Background

Over time, approaches to subject level data review have evolved, along with the needs of reviewers, to link various data sources in a single longitudinal patient record. The patient profile and patient narrative accomplish such a comprehensive data review. However, the approaches to generate these vary widely across the clinical industry. This poster evaluates ways in which visualizations are used to review data at the patient level.

The Data Visualization Project conducted an updated analysis of the current tools used to review subject level data, including the use of interactive visualizations for generating patient profiles and patient narratives. This type of review has not been done in over five years. During this time, technology, regulations, and processes have evolved.

This paper focuses on three types of subject level data representations:

1. Tabular Patient Profiles, or case summaries, display information for a single patient in tabular format, allowing the user to view summarized data about a single patient’s clinical experience. For example, counts and SOCs of adverse events during exposure and/or other information relevant to the trial can be displayed.

2. Graphical Patient Profiles are time-oriented visual presentations of subject level study data requiring little or no external data preparation or programming. These profiles may focus on a specific area such as liver function or depict a comprehensive view of the subject’s time in the trial and include exposure, adverse event, lab, disposition or other data.

3. Patient Narratives are summaries that describe a subject’s clinical experience resulting from participation in a clinical trial. Narratives contain elements of a patient profile but are primarily generated to communicate reasons for the event(s) the patient experienced during their participation in the trial.

Methods: We designed a survey to gather information about the tools currently used to generate the three types of patient data displays described above. This survey was sent to the entire PHUSE Emerging Trends & Technologies Working Group and was conducted over the course of four weeks from December 20, 2017 to January 19, 2017. Both industry and the FDA participated in the survey.

Summary of Results

The authors acknowledge the limitations of drawing from a small survey; however, we distributed the survey to all PHUSE members, people we would consider more motivated and engaged than the average user. Follow-up surveys to determine desired functionality were conducted as a follow-up, as described later in the paper.

Tools

Our survey on tools showed that organizations are relying on a combination of tools to handle clinical trial data analysis needs. Unfortunately, we did not design the survey with enough precision to confirm this, but we assume that this combination includes one COTS tool to handle standard analyses such as AE percentages and Hy’s law analysis, along with programming tools such as SAS and R to handle ad hoc analysis and customized analyses, such as those done for specific therapeutic areas. One clear gap in some of the COTS tool is the ability to handle patient profiles. All four tools include this capability, but set-up for some of the tools can be technically demanding. As reproducibility of study analyses becomes a focus (Ryan, 2019), it would be useful to develop robust testing and reproducibility standards for in-house analyses that are developed to support analysis for regulatory review. For something like patient narratives, where display is likely the key objective, there is likely no issue here; however, if NLP analysis is used without the use of a manual check, robust testing should be implemented before the analysis is used to support decision-making for drug approval.

Graphical Patient Profiles

Display and Use

One of the big findings from this survey was the lack of consensus on most elements of display and use of the tool, with over 25% of the questions (3) scoring points for both critical and very important, along with not needed.

Consensus was seen for only 2 (16%) of the questions. The ability to easily drill down from an aggregated view to a patient profile was considered critical or very important by 100% of the respondents for that question, but the ability to click a point or duration bar of interest to drill into the details of other events was not ranked as high and listed not needed by two respondents. This may indicate that the tools are being used more to investigate identified trends, likely found by routine analysis, than to do novel exploratory research.

The other feature deemed important by 67% of the respondents was the ability to calculate time windows on the fly. This may indicate the importance/need for precise temporality in these analyses, which may be hard to estimate from a graphical display.

The survey indicated a lack of concern for data format for graphical profiles, with only one respondent stating that the use of a specific format (SDTM) was critical. This may indicate that the respondents have the resources to transform data. The ability to work with any clinical data source (even if some configuration was needed) did have three respondents note it as very important.
Tabular Patient Profiles

The survey had requested information on which products companies were using to generate tabular patient profiles/case summary listings. Only one of the products generates tabular patient profiles (JReview), but respondents expanded the response to include summarization of patient information in tabular form; then a wide variety of responses were received including each of the COTS but also many responses mentioning SAS.

