

The amount of programming resource required by the pharmaceutical company should not be underestimated when outsourcing a study. A key learning from outsourcing 4 large, fairly complex, oncology studies is that support will be required to co-ordinate activities internally and to answer questions on standards and processes, especially when the standards being used are novel to both companies. A timely response to questions is essential to ensure a smooth development of the study programs.

KEY MESSAGES

From the experience gained by working together collaboratively we conclude that there are a few key aspects of the relationship between the pharmaceutical company and the CRO which provided a solid platform for successful delivery across this complex programme of studies.

Firstly, by allowing sufficient time at the start of the collaboration to agree expectations, roles and responsibilities and prepare clear documentation, each team was able to prepare themselves for what their upcoming role was to entail. The time spent detailing the processes and plans from both perspectives, and the willingness to adapt strategy and standards based upon suggestions from all team members also helped to stimulate a joint ownership of the study.

It was important to review on an ongoing basis the standards and processes which were being used and to change those that were not working or where efficiency could be gained. During the times of greatest pressure, the best results were achieved when the CRO was at its most flexible to meet challenging requests, and when the pharmaceutical company was at its most understanding of what was possible to achieve.

Through the process of establishing clear lines of communication and setting aside resource to maintain this contact, topics were discussed and issues were able to be resolved prior to them having an impact on the programme as a whole. The buy-in from both sides needed to be as open and transparent as possible meant that expectations were managed and when unexpected situations arose, the solutions that were found suited both parties.

With both the pharmaceutical company and CRO adhering to these ideals, the programming team were able to produce excellent results against the background pressure of both the study and the submission timelines. Standards were developed collaboratively to achieve documentation and a programming structure which was fit for purpose for both sides and both HZ studies. By setting expectations from the outset and delivering ad-hoc requests in a timely manner, over 100 additional outputs were accommodated within the existing study timelines. All delivery deadlines were met across the 4 years of the study, including delivery of over 450 outputs for the pivotal PFS analysis for HZIII, 3 days ahead of schedule and to a high standard. Furthermore, both companies remained flexible post final delivery and were able to quickly turnaround an additional 40 unplanned outputs. This flexible delivery of outputs, in combination with the reporting consistency applied across the 2 phase III studies, allowed the study team to fully understand the data and come to an agreed conclusion on the study.

DISCLAIMER

The views expressed in this paper are those of the authors and not necessarily those of AZ or Quintiles.

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