

Quick Checks for Quick Review

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ABSTRACT

The regulatory authorities require Integrated Summary of Safety (ISS) as a vital component in the submissions for the study drug approval. Similar to ISS, the Development Safety Update Report (DSUR) and IND Annual Report (AR) which are created periodically contain large amount of safety data pertaining to various clinical studies.

When numerous studies are integrated and large number of outputs is requested, reviewer's job to guarantee output consistency and integrity, with the individual underlying studies can be tedious. Furthermore reviewers have to perform checks on these voluminous data within a really short period of time.

This paper presents a tool which comes handy with a checklist. With this tool, there can be several verifications done, like the death/SAE counts, analysis upto a specified cut off date, some customized analysis so on and so forth, at one go. It aims at reducing the reviewers' effort and time spent for writing redundant pieces of codes to dig into the data.

INTRODUCTION

The ISS, DSUR or IND-AR deal which are done at regular intervals involve a large pool of data from number of studies. Since the data is accumulated over different studies over the same molecule or the indication, this metadata can be in large volumes.

To ensure the quality of the deliverables, a review serves to play a very significant role. The review of such huge amount of datasets and reports however, is a labor intensive and tiresome work. The time crunch for the reviews further worsen the matters for the reviewer, be it a programmer or a statistician.

So, what if there is a tool which will come to rescue in this scenario? This paper presents a utility "Quick Checks for Quick Review" which assists in a quick review of the pooled dataset. An endeavor to understand the "demographics" of the "data" using few in-built checks is made.

This tool with the help of a few checks can give a bird's eye view of the dataset. The assessor may then further dig into the data in the areas of concerns. Especially during tight timelines, this tool can be of great assistance as it helps save time.

The paper will cover the following aspects of the utility:

- ❖ Objective
- ❖ Layout
- ❖ Checks
 - ADSL
 - ADAE
 - ADAE
- ❖ Execution
 - Input
 - Output
- ❖ Challenges
- ❖ Enhancements

OBJECTIVE

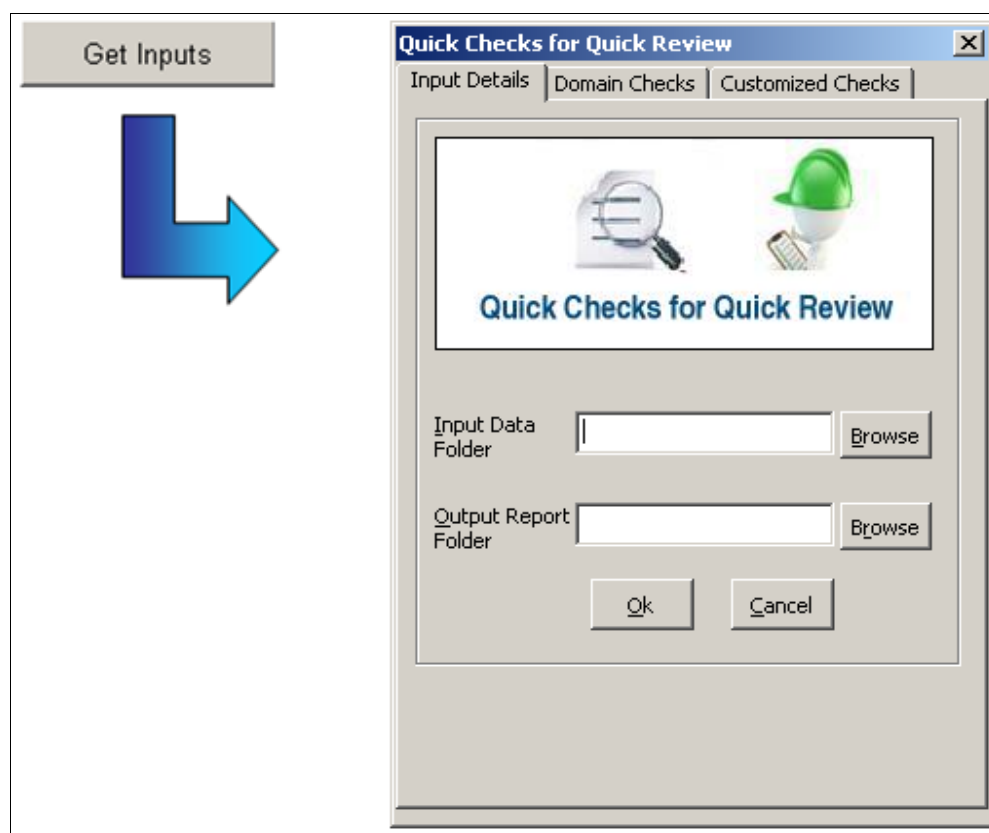
This tool aims at assisting the end user in getting a quick understanding of the data. The customized options help the reviewer to obtain information of interest from the large datasets with minimum efforts and time. Some of the benefits of using this utility are:

1. Increase in productivity
2. No pre-requisite of SAS® programming knowledge
3. Reusability
4. Verifications of some study numbers

LAYOUT

To ensure the utility is easy to use, the number of input parameters is set to the bare essentials. Below figure shows the first screen of the utility.

Figure 1: First Look

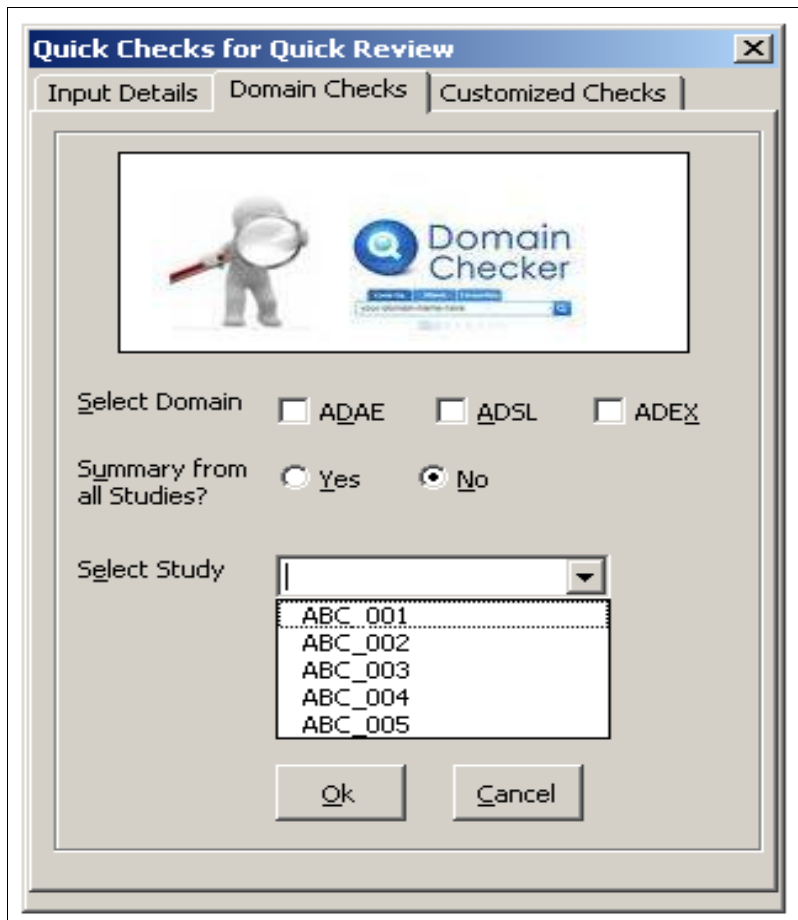


The reviewer is required to enter the input parameters through a VBA based user interface. This means the users are clear what parameters they are specifying, making them more in control and feeling less like they are using a black box. There are three tabs, one for providing the initial input/ output paths, the second for perform domain specific checks and the third to carry out customized checks as per the necessity. All the inputs that provided by the user are utilized in simple SAS macros that are executed in the backend to produce the desired outputs. Since only the parameters are to be defined, it is not mandatory for the user to be accustomed to SAS programming.

To start with the utility is prepared based on the assumption that the input datasets are CDISC standard compliant, thereby having some standard naming conventions. Also it is required to have the information from all studies compiled into a single metadata for each of the domains. Hence, in the input data folder which is defined by the user contains unique ADSL, ADAE and ADEX metadata.