Patient Narratives

Only two of the products generate patient narratives (SAS JMP Clinical and JReview), so while some respondents mentioned these, most mentioned custom programming in SAS and some with Word, etc.

Results

Survey question 1: What tools are currently being used within your company/organization to review summary information for patients? Given the broad definition (as opposed to using “tabular patient profiles”), many tools were included in the ‘Other’ response.

Traditionally, many pharma companies generated tabular patient profiles or case summaries by developing SAS programs to include data for providing an overview of the data for each patient. This approach continued to be used to generate Care Report Tabulation listings (CRT listings or case summaries) for use in-house, as well as a required part of regulatory submissions; however, the SAS programs used were often extremely tedious and time-consuming to develop.

Later, products like JReview, designed to assist with the review of clinical trial data, included a feature to generate customizable tabular patient profiles. This feature allows users to define the contents of the tabular profile interactively and dynamically without any programming involved by just selecting the datasets and items of interest. Other reporting tools, such as Business Objects, have been used to develop these tabular profiles but tend to require a considerable amount of development expertise and time.

Survey question 1 was modified to have a broad definition and used the phrase ‘summary information for patients’, rather than ‘tabular patient profiles’ or ‘case summary listing’. As such, many other tools were included in the response, both COTS tools such as JReview, JMP Clinical and Spotfire, as well as others requiring more coding (e.g. SAS).
Survey Q3 – Tools for Patient Narratives:
A survey asking about how patient narratives are generated showed that SAS was the overwhelming tool of choice for creating narratives, with 11/18 respondents – or 61% – using SAS. Of the respondents using SAS, five added a note that manual work was also done to generate the narrative. Spotfire (1), JReview (1) and JMP Clinical (2) were also used by several respondents to generate patient profiles.

The detailed results are as follows:

Q3
What tools are currently being used within your company/organization to generate patient narratives?
(Select all that apply).
Answered: 16  Skipped: 4

Answer Choices  Responses
JReview  6.25%  1
JMP Clinical  12.50%  2
Spotfire  6.25%  1
Empirica Study  0.00%  0
Other (please specify)  Responses  87.50%  14

Total Respondents: 16

Other responses (count and description of 'other'):
1 SAS/manual
1 R, SAS, writers creating hand-generated narratives in Word and/or Excel
4 SAS
1 SAS programming output and JReview outputs are being used by medical writers to generate the narratives.
1 Not applicable to the FDA (??)
1 Internal tools

Graphical Patient Profiles
Time-oriented, visual presentations of subject level study data requiring little or no external data preparation or programming. These profiles may focus on a specific area such as liver function or depict a comprehensive view of the subject’s time in the trial and include exposure, adverse event, lab, disposition or other data.

Feature Areas
• Display/Use
• Data
• Export/Printing
• Licensing
• Other

Graphical Patient Profiles, Display/Use
1. Scrollable display – horizontally – through available days axis range, and vertically – through different types of data displays (labs, AEs, ConMeds, dosage, etc.).
2. The ability to click a point or duration bar of interest to drill into the details of other events, interventions and/or findings that occurred during that same time point or time duration for that patient. Includes the surrounding events, interventions and findings that occurred during the time period, as well as the details of each event, intervention or finding that occurred (e.g. dose of the ConMed or severity of the event).
3. The ability to include any data item from study data to be presented graphically on a time scale that is in a Standard CDISC Domain.
4. The ability to include any data item from study data to be presented graphically on a time scale that is in a custom CDISC Domain or not in a standard format, even if some configuration is required.
5. The ability to display reference ranges for
1. Vital Signs
2. Labs
3. ECG Data
4. Other _________
6. The ability to display duration bars for
1. AEs
2. ConMeds
3. Dosing
4. Other _________
7. The ability to calculate time (days since any chosen reference point (e.g. reference start date, reference exposure
Data Visualization Subject Level Data Review Summary Report

1. Determine metrics to assess the cost of the development license and the viewing license. For example, Spotfire and Tableau have a license that allows a person to develop visuals and then a reviewer would have a license that allows them to view the visuals online without the need for the full software. We’d also want to know how much a server costs and how many users and how big a file it can handle.

