

Clinical Conclusions

Far from being simply a summary of individual results, a comprehensive and detailed summary allows companies to make informed decisions, explains Michael Whitworth at Quanticate

Producing comprehensive integrated summaries of safety and efficacy is a critical stage of the submission life cycle. These need to be designed and planned carefully in advance to ensure informed decision-making and effectiveness at the regulatory interface. A focus on the approval and whole lifecycle of the product, and not just the submission, will influence the quality and direction of the content. Traceability is key in all respects of the creation of information, from data that leads to knowledgeable decisions and the ultimate wisdom that forms the label of a product.

Guidelines from agencies on the preparation of integrated summaries for regulatory submissions are often lacking in terms of providing specific direction on content. What is important to sponsors at the point of submission can vary, but it is crucial to allocate time and set a budget for thorough integrated summaries (Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE)) that will be certain of meeting the regulator's expectations.

An integrated summary should not just be considered a summary of the details of individual study results held in the Clinical Study Reports (CSR), but rather, is a comprehensive and in-depth analysis of aggregated results used to make informed decisions. This analysis involves a synthesis of the results of individual studies, in an appropriate manner, to provide evidence of the safety and effectiveness of the drug. The integrated summary goes beyond the level of a summary, detailing pooled analyses and discussing them in detail.

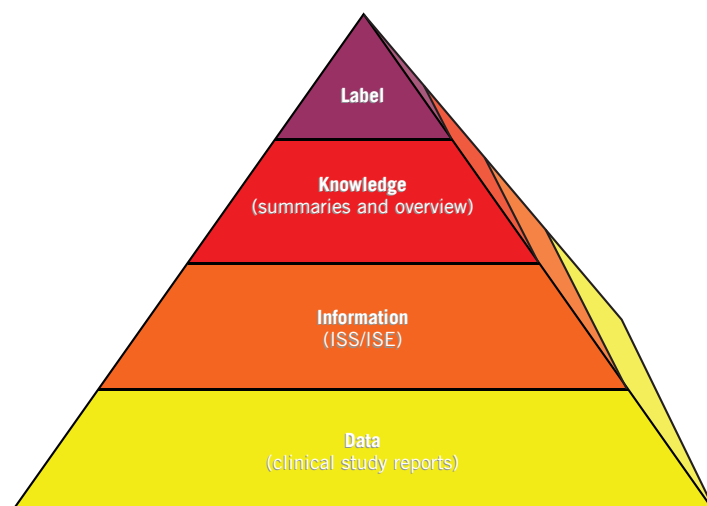
populations are needed to fully support the proposed label? Considerations for maximising the re-use of information are important at this stage. If you are planning several submissions, it is important to manage the traceability of the information from the collected raw data through to the different derived summaries. Managing the consistent derivation of values also needs the effective management of metadata for later use in submission and regulatory defence.

Analysis planning of these summaries may be started alongside the preparation of the Phase II studies to ensure appropriate endpoints, time points and patient populations are being considered. Visualisation of the summaries in terms of creation of output templates is defined at this early stage. These will undergo multiple reviews and updates as the knowledge of the drug increases and as the process becomes more focused, with data becoming available from early phase

EFFECTIVE PLANNING FOR INTEGRATED SUMMARIES

Approvability of a product depends, of course, on the data that is selected for collection during the planning of clinical trials. However, considerable resources, time and money can be saved by planning carefully how the summaries are structured to help make effective decisions and deliver clear messages supporting the target product claims. Consideration needs to be made as to where and when the product will be submitted. Will this strategy for creating the Common Technical Document (CTD) be discussed with authorities and will briefing documents be needed? What studies or

Figure 1: Life cycle flow





studies. Close communication of the relevant programmer, statistician, medical writer and physician is crucial to ensuring that reviews are performed at sufficiently early time points to allow for setup and reporting in a timely fashion. Forming an integrated, well-communicated and close-knit team during the development/review cycle of the summaries will ensure clearer understanding and high quality documents delivered to tight timelines. The close partnership of programmer and statistician provides an integrated approach to a highly technical piece of the CTD with as much detail as possible. Standard summary templates will provide a guideline initially, but will likely require amendments for these summaries.

