Producing comprehensive integrated summaries

Michael Whitworth

Quanticate International, UK

Far from being simply a summary of individual results, a comprehensive and detailed integrated summary allows companies to make informed decisions. This paper discusses the planning, creation, timing, and review of such a process highlighting the resources required and potential pitfalls you could encounter.

Keywords: ISS, ISE, Integrated summaries, SAS, CTD, Submission

Introduction

Producing comprehensive integrated summaries of safety and efficacy is a critical stage of the submission lifecycle. 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 entire 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 lead to knowledgeable decisions and the ultimate wisdom that forms the label of a product.

Guidelines from agencies on 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 time of submission can vary, but it is important to plan time and 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 collectively provide evidence of the safety and effectiveness of the drug. The integrated summary goes beyond the level of summary; detailing pooled analyses and discussing them in detail.

Effective Planning for Integrated Summaries

Approvability of a product depends on the data that are selected for collection during the planning of clinical trials. However, considerable resource, time, and money can be saved by carefully planning how the summaries are structured to help make effective decisions and deliver clear messages supporting the claims of the target product. Considerations need 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 populations are needed to fully support the proposed label? Considerations for maximizing the re-use of information are very important at this stage. If you are planning several submissions then, 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 in order to ensure that appropriate endpoints, time points, and patient populations are being considered. Visualization of the summaries through 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 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 set-up 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

Correspondence to: Michael Whitworth, Quanticate International, Black Box, Wilmslow, UK. Email: Michael.whitworth@quanticate.com

© 2011 Pharmaceutical Users Software Exchange (PhUSE)
Published by Maney
DOI 10.1179/175709311X13152978689502

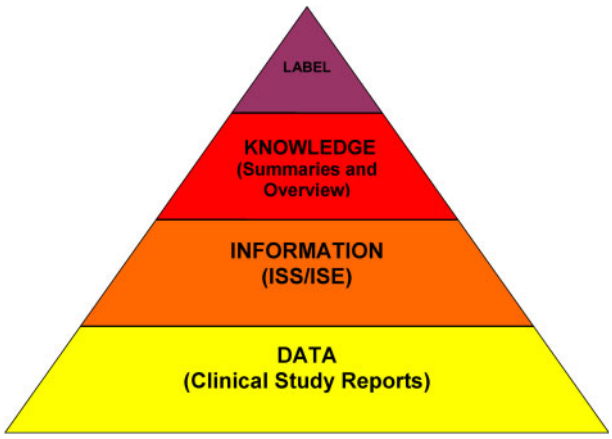

Figure 1 Lifecycle flow

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 initially provide a guideline, but will likely require amendments for the integrated summaries.

Early stage planning of how data, information, and knowledge are stored is also important (Fig. 1). 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 on what basis 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 product's 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 organization and need to be well planned, documented through metadata, and shared with careful consideration.

Creation of Integrated Summaries

Normally, it is a rush to the finish when creating the integrated summaries. The wait for the final data to be delivered for the final clinical study reports can get frustrating as data are 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 — 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.

Dependent on the company/supplier set-up, 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 of review meetings early in people's calendars and making sure that the relevant personnel have performed a quality review before the meeting 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 your requested label. Taking a little more time (e.g. 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 that they have supplied every needed eventuality in terms of summary tables, but there is always something to be learned from other submitted projects.

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 brought to 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 organized, 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 organization, it is always good to 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 really improve the review time of a product and very importantly improve the reputation of your organization 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 supported with the right summaries to best explain and interpret your had work. You may have the right data to support your target product claims, but unless the correct information and knowledge is generated to support this, it could take you a lot longer to approval 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.

Summary

Effective planning of your integrated summaries should start early in the process of the approval of a product. Around phase II, you should start to plan and be prepared to adapt the plan as the knowledge of the product increases. Provide effective communication with the relevant individuals in your teams and ensure close partnerships throughout between your programmers and statisticians. Define upfront, using metadata, the standards of how the data are captured, information is derived, and then stored and how knowledge is acquired and subsequently used. 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.

Appendix

Checklist 1: Hints and tips for initial preparation for authors, contributors, and reviewers

- always ensure that most up-to-date templates and relevant regulatory guidelines are consulted and used throughout the project lifecycle;
- use professional approved style guides, and detail upfront how to cover items not covered in style guides;
- use standardized methods for citation/referencing;
- train authors to write granular documents;
- train reviewers to review electronically CSRs, ISS/ISE summaries, and overview label.