Graphical Patient Profiles, Data

1. The ability to work with CDISC SDTM.
2. The ability to work with CDISC ADaM.
3. The ability to work with both CDISC SDTM and ADaM and merge the two datasets even if some configuration is required for ADaM (not SDTM), including the ability to use population and other subgroup flags defined in ADaM to filter subjects in any dataset.
4. The ability to work with any clinical data source (e.g. a legacy data format) even if some configuration is required.
5. The ability to handle large datasets (datasets that are 2 gigabytes or larger, up to as big as 30 gigabytes).

Graphical Patient Profiles, Export/Printing

1. The ability to save and print patient profiles both individually and in groups (batches).
2. The ability to export graphic display for inclusion in: Word, PowerPoint, PDF, Other _________

Graphical Patient Profiles, Licensing

1. Determine metrics to assess the cost of the development license and the viewing license. For example, Spotfire and Tableau have a license that allows a person to develop visuals and then a reviewer would have a license that allows them to view the visuals online without the need for the full software. We’d also want to know how much a server costs and how many users and how big a file it can handle.

Tabular Patient Profiles

Also called case summaries, these are display information for a single patient in tabular format, allowing the user to view summarized data about a single patient’s clinical experience, for example counts and SOCs of adverse events during exposure and/or other information relevant to the trial can be displayed.

Tabular Patient Profiles, Display/Use

1. Display of nicely formatted tabular patient profile for a selected patient.
2. Sufficient content, display, formatting for use both internally, as well as submitting to regulatory agencies as case summary.

4. Export tabular profile as a PDF or print.
5. Batch processing (generation of tabular patient profiles – resulting in one PDF per patient) to reduce time of generation.
   - The ability to specify criteria (e.g. based on country or treatment group) for patients to be included in generation of PDFs showing the tabular patient profiles.
6. The ability to easily drill down from an aggregated view to a patient profile.
7. Settings that allow for bookmarking and commenting on interesting finds when reviewing patient profiles.
8. Highlight new or updated data since last patient review.

Tabular Patient Profiles, Data

1. The ability to work with CDISC SDTM.
2. The ability to work with CDISC ADaM.
3. The ability to work with both CDISC SDTM and ADaM.
4. The ability to work with any clinical data source (e.g. a legacy data format).
5. No external set-up time, e.g. no need for external data transformation or data programming/preparation – all handled by the application.
6. The ability to handle large studies with a large amount of data per patient. (Should we define a size here? Is this related to number of patients or amount of data for each patient or both?)

Tabular Patient Profiles, Definition within Product

1. The ability to include any data item from the study to be presented in tabular format – with multiple tables/domains presented for one patient at a time.
2. The ability to filter at the row level – to decide which rows should be displayed for specific tables/domains, for example to display only ConMed from a drug class of interest.
3. The ability to sort data in any of the included domains of selected items, as appropriate for the data of that domain, for example ordering AEs based on onset date rather than alphabetical sort on AE verbatim text or visit number collected.
4. The ability to control formatting, font, color highlighting.
5. The ability to define/save multiple tabular patient profiles – with different content – for different targeted use.
6. The ability to calculate time (days since reference date) on the fly – without external data set-up or processing.

Tabular Patient Profiles, Export/Printing

1. The ability to save and print patient profiles.

Patient Narratives

Patient Narratives Execution/Display/Use

1. Interactive display of generated ‘automated text’ – with the ability to insert ‘free text’ additional content where desired – after review of the ‘automated text’ for any of the patients.
2. Generate the completed narrative including any embedded reports or graphs (only including data for the current patient).
3. Save the generated patient narrative as a PDF or RTF or other format.
4. Batch schedule/batch processing of patient narratives –
resulting in separate RTF files per patient.