The planning in terms of how data, information and knowledge are stored is also important to consider at an early stage. During a product's lifecycle the data points collected in clinical studies can be used in endless ways for information creation and decision points. Building the right information store and simple traceability will mean that you will be able to easily see the basis upon which data decisions were made and, more importantly, effectively respond to questions during regulatory defence. Including the planning upfront and using effective tools to manage the traceability will have enormous benefits to your products label in the long term. Every piece of data, information and knowledge that is created in the product's lifecycle supports the statements made in the label for the safety, efficacy and populations defined. These pieces of intellectual property are the crown jewels of your organisation and need to be planned carefully, documented through metadata and shared with consideration.

CREATION OF INTEGRATED SUMMARIES

It is normally a dash to the finish line when the integrated summaries are created. The wait for the data to be delivered for the final clinical study reports can get frustrating as data is being cleaned and the individual study team process the data. Hopefully, by this time your programs are ready to produce all the summary tables that were defined in the templates, and they have been tested and validated to run like a validated application that is robust enough to tackle every eventuality of data. Your project teams should have reviewed the tables using blinded and unblinded data to make sure that they have all the graphs and summary tables required to best interpret the information.

Depending on the company/supplier setup, coordination of the review cycle will generally be done within the biometrics team. Getting the input of medical writers and physicians before the unblinding of the Phase III studies is vital but difficult to achieve. Planning review meetings early in people's calendars and making sure the relevant personnel have performed a quality review prior to the meeting to

Delivering an electronic European submission

Project scope

A CRO was contracted to produce reports, including clinical study reports (CSRs), for two placebo controlled trials, along with two further CSRs for a sponsor's open-label extension studies. All four studies were reported from disparate databases, required statistical analysis plans (SAPs) and CSRs, as well as an ISS and ISE for Module 2.7 and input into Module 2.5. The project started in December 2008 and was delivered on time in September 2009.

Execution

The CRO introduced a standard naming convention across all databases. The SAPs and mock-up tables were all produced in a standard fashion, taking care not to introduce unnecessary inconsistencies. A significant amount of time was spent standardising the data into similar formats of derived datasets. This was time well spent, as once the data were in standard format, it was possible to write a single programme to produce output for the four studies.

Tight timelines and a heavy workload made it necessary to create teams of programmers and statisticians who worked on specific endpoints across all studies to maximise re-use of code, rather than separate teams working on individual studies.

Much of the effort was focused on writing detailed analysis plans to ensure that rework post database lock was minimal; all definitions were clearly defined and there were a significant amount of programmer notes to reduce the risk of misunderstanding.

All studies had two dry runs to iron out any issues. It was important to dedicate time to making sure that sufficient peer review was undertaken to ensure consistency between endpoints programmed by different teams.

The four databases were frozen between late April and early May. All tables, listings, figures and statistical reports were finalised by mid-late June. Through standardisation of databases and re-use of code, the analyses for the CSRs, statistical reports, ISE and ISS were produced in less than three weeks from mid June to early July. Due to the tight timelines, project management and teamwork were key to delivering the final submission-ready documents; the statistician and medical writer worked closely with the client reviewers to ensure final documents were produced and reviewed in a consistent and timely manner. Given the delay in obtaining final and draft data, this case study shows what can be achieved by careful planning and coordination across teams of programmers, statisticians and medical writers without compromising quality.

enable a productive review can be critical in saving on re-engineering of the project's critical path.

There are many different drivers for getting the submission out of the door as soon as possible. However, the rush can affect the review time by authorities and may even affect the size of the label you are requesting with the authorities. Taking a little more time, say a week, to review all the data, information and knowledge you are supplying in support of the label can be of great benefit. It is important to pre-empt the questions that may come from the authorities. Most project teams think they have supplied every eventuality in terms of summary tables, but there is always something to be learnt from other submitted projects.