Checklist 2: Hints and tips for safety summaries

- choose a single dictionary, and include 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, e.g. if presenting >5% common adverse events (AEs), use this cutoff 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 most current criteria;
- for laboratory data, apply conversions where necessary to ensure the same unit of measure for each parameter if multiple laboratories within/between studies;
- ensure availability of clear documentation relating to individual laboratory reference ranges. Lack of clarity prompts questions around this.

Checklist 3: Hints and tips to get the basics right — writing

- give clear, concise, objective statements;
- ensure acceptable grammar and punctuation;
- be consistent in writing style and follow Quality Control (QC) checklists to ensure intra- and inter-document consistency;
- craft key messages accurately, avoid mixed messages, and ensure the same message throughout by focussing on label claims;
- ensure scientific interpretation, not regurgitation;
- use an easy-to-read layout: 100% zoom, 12 pt font, Times New Roman;
- provide easy navigation through sufficient and accurate hyperlinks and bookmarks;
- find the right balance between content re-use and avoid redundant repetition;
- avoid repeating detail already given in the individual summaries of clinical trials; use hyperlinks in place of cutting and pasting the same information;
- for legacy trials, use the body of the CSR as the source, not the CSR synopsis.

Checklist 4: Hints and tips to get the basics right — statistics

- do not use secondary data unless they support label claims or reveal an issue;
- provide comprehensive, detailed, in-depth analysis of results in aggregate with a clear rationale for the methods used;
- utilize both positive and negative trials;
- compare trials of similar designs;
  - weighting of sample size;
  - examine by common covariates or stratifications;
  - consider controls, durations, patient populations, endpoints, drop-outs statistical analyses:
    - consider inconsistencies in the data;
    - consider areas needing further exploration.

Checklist 5: Hints and tips for worst practices for producing an integrated summary

- not providing one!
- being too brief;
- excluding data that do not support the effectiveness conclusions;
- excluding pertinent safety data;
- pooling data that should not be pooled;
- relying on results from *post hoc* meta analyses;
- discussing experimental endpoints, rather than focussing on primary and co-primary endpoints;
- including datasets without explaining how they were derived.

Checklist 6: Hints and tips for efficacy summaries

- 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 impact 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 (e.g. 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; it provides a more credible analysis;
- include clinical information relevant to dose recommendations and individual dose responses;
- remember that listings are not required anymore by FDA; SAS viewer is used.

Checklist 7: Hints and tips for improving reviewability

- use effective hyperlinks and bookmarks: all documents from protocol through to summary should be hyperlinked and bookmarked at time of preparation rather than at the end;
- write with electronic review in mind and follow FDA Good Review Practices: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf;
- create an efficient work flow;
- produce submission-ready documents at all stages and employ a consistent QC checklist to make this happen.

Checklist 8: Hints and tips for planning for lifecycle management

- employ methods and tools for information sharing and knowledge management early in the process;
- reviewers need to know what has changed and why;
- consider impact of changes on future documents;
- incorporate best practices for change history.

Cost

Some factors that may reduce cost include, but are not limited to, the following:

- make all studies similar in structure (e.g. CDASH format as CRF standard);
- make full use of available macros. Standardize reporting across the clinical program for efficient re-use of macros, along with standard formats for tables, listings and figures;
- supply all data as CDISC SDTM SAS transport files or SAS datasets;
- integrated summaries based on SDTM and ADaM domains provide a platform for FDA submission;
- supply clean and complete data;
- code all studies to the same dictionaries and same version;
- prepare submission-ready documents throughout the project lifecycle;
- apply consistent style and formatting;
- to reduce the number of review cycles, agree to the key messages upfront.

QC recommendations

Preparation of datasets/domains

- carefully check data received for validity, appropriateness, and completeness;
- where mapping to SDTM is required, use double programming as part of the QC methodology;
- note the version of SDTM in all programming;
- note the version of MedDRA where applicable;
- ensure that all SDTM domains created follow IG v3.1.1 (or IG v3.1.2);
- create an SDTM Data Warehouse for each required domain eCTD requirements: Create define.xml, blankcrf.pdf, and SAS transport files;
- ensure that define.xml is created for all studies plus an overall define.xml for the ISS/ISE;
- agree to the level of hyperlinking on blankcrf.pdf;
- agree to the style and formatting requirements and include checks for the same on document QC checklists.

Integrated summary analysis plans

- allow for multiple reviews to ensure high level and full team input to minimize late changes on the critical path.

Output production

- produce a QC plan documenting level of QC, type of QC, and documents to QC against;
- document all QC stored electronically for ease of team reference;
- ensure that the differences between dictionaries and study level summaries are documented carefully.

Copyright of Pharmaceutical Programming is the property of Maney Publishing and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.