**Patient Narratives, Definition within Product/Environment**

1. The ability to define a patient narrative template – defining where/when to insert data items from the study (similar to MailMerge in Word).
2. The ability to define ‘conditional’ inclusion of template text based on a condition definition, i.e. if a patient reported a serious AE, then include a paragraph describing the serious AE.
3. The ability to include ‘aggregate’ function versions (min, max, mean, etc.) of data items – with definition of filtering of rows to be included, for example max systolic BP post baseline.
4. The ability to insert reports or graphs to further illustrate information within the narrative.
5. The ability to define/save multiple patient narrative definitions – with different content – for different targeted use.
6. The ability to define the criteria for selection of patients who need to have narratives generated.
7. Works with any clinical data source – CDISC, or legacy data format.
8. No need for external data transformation or data programming/preparation – all handled by the application.

**Patient Narratives, Data**

(NO RESPONSES – FOLKS GETTING TIRED! – but assumed to be the same as the other types of output – graph patient profiles and tabular patient profiles)

1. The ability to work with CDISC SDTM.
2. The ability to work with CDISC ADaM.
3. The ability to work with both CDISC SDTM and ADaM.
4. The ability to work with any clinical data source (e.g. a legacy data format).
5. The ability to handle big data. (Should we define a size here? Is this related to number of patients or amount of data for each patient or both?)

**Patient Narratives, Export/Printing**

(NO RESPONSES – FOLKS GETTING TIRED! – but assumed to be the same as the other types of output – graph patient profiles and tabular patient profiles)

- The ability to save and print patient narratives.

**Tabular Results of Survey of Functional Capabilities**

The detailed results of asking participants to vote for each of the areas of functionality – by importance level (critical, very useful, useful, nice to have and not needed) – are included in the attached spreadsheet.

After entering the number of votes for each of the levels of importance, we combined them by weighting each as described in the spreadsheet, i.e. critical by 5, very useful by 4, and so on. We then totaled the number of votes times the weighting factor to determine an overall score for each area of functionality – for the original survey, then the Cincinnati SDE survey – and added the total score for both of the surveys, resulting in an overall score. We then sorted these within each section to determine the highest/most important features for each section.

The ‘Display/Use’ category for each type of product category appeared to be of most interest to the participants. Here’s a recap of the top three areas of functionality by product category:

**Graph Patient Profile – Display/Use**
1. Display reference range.
2. The ability to include any data from the study from SDTM.
3. Drill down from aggregate view to patient profile.

**Tabular Profile – Display/Use**
2. Display nicely formatted tabular profile.
3. Batch processing of profiles.

**Patient Narrative – Display/Use**
1. Interactive display of generated automated text.
2. Save generated narratives as PDF or RTF.
3. Generate narrative with embedded reports or graphs.

**Tool descriptions (based on tools mentioned in the first survey)**

Here we review commonly used tools for viewing subject level clinical trial data. The choice of tools was limited to the most widely used COTS tools, as found in our survey.

- **JReview**
  - Data Requirements and Set-up
    Works directly against SAS datasets (with SAS Share) or directly against a variety of clinical data sources/databases. Works with CDISC SDTM/ADaM or legacy data structures. Once environment is set up, uses study metadata available in the environment – no additional study set-up required.
  - Relevant Features/Highlights of Functional Characteristics
    - **Tabular Summary**
      Tabular Patient Profiles/Case Summaries and a variety of tabular reports, as well as clinically relevant study graphic visualizations. No external programming needed.
• **Graphical Patient Profiles**
  Built-in graph patient profiles – no external data set-up required. Days on drug (days since reference date) calculated on the fly – against target data. Also included is the ability to define intelligent patient narrative templates (multiple templates can be defined for different purposes). The system also selects patients who need narratives generated based on criteria defined by the user. And, of course, the system includes a wide variety of clinically relevant graphic visualizations, reports, crosstabs and other built-in clinical templates for a quick definition of these, using a drag and drop interface.

• **SAS JMP Clinical**
  • Data Requirements and Set-up
    • Requires CDISC SDTM data structures plus ADSL dataset.
  • Relevant Features/Highlights of Functional Characteristics
    • **Tabular Summary**
      A wide variety of tabular reports or graphic visualizations are available.
    • **Graphical Profile**
      Built-in graph patient profiles – days since reference date.

