1. Introduction

Large, global late phase studies inevitably involve huge amounts of data of varying quality. Data frequently needs
cleaning up prior to locking the database, a responsibility
typically lying with data management. The ability to look at
multiple extracts of data while the study is ongoing and
blinded has enabled us to develop novel methods and
processes for increasing the confidence in data quality.

Forced expiratory volume in one second (FEV₁) is the volume
of air expelled from the lungs in one second. This is measured in millilitres or litres depending on the equipment.

Outliers in FEV₁ can commonly be caused by a decrease in
subject effort, illness or equipment failure. These values
would not be considered valid and including many subjects
with these values in the analysis can cause variations that
can not represent the true treatment differences. Looking
at these in a visual way emphasises the importance of
ensuring that these outliers are genuine data points.

A respiratory exacerbation is an event, such as pneumonia or a COPD exacerbation that affects the airways and hence
the patients ability to breathe. Respiratory tract exacerbations
may present over a period of a few days with symptoms
progressing. Due to this, sometimes these events can be
recorded as two separate exacerbations when they are
actually the same event progressing over time. When rates
of respiratory tract exacerbations are an endpoint, recording
duplicate or overlapping events will alter results.

The need for identifying these two different situations is
apparent. Previously, clinicians would spend time looking
towards vast amounts of data, however, these Patient Profile
review tools have made clinical review a quick and easy
process stressing the importance of these data on our endpoints.

2. Measures of

FEV₁, Rate of Decline

The rate of decline is measured in millilitres per year and a raw
rate of decline can be calculated simply using linear regression.

When calculating the slope extreme values of FEV₁, caused by
respiratory events or equipment malfunctions can lead to
differences in the rate of decline that do not represent the true rate
of decline of the subject. This is illustrated here in this example plot
of FEV₁ (ml) against Time (weeks). As illustrated in the figure,
changing the final data point to be
an outlier (red) changes the raw
rate of decline quite substantially.

Subjects with outliers can be found
easily, but the influence on the
results is more difficult to explain
without a visual/graphical option.

3. Rate of Exacerbations

For Rate of Exacerbations, the data was presented in a patient profile bar plot, with one plot per overlapping event. Information on medications taken at the
time of the respiratory exacerbation was included as well as duration of the event in days.

Presenting this information in a visual way, it is apparent that the 2nd Adverse event is not a second event but actually the same exacerbation event which
probably started on 31st December. This event would increase the rate of exacerbations for this subject. In this example, the case is easy to deal with,
however, when events are separated by a few days or even a week, the case is
not so simple, and having the medications taken by the subject is more
important.

These profiles were reviewed by the clinical team and further action was taken of
querying the data or sending the exacerbation profile to the site and asking
them to clarify the data. When the site can visually look at the profile, it is
immediately clear if they have made any misrepresentation of what happened
in the recorded data, and if not they can explain the differences for the clinical
team to review.

4. FEV₁ Rate of Decline

The need to have a visual tool to ease the clinical review was
identified, with an emphasis on user ease and content
needed to reach a clinical decision on further action.

Using a combination of excel and SAS, the following tool was
developed. Some clinical review rules for FEV₁ rate of decline
were identified including large differences between
screening and baseline values and calculated individual rate
of declines greater than 75ml/year. Utilising these rules, a
review spreadsheet was created identifying the subjects
programmatically in SAS. Filtering on subject number gives
the individual subject information on one page, including
treatment information, previous queries, responses and any
previous review information.

Upon reviewing the spreadsheet, decisions can be made as to whether to take
any further information, if a query has been answered previously with an appropriate
clinical reason for the discrepancies in FEV₁, between visits then the decision may be
made to not take any further action with the data, as it represents the true values.

Previously, upon reviewing the data, query history for subjects would not have
been available to view as easily.

Once all subjects have been reviewed and decisions whether to issue a profile
made the spreadsheet can be read into SAS and a PDF version of the patient profile
is created and issued to the site for review. This document contains the clinical
review comment, the graphical representation of the FEV₁ data and space for the
site investigator to comment to explain any large variations. Placing all of
the information into one document makes the anomalies in the FEV₁ data visually
clear to the investigator at the site, whilst providing anymore information they need to
investigate.

The PDF profiles can be issued to sites for their review. If they see any immediate
data entry issues with the FEV₁ data, it is assumed these will be corrected and the
subject will no longer be picked up by the clinical rules set initially. Alternatively,
the Principal investigator can return and comment on the discrepancies in the box
supplied. These comments can also be entered into an electronic data capture
system to track. The comments from the site should explain the discrepancies seen
in the data and can be reviewed by a clinician to make sure they make sense medically.

5. Summary

• Reviewing study data in the traditional way can be a time consuming process.
• Data can be difficult to review when displayed in typical dataset standards such
  as listings. Having unique tools can help our clinical colleagues keep track of their
  review more easily.
• Visual tools can assist with understanding of impact on endpoints for both clinical
  reviewers and investigators at sites.
• Seeing an outlying on an FEV₁ plot, or seeing clinical events overlapping in front of
  you in a diagram highlight the effect these would have on analysis.
• Using more advanced programming approaches to identify and display individual
  subjects can have benefits for all departments, data management, clinical and
  statistics and programming.
• With increased communication between departments and providing these visual
  tools created from a statistical standpoint to data management, we can help increase
data quality and hence contribution towards endpoints.