

## Tips for Producing Comprehensive Integrated Summaries

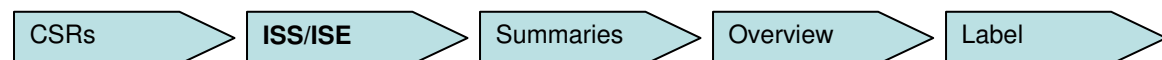
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While the pyramids were built over 200 years, construction of an integrated summary shouldn't have to take that long!

Guidelines from agencies on preparation of integrated summaries for regulatory submissions are often lacking in terms of providing specific direction on content. Indeed, some guidelines are old and/or in draft format. Recognising that managing the cost and quality of producing integrated summaries is important to sponsors, herein, we have summarised tips for preparation of comprehensive, well-written, and focussed integrated summary documentation.

An integrated summary is not merely a summary of the details of individual study results, but rather, is a comprehensive and in-depth analysis of aggregated results. This analysis involves a synthesis of the results of individual studies, in an appropriate manner, to collectively provide evidence of safety and support for the claimed effectiveness of a study drug. The integrated summary goes beyond the level of summary; detailing pooled analyses and discussing them in detail, as well as including more extensive analyses that would not easily fit in a summary document.

### Life Cycle Flow



### Tips

#### *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

#### *Initial Preparation for Authors, Contributors and Reviewers*

- Always ensure most up-to-date templates and relevant regulatory guidelines are consulted and used throughout the project lifecycle
- Use professional approved style guides, and detail how to cover items not covered in style guides upfront
- Use standardised methods for citation/referencing
- Train authors to write granular documents
- Train reviewers to review electronically



### *Get the Basics Right - Writing*

- Clear, concise, objective statements
- Acceptable grammar and punctuation
- Consistent writing style and Quality Control (QC) checklists to ensure intra and inter document consistency
- Accurately crafted key messages; no mixed messages; same message throughout; focus on label claims
- Ensure scientific interpretation, not regurgitation
- Easy-to-read layout: 100% zoom, 12 pt font, Times New Roman
- Easy to navigate – sufficient and accurate hyperlinks and bookmarks
- Find the right balance between content re-use and avoid redundant repetition. Content re-use does not mean simply copying and pasting from one document to another
- Avoid repeating detail already given in the individual summaries of clinical trials; Don't cut and paste – hyperlink instead
- For legacy trials, use the body of the Clinical Study Report (CSR) as the source, not the CSR synopsis

### *Get the Basics Right - Statistics*

- Don't 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
- Utilise 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, dropouts
- Consider inconsistencies in the data
- Consider areas needing further exploration

### *Safety Summaries*

- Choose a single dictionary, and include dictionary and version in the methods. If older dictionaries 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 cut-off throughout)
- Reference Quantitative Safety Analysis Plans (QSAPs) where applicable
- Discuss statistical issues with AEs; search the database for related AEs
- Always show gender specific denominators
- Mention denominator over time
- Graph representation is good
- Present clinically significant criteria for laboratory, ECG, vital signs and AEs, where applicable, referencing most current criteria



- Multiple labs – ensure reference ranges in same unit of measure (applying conversions, where necessary)
- Lab ranges and lab cut-offs often come up when reviewing

#### *Efficacy Summaries*

- Mention limitations of sample size
- 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 drops 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
- Data format is important (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
- Listings are not required anymore by FDA; SAS viewer is used

#### *Improve Reviewability*

- User 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 – 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 – employ a consistent QC checklist to make this happen

#### *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 standard)
- Make full use of available macros. Standardise 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, applying consistent style and formatting
- To reduce the number of review cycles, agree the key messages upfront

## **Quality**

### 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 all SDTM domains created follow IG v3.1.1
- Create an SDTM Data Warehouse for each required domain
- eCTD requirements: Create define.xml, blankcrf.pdf & SAS transport files
- Ensure define.xml is created for all studies plus an overall define.xml for the ISS/ISE
- Agree level of hyperlinking on blankcrf.pdf
- Agree style and formatting requirements and include checks for same on document QC checklists

#### *Integrated Summary Analysis Plans*

- Allow for multiple reviews to ensure high level and full team input to minimise 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



## **CASE STUDY 1 – Deliver an Electronic European Submission**

### ***Project Scope:***

Quanticate was contracted to produce reports and write CSRs for two placebo-controlled trials, along with two further CSRs for our customer'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:***

We introduced a standard naming convention across all databases. The SAPs and mock 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 very well spent because once the data were in standard format it was possible to write a single program 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 re-work 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 and 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.