CHECKS

Figure 2: Domain Checks Tab

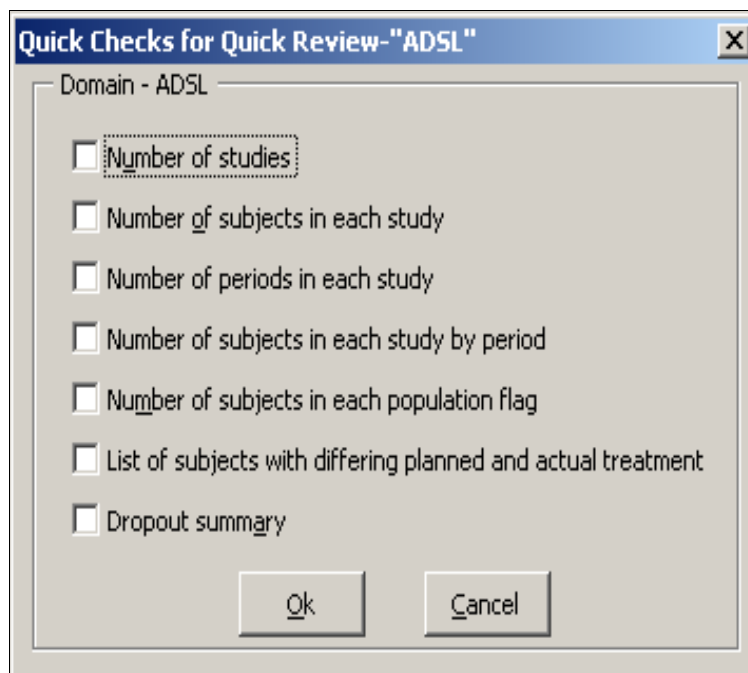


The utility comes handy with a list of checks that the user can choose as per the necessity and get the output report. The present version of the tool produces a report for some pre-defined checks on the domains ADSL, ADAE and ADEX. The domains of interest need to be selected through the checkboxes. By default, the utility gives the summaries for all the studies. If the exhaustive report from all studies is not required, then the user can select the specific study number from the drop down menu. This will restrict to the analysis to that particular studyid. From the description given, the checks are self explanatory and easy to understand. The utility covers the following checks –

1. ADSL

The Subject Level analysis data set forms the basic foundation for all the datasets. To peep into the demographics of the study, the following checks can prove useful:

Figure 3: Checks on the Subject Level Domain



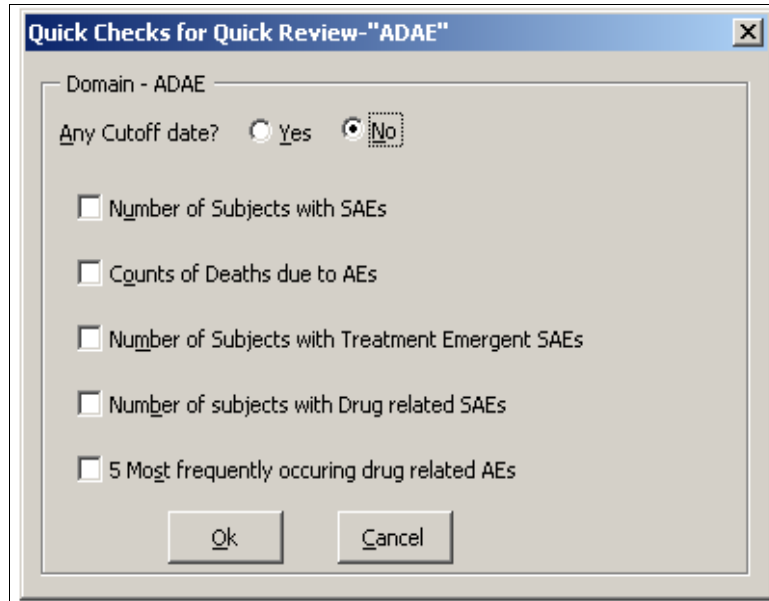
As elementary checks, the number of studies and the number of subjects belonging to each of the studyid present in the data will be summarized in the first two checks. To understand the nature and designs of the various studies, the number of periods and the patient counts in each period will be covered in the next two points. The ADSL data usually covers all the population flags information. So treatment-wise counts of subjects for each of the population flag like the safety, FAS and ITT will be reported if the fifth check is selected. It may also be of interest to a reviewer, to know if any subject does not receive the actual treatment as per the plan. A listing of all such subjects who have inconsistent planned and actual treatments will be made in the sixth point, Along with this, frequencies of dropouts from each of the study will be described on the last check.