• **Narratives**
  Patient narrative template defined in JReview with data substitution, conditional processing for inclusion of text blocks based on patient data, and embedded tables and figures. Patient narratives are generated for patients selected based on reason for narrative specifications. Configurable patient narrative for automatic generation of patient narrative.

• **Summary** ([http://www.i-review.com/jreview.html](http://www.i-review.com/jreview.html))
  JReview is a clinical data review and analytics tool developed specifically for review of clinical research data. Graph patient profiles can be defined including any data from the study – whether the study is in standard CDISC SDTM or ADaM format or legacy data format. No external programming is needed – all ‘days since reference date’ are calculated at run-time in JReview. JReview also includes easy definition of tabular patient profiles, where the user can select which datasets and items they’d like to include.

  • JMP Clinical lets medical officers instantly generate
patient profiles for an individual or group of subjects simply by selecting subjects, and it displays clinical results visually, making it easier for nonstatisticians to understand. Patient profiles are customizable, displaying data from any combination of the core safety domains. Once the reports are tailored, users can save the view as a template or print the report in PDF or RTF, making for straightforward communication of findings among review groups.

- **JMP Clinical** can compose a configurable patient narrative for each subject who experienced a serious adverse event during the clinical trial. Reviewers and medical writers enjoy the speed of this programmed process, using the write-ups as a starting point for the final patient narratives compiled in the Clinical Study Report (CSR) required by the FDA.

**Spotfire**

- **Data Requirements and Set-up**
  - TIBCO Spotfire works with raw and SDTM SAS datasets. Data provided in Excel or CSV files can be converted to SAS datasets and then imported into Spotfire.

**Empirica Study**

- **Data Requirements and Set-up**
  - Data must be in CDISC SDTM format: other formats (including ADaM and legacy) cannot be loaded. A Define-XML can be provided or generated from the data. Once the data is loaded, no other set-up is needed. Configuration options allow the set-up of customized dosing groups, timeframes and other analysis variables.

- **Relevant Features/Highlights of Functional Characteristics**
  - **Tabular Patient Profiles**
    Tabular Patient Profiles Case Summaries are presented as raw CDISC data for the individual patient selected and navigation assistance is provided.

- **Graphical Patient Profiles**
  Individual lab and vital signs profiles can be displayed as graphics, with all selected subjects displayed together. No external programming needed.
A second type of graphical patient profile exists to display a subject’s entire experience in the study. This profile shows one subject’s safety information including exposure, adverse events, concomitant medications, vital signs, lab, ECG data and disposition information. Navigation tools allow the user to easily browse through sets of patient profiles for a group of subjects.

- **Narratives**
  No support for narratives is available using the standard configuration.
- **Empirica Study**
  is an interactive tool that allows the user to review patient level data in a variety of formats. It includes specialized patient profiles to display measures such as hepatotoxicity and vital signs, along with easy navigation tools to browse through sets of patient profiles for a group of subjects. In addition, the user can easily switch from one view to another, as well as drill down to specific areas of interest or to the underlying raw data supporting the visualization.

**Tableau software**

- **Data Requirements and Set-up**
  - Works directly with SAS datasets (or directly against a variety of clinical data sources/databases like Excel files, CSV files, etc.). Works with any kind of data: CDISC SDTM/ADaM or legacy data structures. Requires a little bit of data manipulation in order to set up the environment (e.g. SAS DI Studio or any other available solution). Once environment is set up, it uses the study data and metadata available in the environment – no addition required.
- **Relevant Features/Highlights of Functional Characteristics**
  - **Tabular Summary**
    - Not developed so far but would probably be possible.
  - **Graphical Patient Profile**
    - Patient profile gives in one screen all necessary information, from different domains, of data to be reviewed by both data managers and medical reviewers.

- **Narratives**
  - Not developed so far but would probably be possible.
- **Summary**
  Tableau is an interactive visualization tool. All dashboards can be connected. It allows the user to easily switch from one to another and better understand the subject experience within a specific clinical trial or have a global view on all subjects within one or more clinical trials. Filtering by selecting a variable value in a drop down list or in the visualization itself allows the user to limit what is being viewed. It is possible to drill down from an aggregated summary to a patient level summary. Available information can be restricted based on the access rights profiles.