Intelligent outputs – Telling the story

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ABSTRACT

There has been a heavy focus on informative graphics in the past few years, but not all data types can be easily graphed. So for adverse events are we actually providing clinicians with the information they require to make appropriate decisions for the drug's development?

There has been a large overhaul in standard safety outputs at GSK in 2007 for Phase I trials, revisiting the ICH guidelines and current practice.

The choice of output produced is imperative to prevent clinicians misinterpreting the output or missing something of importance.

INTRODUCTION

In this paper I will highlight the difference some minor changes to programming practice can make in aiding clinicians and medical writers to concisely yet completely 'tell the story' of each clinical trial and make informed, timely decisions regarding the clinical development of the drug.

The paper focuses on the standard safety package output for a 'typical' Phase I clinical trial. However, the mentality surrounding the changes can be applied to efficacy, pharmacokinetics, pharmacokinetic outputs, non-investigational product trials etc.

Glaxosmithkline (GSK) uses a set of reporting display outputs that begun development in 2002. The concept was to have a set of displays that:

- Were flexible enough to be used across most studies and hence report outputs would be consistent within submissions, across compounds and across all of GSK
- Provided an accurate and easy method to compare studies reported five years apart
- Allowed enough flexibility that the same programs/macros could be utilised for each study to prevent unnecessary rework.

There is now an extensive online library of displays for safety (including displays like exposure to medication, demographics), pharmacokinetic and many pharmacodynamic and efficacy endpoints.

WHY IS THERE A NEED TO RETHINK OUTPUTS

- No more phonebooks
- Are we 'telling the story'?
- ICH constraints and in house standards – how constrained are we?

- Different sites (UK/US/Italy) using differing outputs for the same data

WHO NEEDS TO BE INVOLVED

- Programmers
- Statisticians
- Medical writers
- In house standards experts
- Physicians
- Regulatory

MYTHS

1. One size fits all
   - Differing phases IP/Non IP/Phase I, II, III, IV – most standards at GSK were aimed at later phase (II/III) efficacy trials
   - Standards should depend on study design e.g. crossover/parallel, single/repeat dose
2. You must do the same as the last study
   - Create a balance between reinventing the wheel and using a bicycle wheel for a car
3. Everything must be listed and summarised
   - There is definitely a principle of if you are not sure a listing/summary is required then produce it just in case. By defining and discussing what is needed at the analysis plan stage this can be avoided.

BALANCE

1. ICH E3 Quotes…

"Depending on the nature and importance of such studies (e.g. clinical pharmacology), a less detailed report might be appropriate"

"The report with its appendices should also provide enough individual patient data, including the demographic and baseline data, and details of analytical methods, to allow replication of the ***critical*** *analyses when authorities wish to do so."*

"The data listings requested as part of the report (usually in an appendix) are those needed to support ***critical*** *analyses."*

*"****When required*** *by regulatory authorities, the results of all safety-related laboratory tests should be available in tabular listings"*

ICH E3 doesn't always 'require' all outputs often words such as 'may', 'can', 'could', depending' are used.

2. In-house principles (a few examples)

- Landscape (expect Figures may be portrait if necessary)
- 9 by 6 inches, 10pt, Courier
- Conserve space
- For sparse data, a listing may be sufficient rather than a summary

- If no data then display 'No Data Available' or No Data to Report'
- Summaries on single page where possible

SUGGESTIONS FOR CHANGE

1. Outputs conditional on events
    - Data driven outputs e.g. summary of SAE. In most Phase I studies there will be relatively few SAEs so a listing will suffice.
    - Summary of exposure to study drug. Not applicable for single dose study

2. Tell the story
    - Subjects who had 100% normal safety do not tell the story, the abnormal subjects do
    - Listings of abnormal values (listing of all values for subjects with abnormal values and listing of just the abnormal values)
    - Listing of inclusion/exclusion criteria, subject withdrawal and end of study record. Making sure they provide the necessary information for the medical writers

3. Reduce outputs

- Programmer responsibility as well as statistician
- Reduce number of full listings where possible, agree with authorities in advance if required
- Consider if both a listing and summary are required for each type of output (e.g. concomitant medications in a small study would only require a listing)

4. More targeted displays

- When programming, consider what displays are for, e.g. one reason for a demography summary is to show that demographics are consistent/equal across treatments, hence the table needs to have a column for each treatment, but an overall column is also useful.
- Consider creating labs/ECG/vitals listings for AEs of interest
- Labs by organ as per ICH "As not all tests can be displayed in a single table, they should be grouped logically (haematological tests, liver chemistries, electrolytes, urinalysis, etc.)."
- AEs by highest frequency of event - not by class then frequency of event.
- Concomitant medications by generic term rather than ingredient

PRODUCTION

The workstream produced

- List of required, optional, conditional, not recommended displays
- Proposal that a display is only 'required' when it is a clinical safety concern for clinical pharmacology
- Guidance documentation and training where principles are now better defined
- Continuity - One place for all data standards that can be referenced for all sites and is stand alone
- Macros to produce the new targeted displays (Dec 07)

MOVING FORWARD AND CONCLUSIONS

- No more phone books – But still remaining within the boundaries of ICH and in-house standards
- Telling the story - Giving the results in the most useful form for medical writers, physicians and regulatory

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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