These counts can be cross verified with the demographic tables, which can thus serve the purpose of a re-validation performed by the reviewer.

2. ADAE

The adverse event dataset plays a key role in assessing the safety of the study intervention.

Figure 3: Checks on the Adverse Events Domain



The screenshot shows a Windows-style dialog box titled "Quick Checks for Quick Review-ADAЕ". The dialog has a tab labeled "Domain - ADAЕ". Inside the dialog, there is a section "Any Cutoff date?" with two radio buttons: "Yes" and "No". The "No" radio button is selected. Below this, there are five checkboxes, all of which are currently unchecked:

- ☐ Number of Subjects with SAEs
- ☐ Counts of Deaths due to AEs
- ☐ Number of Subjects with Treatment Emergent SAEs
- ☐ Number of subjects with Drug related SAEs
- ☐ 5 Most frequently occurring drug related AEs

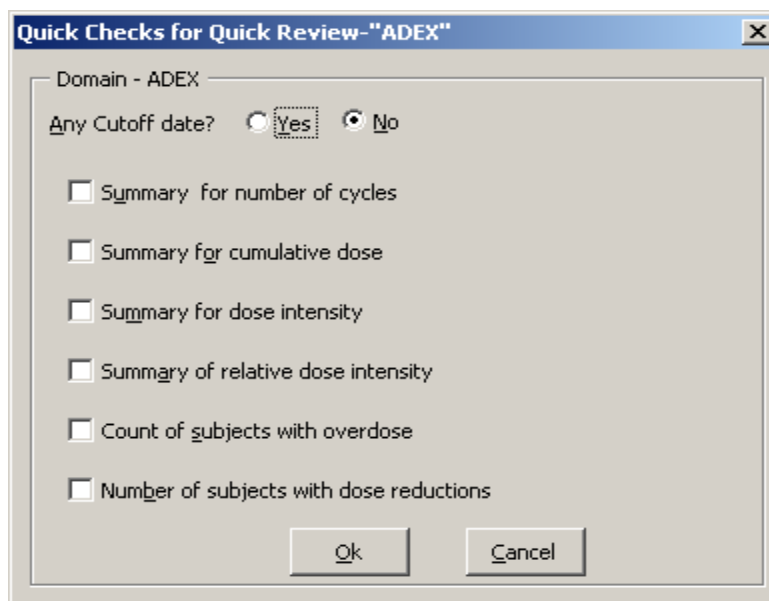
At the bottom of the dialog, there are two buttons: "Ok" and "Cancel".

For the ADAE dataset the utility provides study wise by treatment summaries for number of subjects experiencing serious adverse events (SAE), count of deaths due to AEs. The third and the fourth checks sum up the frequencies of subjects experiencing SAEs, but which are treatment emergent and drug related respectively. The last check in this group provides a list of the top 5 most frequently occurring adverse events which are related to the study drug.

3. ADEX

The Exposure domain covers the details of subject's exposure to protocol-specified study treatment. It is crucial in making decisions about safety and efficacy of study treatment. It is useful to examine the subjects' compliance towards the study treatment.

Figure 4: Checks for the Exposure Domain



Quick Checks for Quick Review-"ADEX"

