Safety Services:
A Critical Component of Your Oncology Program

Highlights

- Synteract managed safety services for the sponsor's three compounds in 10 oncology trials.
- It addressed a number of partner, data quality, enrollment, translation, and other challenges.
- Synteract's flexibility allowed the sponsor to continue its projects without interruption.

Introduction

Nowhere in clinical trials is the risk/reward aspect more considered than in Safety Services. The safety component is one that is a critical factor in the overall strategic development plan, both for patient protection and for the success of the product, for any new healthcare drug or device. Every clinical

trial conducted must be reviewed and approved by an IRB (Institutional Review Board) and/or Ethics Committee, whether in the US or globally, and all safety data must be submitted to the regulatory authorities as part of your new drug application.

Therefore, all aspects of your safety services must be well-documented and tracked, no matter how long the study takes, nor how many changes are made along the way. Communication is important and can make or break the success of the safety process. Synteract offers its Safety Services as part of a full-service project, or as standalone services, working with the sponsor and other vendors as members of the full clinical trial team. A recent experience in which we were hired to manage only the Safety Services provides a good case study in doing things right, despite challenges.

Some studies require very long timelines. The case we're reviewing here is longer than 10 years running, and services are now concluding. During that amount of time, a lot of change can take place – from personnel, to ownership of the drug, to changes in other vendors working on a project – and in this case, ALL of those things happened. But Synteract maintained its role, managed the historical data, and helped the sponsor get approval for the first of its drugs while additional compounds were still under study.

Complexity Adds Challenges

In this case, ten, originally US-based, oncology drug trials, covering three different compounds, were running concurrently. Synteract was hired to manage the Safety Services component, originally for just one of the compounds, but eventually for all three. Each study had a different endpoint; some were for

progression-free survival, and others for increased survival time. These compounds applied to multiple different types of cancer, with different mechanisms of action, and serving different populations, thus making the study parameters complex. Adding to the complexity, halfway through the trials, two different European companies came in as investors and partners to the sponsor – but for different compounds – and suddenly everything had to be globally-facing as the partners would be applying for approval outside of the U.S. while the original sponsor would be applying for an NDA within the U.S. Each study had a different timeline, and each compound had a different sponsor study team as well.

Luckily, Synteract was brought in at the very beginning, giving us the opportunity to comment on the Safety Data Exchange Agreements (SDEA), write (and if needed update) the Safety Management Plans (SMP), receive the SAEs, review labs and tests, query sites, write the narratives, and put it all together for regulatory submission, starting at the outset for each compound. Another important element is that Synteract maintained the same safety lead for the entire length of the program, adding to our historical knowledge and ability to problem solve issues quickly for the sponsor.

Compound #1: When Partners Offer Support But Also Difficulties

When the European pharma company came in on Compound #1, it added seven more global studies using that compound, in the EU, Russia and Eastern Europe, and increased communications requirements for cross-reporting. This was a Phase 1B / II study that had already been underway for several years at that point. The Synteract safety database, already 4 years old, had to be replicated in the partner database, as the partner wanted a comprehensive database of their own for Compound #1,

thus creating two parallel databases with the same information. So the entire Synteract database had to be mapped and migrated electronically to the partner, in order to establish the Synteract-managed cases as new reports in the partner database. Despite the fact that the partner was using a home-grown database instead of the Oracle AERs database we were using, our expert in-house Argus/AERs team figured it out and made it happen.

We reviewed the SDEA for discrepancies with the current process and timelines; met with the partner weekly as the sponsor's designee to harmonize safety processes and timelines; and updated the SMP. We increased resources quickly to process the increased volume of cross reports and to support the increased number of studies, so that SAEs could be reported quickly to regulatory authorities.

New and updated information was required to be shared immediately between the sponsor and partner –which sometimes caused the same SAE to have two causality interpretations and two differing case IDs. While the two cases were linked for regulatory authority submissions, over time this began to create increasing confusion between the sponsor and its partner due to parallel reports being assessed by different teams using differing investigator brochures. Therefore, Synteract updated the process to include the partner performing case processing tasks for all SAE reports, with Synteract simply copying their reports into our safety database. Although this decreased our scope of work financially, Synteract did it because it was the best thing for the sponsor and the trial data.

However very quickly, Synteract found that the partner's case processing quality was of concern because they were not doing the same due diligence on SAE cases as the sponsor. Consequently, reports were not as thorough as when Synteract processed the SAEs. Our response? Synteract safety

experts dug in deeper to investigate SAE cases to ensure the final reports were on par with the previous expectation for quality. We increased our role in query management to send additional information to the partner, additional queries to the site, and as a result, improve the quality of their reports. Again, a choice was made to support what was best for the drug developer, as well as for the prospective patients who would use the drug.

