Paper DM08

Working with a CRO/TPO Using SDD to Implement an Adaptive Design Clinical Trial Monitored by a DMC

Maruful Chowdhury Eli Lilly & co.
Barry Brolley, Eli Lilly & co.

ABSTRACT

Traditional clinical trials are in of themselves complex due to various factors, such as dictionary look-ups, conversion of tables, different ways of collecting case report forms, and so forth. Although adaptive trial designs have become more accepted, with the expectation of improvements such as greater dose selection, efficiency and earlier conclusions, these can be even more complicated, with patient allocation schemes and such. Furthermore, with adaptive designs, another level of complexity is added, if and when it becomes necessary for a separate Data Monitoring Committee (DMC) to be set up to review safety and efficacy data. SAS® Drug Development (SDD) will accommodate, or allow for, multiple entities to work on the same platform seamlessly, and so hopefully mitigate some of these complexities. However, there are then the challenges, for example, to ensure that the study data is blinded when the sponsor and the Contract Research Organization (CRO) both are working in SDD. This paper addresses the concerns and benefits of using SDD in a seamless adaptive design using a DMC and CRO.

INTRODUCTION

A large randomized multi-center clinical trial that is investigating a prospective new drug inherently possesses challenges, and so, is often fraught with difficulties in implementation and execution. It is also known that approximately 45% of all compounds in Phase 3 development fail due to lack of efficacy and/or safety (Kola and Landis 2004). Consequently, adaptive designs are starting to be employed, with the rationale that they may reduce late-stage attrition rates, improve selection of the "right" doses for Phase 3, or terminate development of ineffective or unsafe therapies earlier. An adaptive design uses accumulating data to make decisions on various aspects of the study, without undermining the validity and integrity of the trial (Gallo et al. 2006). In order to maintain the validity and integrity of the trial, the adaptations must, of course, be pre-specified. All clinical trials require safety monitoring (21 CFR 312.32-c), but not all trials require monitoring by a formal committee external to the trial organizers and investigators. However, in order to evaluate the validity and integrity, a DMC can be appointed by the sponsor to evaluate the accumulating outcome data in the trials. A seamless adaptive design allows trial objectives that are normally achieved through separate trials in Phase 2 and 3 to be addressed in a single trial. Specifically, the adaptive dose-finding design should lead to a dose selection decision of the type normally associated with Phase 2. With this seamless adaptive design framework, it is then best advised to involve an independent DMC to periodically review ongoing data for safety. When the study is double-blinded, with multiple combinations of investigational drugs that are being tested, the DMC will then need to see the un-blinded data as to provide recommendations. The DMC, for example, may suggest stopping enrollment of subjects in one or more treatment arms, if the adaptive algorithm is not working correctly. The algorithm may possibly be assigning subjects to treatment arms that have comparatively more adverse reactions. Since the sponsor may introduce bias, it is not advised for the sponsor to create and see the un-blinded tables that are to be reviewed by the DMC. Therefore, a separate, independent, part of the DMC, which has the statistical capabilities to analyze and create un-blinded tables for the original DMC to review, will need to be established. Furthermore, tables created independently by the CRO for DMC, require the CRO to access real time study data. This is necessary, because the need for consistency with sponsor look-up tables and dictionaries. Therefore, it is important for the CRO to be working in the same platform as the sponsor. SDD being a relatively new web based platform, enables multiple users simultaneously access, and so, was chosen as the platform, with the expectation that it would help alleviate some of the aforementioned complexities. However, SDD is in of itself a novel technology, and so might present challenges also. In this paper, various aspects of SDD that can help ameliorate some of the above concerns are highlighted.

STREAMLINING THE PROCESS USING THE CAPABILITIES OF SDD

In clinical trials, patient privacy is sacrosanct, and so the aforementioned data transfer from the sponsor to the DMC to generate un-blinded TFLs must be carefully planned. A simple hand-off of the CRF data between sponsor and DMC is then not advised. SDD, being a web-enabled GUI provides the opportunity where both sponsor and the DMC can work on real time study data and therefore, there is no need to transfer data between companies. SDD is also a stand alone application and hence the sponsor can create an SDD account for the DMC member without letting the DMC member access rest of the confidential company information and/or applications. However, this must be carefully planned in conjunction with IT or the SDD support group. It is important to allow flexibility for the DMC members to get help, and to access additional company specific SDD information, if stored outside of SDD.

Another feature of SDD is its ability to apply various levels of access control for files (objects) within folders (containers). For example, groups can be created with read and write, read only with no write, or no access at all. Groups who have no access to certain folders will not even see that the folder exists in SDD. This can be challenging and pose some minor issues however. Since the folder itself does not provide any information other than the folder name, not being able to see the folder can create confusion as to whether the folder actually exists or not, or whether someone accidentally deleted it or not. The benefit though, is that utilizing these various access restrictions in SDD can help to create a 'virtual firewall' between two groups, namely the sponsor and DMC member(s). It should be noted that in the implementation of this virtual firewall careful planning is necessary. In order to do this, the folder structure within SDD needs to be first created. The folder structure would contain a list of folders and sub-folders in which various operations by sponsor and the DMC members will be carried out. Separate groups with special access restrictions would then be created, one for the sponsor, and another for the DMC. DMC members would then be given read access to the sponsor area, and, of course to avoid bias, the sponsor would not be able to access the DMC work area. Before study data is un-blinded by the DMC members, this folder structure should be tested thoroughly to ensure that proper access restrictions are in place. This can be very challenging since SDD offers multiple level of access restriction based on files, folders, and groups created, and needs consultation with SDD support group.