Domain - ADEX

Any Cutoff date? ☒ Yes ☐ No

☐ Summary for number of cycles

☐ Summary for cumulative dose

☐ Summary for dose intensity

☐ Summary of relative dose intensity

☐ Count of subjects with overdose

☐ Number of subjects with dose reductions

Ok Cancel

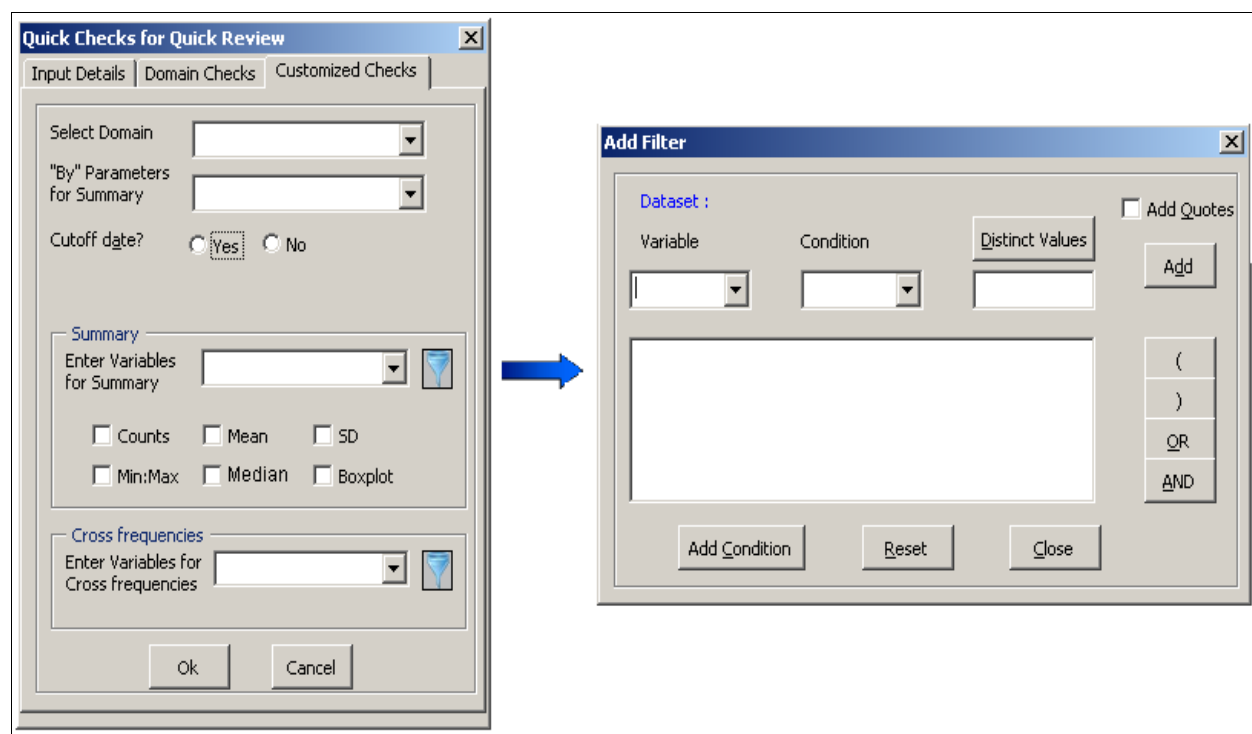
Exposure data is summarized to give the basic descriptive statistics for the number of cycles, the cumulative dose, dose intensities and the relative dose intensities. The numbers that are provided for these four variables are the mean, minimum and maximum. Similarly for each study, the counts of subjects with overdose and dose reductions will be calculated across the different treatment groups in the studies.

For the ADAE and the ADEX dataset, the tool gives the option of specifying a cutoff date. Once this date is provided, only the records with the event dates like AE start date or the cycle start date upto the cutoff timepoint will be considered. Thus the user will have the flexibility to have the analysis run upto a particular timepoint as required.

4. CUSTOMIZED CHECKS

It may also be important to investigate distributions of some variables or the cross frequencies of particular variables to explore the relationships amongst groups and so on. For this the user may require to repeatedly write and execute programs involving the means or freq procedures in SAS® for performing the analysis. The customized checks can help reduce the redundancy.

Figure 5: Customized checks and the Filter window pop-up



The customized checks can be made for the variables from any domain. An option of sub-grouping for any other variables can be made by choosing the right 'by' parameters for the summary. If any time span restrictions are to be levied, the same can be done by adding the cut-off date. Summaries and the counts for the cross tabulations can be performed for the variables. If any additional filter conditions need to be applied on the data, then same can be done through the 'Add filter' window that pops up after clicking on the filtering button.