## Case Study 2 – CDISC Mapping for Data Integration

### ***Project Scope:***

Quanticate was contracted to provide mapping to CDISC standards for three studies (Phase I and two Phase IIIb) for a new indication of a marketed drug. These three studies were to be integrated with one other study (Phase IIIb) already in CDISC SDTM format in order to provide all studies in a consistent format for the integrated summary.

The three studies mapped by Quanticate were prepared according to Implementation Guide (IG) version 3.1.1. Quanticate provided all required domains for submission to the FDA, including all subsidiary documentation pertinent to the submission, such as define.xml.

All studies were run, data managed and reported by suppliers other than Quanticate; although requested to follow the same CRF format, there were crucial differences on how questions were asked and responses data-based. Annotated CRFs were essential to ensure accurate interpretation and selection of correct variables, though documentation describing the data source was lacking.

The studies themselves differed in design (two parallel group, one cross-over), and they had complex paper diaries collecting both safety and efficacy data over a long period of time. As is often the case, there was a percentage of missing data for patient diaries. This created multiple algorithmic challenges relating to assignment of treatment and dosing for both safety and efficacy endpoints. During the initial mapping phases, clear and effective communication became key to resolving complex issues involving several third parties to ensure that assumptions made were followed through for all studies, and understood by all parties involved.

### ***Execution:***

Task schedules were created for each assigned programmer. These included:

- Individuals assigned to particular domains across the studies to ensure project consistency (either as creator or reviewer)
- Study and data familiarization at a macro or micro level
- Assessment of formatting differences (e.g., a yes/no response may be recorded as 1/0, y/n/unk, y/.)
- Creation of clear guidelines for documentation of mapping and QC procedures for mapping documentation, as well as domain QC
- Documentation of 100% variables/database (to agree dropped variables such as Data Management–specific variables with the sponsor)
- Concurrent review of mapping documentation, domain by domain, to ensure consistency such as consistent identification of distinct domains, use of SDTM-controlled and sponsor-specific terminology
- Full documentation of mapping using the SDTM domain documentation with additional columns to explain where the contents originated, along with any specific mapping instructions or transformations (i.e., date held in four variables – day, month, year, numeric – had to create one value following ISO 8601 format)



- Programming of the domains was performed on a domain by domain basis in order to maintain consistency of domains between studies and maximise code efficiencies. This also facilitated efficient updating based on any amendments in sponsor-specific terminology.
- Standard macros were used wherever possible (e.g., date formatting to ISO standards) and formatting, where appropriate, to create values (i.e., the format catalogue could be used to create a study-specific decode of a numeric race value without having study specific details in the macro)
- QC of the domains used author QC, followed by independent QC, using a mixture of the following techniques:
  - Confirmation of CDISC structure
  - Peer review of code
  - Derivation re-programming (excluding trial domains)
  - Three subjects checked against raw data
  - Basic statistical checks on variables
  - Proc CDISC (where possible as this was only available for a few domains and IG v3.1 at the time)

Part of the integration involved assessing the dictionaries applied, along with identifying potential differences resultant from use of different versions of dictionaries. All studies were brought up to the latest version of MedDRA for adverse event reporting, using a straightforward LLT merge. Additional information was provided as part of the submission to demonstrate the differences, where present, to the individual study reports.

Not all the studies used central laboratories or SI units. Therefore, consideration was made for standardisation of lab units. For this, spreadsheet of units was created and conversions, which were sponsor approved, were then used for creation of the domains.

Trial Design domains were created manually by reviewing the protocol to source the relevant information, and creating spreadsheets for client review and approval before importing into SAS. QC of the domains was performed against approved spreadsheets.

The define.xml file was created primarily using a macro. The QC process involved reviewing the contents, checking the file and contents against the CRT-data definition schema, ensuring the XSLT template was associated correctly and tested in an appropriate browser.

The submission was successfully filed on time, with minimal re-runs following review by the sponsor. Following this submission, Quanticate did reduce some of the QC process, recognising that the full suite of checks performed was not required for all domains.

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