Compound #2: When Product Complaints Sink a Project

Compound #2 posed a different set of problems, with no partner involvement this time. The Phase II study criteria was such that the process of identifying subjects was proceeding very slowly, so the sponsor added investigative sites in India to speed up enrollment. With the addition of India to the trial, we added new case processing and regulatory timelines and added a vendor for submissions within India. Due to the increased pace of SAEs, we also trained and added Safety resources to the project with the goal that SAEs could be closed and reconciled within 30 days.

Adding sites in India required the sponsor to bring on an Indian manufacturer of the investigative product – who, unfortunately, didn't make the compound well – causing high amounts of particulate matter to form. Product complaints ensued. Synteract changed processes to include processing product complaints regarding the manufacturing in addition to processing SAE reports, added another layer to the tracking, compiled the data, offered insights on product trending, and provided metrics weekly to the sponsor to keep them apprised.

Abruptly, the study of Compound #2 was shut down due to a lack of efficacy. The Synteract Safety team quickly closed out the study, completed all queries, and finalized reports on the data so the compound could be re-evaluated for changes and potential further study in the future. Despite these problems with the product, the science may still be viable and only by closely examining the SAEs and product complaints can the sponsor hope to fully determine why their results did not align with their expectations.

Compound #3: When Multiple Languages Require Translation and the Partner Jumps Ship

The sponsor partnered with a different European company mid-trial for Compound #3. This new partner started 11 global studies simultaneously involving Compound #3 – in Latin America, Japan, and all over Europe – which required Synteract to provide everything for case processing translated into English. But that was only the tip of the iceberg! All of these countries' regulatory bodies had different reporting timelines and different requirements for reports – so it was incumbent upon Synteract to update the safety plan to ensure that all of these different regulatory needs were met. Synteract again reviewed the SDEA for discrepancies with the current process and timelines, met with the partner as the sponsor designee, and updated the SMP and all tools being used for the project. More resources were added to the project team as well as a vendor for EU submissions, which at the time was not a service provided by Synteract.

The sponsor wanted to have one comprehensive global safety database, so we changed the process to include having all SAE reports globally, no matter the language or the study of origin, be sent to

Synteract and copied into our database in English – which turned out to be a very good thing because the partner broke the partnership agreement mid-project, with the majority of their studies still active. The sponsor then had to decide if they were going to continue to provide drug to the participants already involved in the partner's studies, or shut the trials down. Additional questions arose concerning harmonization of the narrative templates used across all of the studies, management of the foreign sites, and points of contact for European vendors involved. Luckily, we had solutions!

Analysis of the SAE reports showed that follow up queries were not being sent to sites by the partner, and we communicated the identified discrepancies to the sponsor. The sponsor then decided to increase our scope of work to manage all SAE queries, allowing the site activities to continue without pause, and elevating the quality of the SAE narrative at the same time. Synteract took on the distribution of all regulatory reports to the vendors involved with submission activities, and uploaded all of the partner's INDSRs to the sponsor's share-file portal, to provide the sponsor with access to their files. These activities required additional staff to be added to the project teams and quick changes to the process, but it enabled hundreds of subjects to continue with their treatment. If Synteract had not held the comprehensive database, the money already spent by the sponsor would have been lost.

Solutions Always Exist If Your CRO is Flexible Enough to Find Them

Now, over ten years from when the first study began, the Synteract team is just wrapping up our work on the last of the three compounds with this sponsor. Our flexibility and perseverance to find and implement solutions to challenges allowed the sponsor to continue their projects without interruption.

Best of all for the sponsor, the first compound submitted for FDA approval has now received it. The Synteract team is proud to have worked collaboratively and share in the success of this program.

About Synteract

Synteract is an innovative, full-service CRO supporting biopharma companies across all phases of drug development to help bring new medicines to market. Synteract has conducted 4,000 studies on six continents and in more than 60 countries, working with more than 26,000 investigative sites and 750,000 patients. It has contributed to more than 240 product approvals. Synteract offers a notable depth of expertise in oncology, general medicine, dermatology, and neuroscience indications, as well as rare and orphan, pediatric, and immunotherapy studies.

For more information on how we can support your clinical trial, please visit www.synteract.com/Services/Safety-Services or ContactUs@synteract.com.