EXECUTION

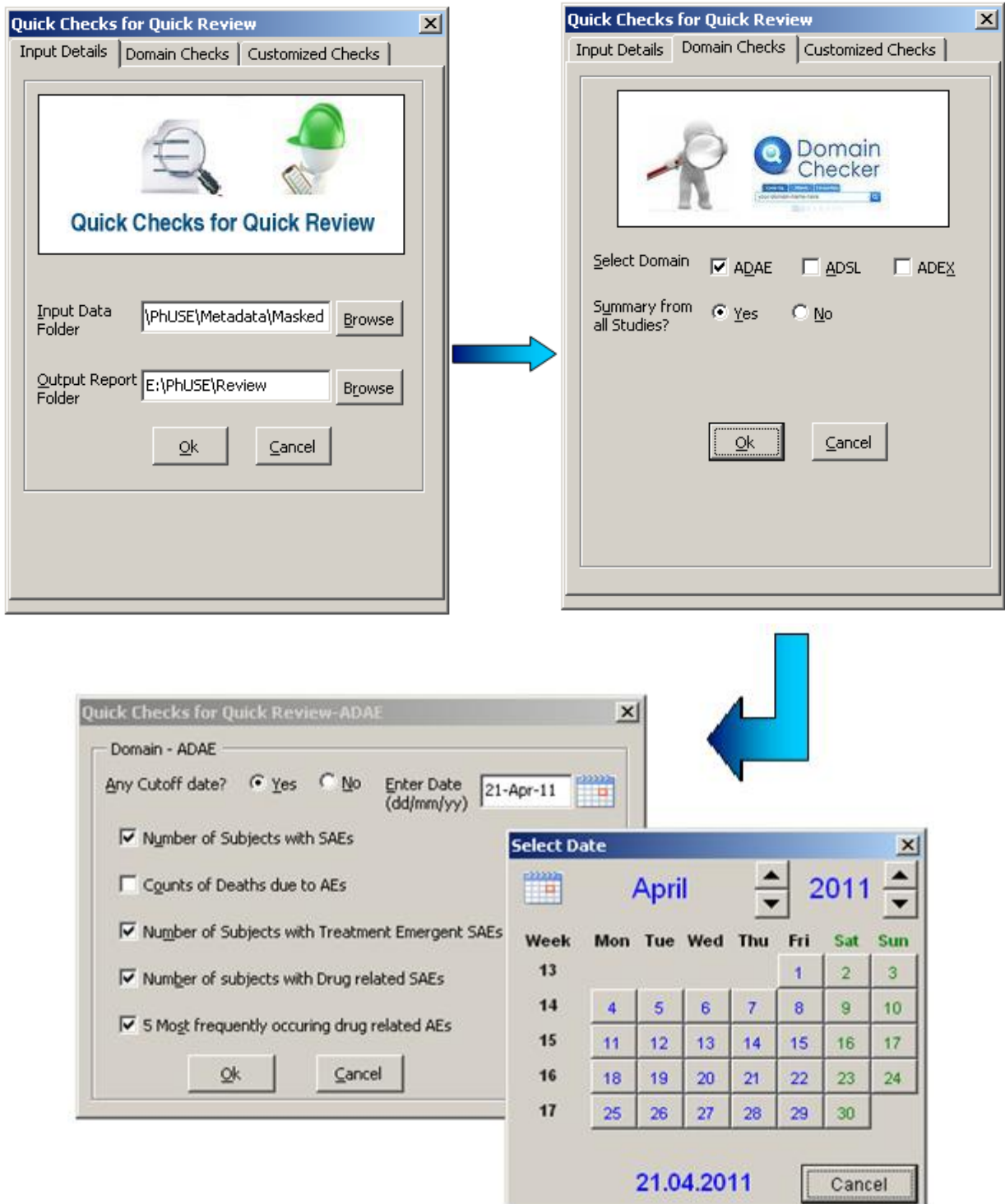
The illustration of the working of the utility can be seen through an example of the ADAE domain.

1. INPUTS

As the first parameters, the user is required to enter the path of the location where the metadata are placed and the path where the output report needs to be saved. Currently the tool is can be used for reviewing the subject level, adverse events and the exposure domains. This can be done through the 'Domain Checks' tab. Also some tailored summaries as per the requirements, for exploring the basics of the data, is possible through the 'Customized Checks' tab. As per the requirements the user can define the inputs by just clicking on the options of his/her choice and get a customized output from the tool.