Lastly, it is possible that a sponsor may be using their existing company standards in creating the reporting database, with corresponding Analysis Data Sets (ADS) and tables. Consequently the DMC may or may not be familiar with these. However, with proper access restriction in place, the sponsor can create a blinded reporting database, and hence still be consistent with the company standards. Note that the sponsor can create predefined blinded tables (Tables, Figures, and Listings – TFLs) that can be used by the DMC to monitor and review study safety, and provide recommendations. There are multi-fold benefits to this: the study reporting database can be integrated with other company study data to create integrated safety reports; the DMC members would spend less time working directly with the CRF data (which is not always easy to create tables from); and finally, having the tables created by sponsor again would save time for the DMC member as well. The final question that needed to be addressed was how the sponsor would create blinded ADS and TFLs, and then next provide them to the DMC for them to create un-blinded ADS and TFLs. It was found that, SDD offers the opportunity to create an input process where multiple libraries can be read in to execute ADS and TFLs codes. One of these input processes would be where the sponsor would create ADS and TFLs that are a 'scrambled' or 'blinded' treatment file, which the DMC member would then change to read 'unscrambled' or 'un-blinded' treatment file. This un-blinded treatment file would then reside in the DMC folder structure in SDD where the sponsor would have no access. This and the other before mentioned steps are outlined below:

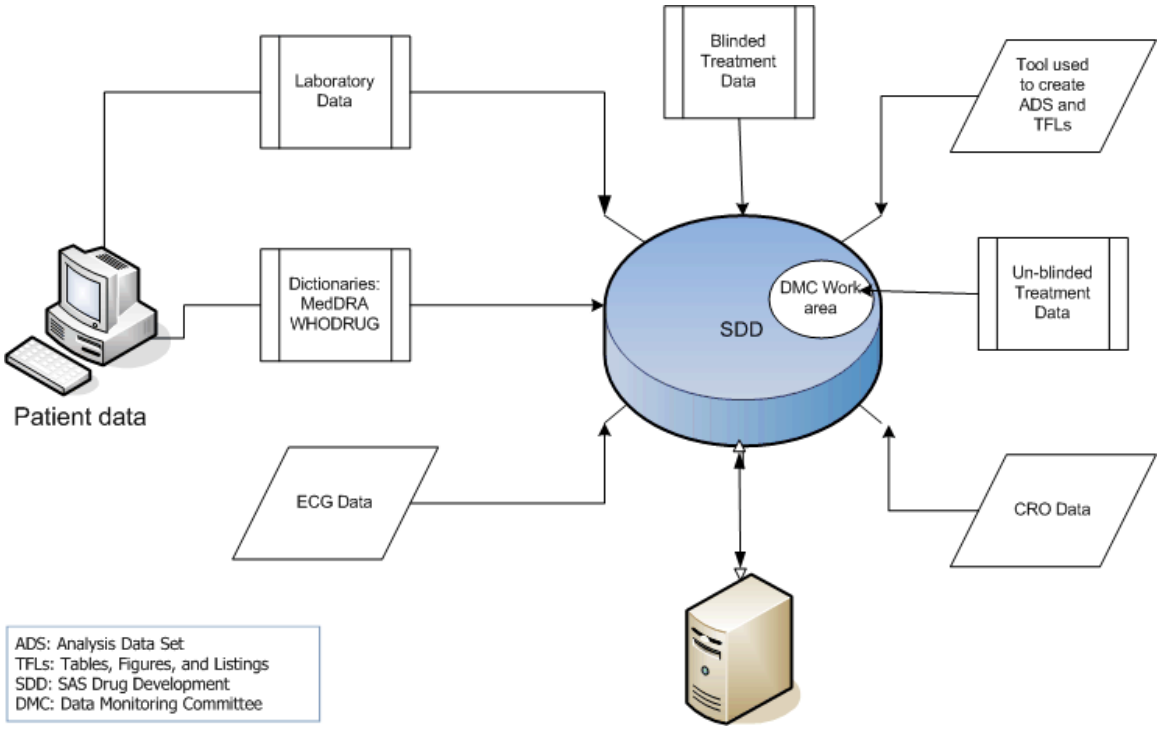

Figure 1. Diagram showing the multifarious and simultaneous processes for a successful implementation

CONCLUSION

Although many seemingly insurmountable difficulties were encountered at every turn, it was found that the benefits outweighed the risks. Therefore, it can be recommended that SDD be considered in such complicated scenarios as above, and may be beneficial. However, the learning curve is steep, and so, interested parties are encouraged to contact the authors with help in the implementation of SDD for an adaptive design utilizing a CRO and DMC.

REFERENCES

Department of Health and Human Services, Title 21 Food and Drugs, FDA Code of Federal Regulations 312.32 pp. 70-72

Gallo P, Chuang-Stein C, Dragalin V, Gaydos B, Krams M, Pinheiro J. 2006. Adaptive designs in clinical drug development - an executive summary of the PhRMA Working Group. J Biopharm Stat 16(3):275-283.

Kola I, Landis J. 2004. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 3(8):711-715.

ACKNOWLEDGMENTS

The authors would like to thank Mr. Zachary Skrivanek, Sr. Research Scientist, Eli Lilly & Company for his technical insights and review.

Contact Information

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

Maruful Chowdhury	Barry Brolley
Eli Lilly & Company	Eli Lilly & Company
Lilly Corporate Center	Lilly Corporate Center
Indianapolis, IN 46285	Indianapolis, IN 46285
maruful@lilly.com	brolleybn@lilly.com