Efficacy summaries checklist

- Mention limitations of sample size
- Include age, sex, race and geographic location – clinically relevant demographic factors
- Consider US versus non-US. Does this have an affect on efficacy? Describe regional differences
- Deal with the drop-outs – planned versus actual
- Consider and discuss risk benefit
- Analyse positive and negative findings
- Focus on pre-specified endpoints
- Consider sub-populations
- Use graphical representations, such as Forest Plots
- Use consistent data formats (for example, convert to the same unit of measure)
- Use tables to combine and present data. All cells should have something or it may be construed as missing; use consistent footnote symbol order for every table
- When pooling data, discuss and present selection process
- State and discuss problems, which provides a more credible analysis
- Include clinical information relevant to dose recommendations and individual dose responses
- Remember that listings are not required by the FDA anymore; SAS viewer is used

Safety summaries checklist

- Choose a single dictionary, and include the dictionary and version in the methods. If older dictionaries were used and re-coding is not possible, include details and/or a footnote to explain
- Consistent terminology (for example, if presenting more than five per cent common adverse events (AEs), use this cut-off throughout)
- Reference quantitative safety analysis plans (QSAPs) where applicable
- Discuss statistical issues to do with AEs; search the database for related AEs
- Always show gender (or subgroup) specific denominators
- Indicate denominator over time
- Make use of graphical presentations
- Present clinically significant criteria for laboratory, ECG, vital signs and AEs, where applicable, referencing the most current criteria
- For laboratory data, apply conversions where necessary to ensure the same unit of measure for each parameter if multiple laboratories exist within/between studies
- Ensure availability of clear documentation relating to individual laboratory reference ranges. Lack of clarity prompts questions around this

REVIEW OF INTEGRATED SUMMARIES

The quality of the integrated summaries can have a direct impact on the speed at which submissions are reviewed by authorities and at which a product is introduced to the market. This can also have a direct impact on the quality of the label approved. It is in the best interests of the sponsor to ensure only one review cycle. It is essential that summaries are presented in the correct way and that information supporting the label is well organised, traceable and understood in preparation for regulatory defence questions. The ultimate measure for a quality submission is the number of questions asked and the turnaround time in response. The

emphasis in all cases should be on the approval of a product and not just the submission.

If the resources are available within your organisation, put together a plan for forming a team of experts to review the summaries developed for your submission. They should have a critical view to try and prompt questions that regulatory reviews potentially might have. Pre-empting these questions could significantly improve both the review time of a product and the reputation of your organisation in the longer term.

Ultimately, an optimal clinical programme with great vision, design and strategy will provide you with the expected results to support your label, but this does need to be backed-up with the right summaries to best explain and interpret your hard work. You may have the right data to strengthen your target product claims, but unless the correct information and knowledge is generated to support this, it could take you a lot longer to get to the approval stage if your planning and summaries are not thought through. The summaries must communicate the vision defined through its selective programme design and expert interpretation of the quality data generated.

CONCLUSION

Effective planning of your integrated summaries should start early in the process of the approval of a product. At Phase II, you should start to plan and be prepared to adapt the plan as knowledge of the product increases. Communicate effectively with the relevant individuals in your teams and ensure close partnerships throughout between your programmers and statisticians. Using metadata, define the standards of how the data is captured, how information is derived and stored, and how knowledge is acquired and subsequently used upfront. This will pay dividends in the traceability of the crown jewels of your product in the long run. Don't rush the end game and be ready for any questions that may come your way.

About the author

Michael Whitworth is a Consultant Business Development Manager with clinical biometrics CRO Quanticate. Prior to joining Quanticate, Michael worked in a variety of positions with AstraZeneca Pharmaceuticals for over 20 years. His experience encompasses statistical programming,

business analysis and a range of management positions in the US and UK. He most recently led a programme across R&D and operations that focused on the definition and traceability of regulatory knowledge in support of interactions with regulatory authorities. Michael's experience has focused primarily on the approval of products with regulatory authorities and he now works in a consultative manner with sponsors who seek more strategic outsourcing practices. He has a degree from Leeds Metropolitan University in Mathematics, Statistics, and Programming. **Email:** michael.whitworth@quanticate.com