PhUSE 2013

Figure 6: Inputs to the Utility



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2. OUTPUT:

The output of the utility is provided in a word document which will be placed at the path specified by the user. A separate document for each domain as well as the custom-made checks will be created with domain name, 'Customized Checks' as the filename. All the summaries answering each checkpoint selected will be reported in the documents with the appropriate titles for easy understanding. Below is an example of the inputs provided by the user and the corresponding output from the tool.

Figure 7: Snapshots of the Output ADAE.doc

02:24 Monday, September 02, 2013 1			
Number of Subjects with SAEs			
Analysis excludes observations beyond the cutoff date: 21 April 2011			
STUDY=ABC-003			
Obs	Treatment	Frequency Count	Percent of Total Frequency
1	Treatment 1	1	16.6667
2	Treatment 2	5	83.3333
STUDY=ABC-004			
+			
Obs	Treatment	Frequency Count	Percent of Total Frequency
3	Treatment 8	1	50
4	Treatment 9	1	50

02:24 Monday, September 02, 2013 2			
Number of Subjects with Treatment Emergent SAEs			
Analysis excludes observations beyond the cutoff date: 21 April 2011			
STUDY=ABC-003			
Obs	Treatment	Frequency Count	Percent of Total Frequency
1	Treatment 1	1	16.6667
2	Treatment 2	5	83.3333
STUDY=ABC-004			
Obs	Treatment	Frequency Count	Percent of Total Frequency
3	Treatment 8	1	50
4	Treatment 9	1	50

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02:24 Monday, September 02, 2013 3

Number of Subjects with Drug Related SAEs

Analysis excludes observations beyond the cutoff date: 21 April 2011

STUDY=ABC-003

Obs	Causality	Treatment	Frequency Count	Percent of Total Frequency
1	POSSIBLY RELATED	Treatment 2	1	100

STUDY=ABC-004

Obs	Causality	Treatment	Frequency Count	Percent of Total Frequency
2	PROBABLY RELATED	Treatment 8	1	50
3	PROBABLY RELATED	Treatment 9	1	50

02:24 Monday, September 02, 2013 4

5 Most Frequently Occuring Drug Related AEs (Probably/Possibly related)

Analysis excludes observations beyond the cutoff date: 21 April 2011

Obs	AEBODSYS	AEDECOD	COUNT	PERCENT
1	Gastrointestinal disorders	Nausea	20	20.6186
2	Gastrointestinal disorders	Vomiting	17	17.5258
3	Gastrointestinal disorders	Diarrhoea	12	12.3711
4	Gastrointestinal disorders	Abdominal pain	8	8.2474
5	Gastrointestinal disorders	Abdominal pain upper	5	5.1546
6	Nervous system disorders	Headache	5	5.1546

Thus with the help of the tool, by entering the desired inputs through a user-friendly interface, the outputs can be simply obtained at a click. This also does not require the user to be an expert in SAS programming. The basic formats in which the outputs are produced are easy to understand and interpret.

CHALLENGES FACED

The variables reported in the dataset heavily depend upon the study design of the trial. Also since the metadata consists of multiple studies, the designs are bound to be distinct. Hence extracting the correct information from the dataset taking into account the nature and plan in which the studies were conducted posed a challenge while developing the utility.

FUTURE ENHANCEMENTS

The current version of the tool is based on some pre-defined checks on only three domains. However there may be various other checks that are required by the reviewer. To cater to these requirements it is planned to address the following upgrades-

- Add checks on other domains like the laboratory, ECG, vital signs and so on.
- Shift tables to understand treatment-emergent patterns of shifts in grades of categories from baseline vs. post-baseline
- Summary for the worst post baseline CTC grades.
- Adverse events on or after one day of the infusion date.
- Other graphical options like the histogram, pie chart and so on.
- Flexibility to use datasets which are not ADaM compliant.

CONCLUSION

A good review of all datasets and documents takes time. Nevertheless it is an essential part in the process. With the help of the utility discussed in this paper, some simple checks can be made effortlessly to gain a glimpse of the bigger picture. Repetitive tasks can be performed more efficiently. This may set aside some valuable time for the reviewer's to focus on matters of greater concerns.

REFERENCES

CDISC ADaM Implementation Guide Version 1.0.

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CONTACT INFORMATION

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