PhUSE 2015

Paper TS07

Innovative approach to building an adaptive trial design in Medidata Rave®

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ABSTRACT

Recently, clinical trials with adaptive features have received much attention due to their efficiency and flexibility specifically because the trial can be redesigned while the study is ongoing. As a result, it is more informative and it is more likely to demonstrate an effect of the drug, if one exists.

An eCRF is always designed to be in-line with the visits and assessments as defined in the study protocol. Traditionally, protocols were written rigidly and therefore everything mentioned in the original protocol was fixed in the eCRF. Updates to the protocol, such as the addition of assessments or visits, resulted in an amendment of the original protocol with additional review rounds and a delay in the deployment of the amended protocol as result. On top of that, making updates to a Rave® design due to the protocol amendment can be a lengthy process because of the related migration process.
This is no longer acceptable from a timeline perspective when dealing with an adaptive clinical trial. Updates requested by the safety meetings need to be processed as soon as possible so all patients (ongoing and newly enrolled) can follow the amended schedule. Therefore, updates on the amendment need to be visible in the eCRF sooner rather than later.

Nowadays, protocols are written from a more flexible, adaptive perspective. The visit schedule can be adjusted or additional assessments can be made without the need for a protocol amendment depending on the outcome of safety meetings.
The protocols are written in such a way that, based on the safety meeting, modifications in the study conduct are allowed and are also clearly pre-defined. These modifications which may include, but are not restricted to, changes in study drug administration schedule, study drug administration, recommendations for best-supportive-care measures, pharmacokinetic or biomarker sampling times are allowed. A novel approach is needed from an eCRF design perspective to facilitate the implementation of adaptive trials to make sure IDMC decisions can be implemented as soon as possible.
SGS Life Science Services continues to broaden its experience in building eCRFs in EDC systems. One of the investments we are making is defining and implementing a novel approach for the adaptive trial design within Medidata Rave®.

This paper and associated presentation explain how an eCRF can be built with a future-proof adaptive design. At the start of a trial, the entire study team and relevant stakeholders will identify all possible data points that can be influenced by decisions made during the trial. Those data points will be designed so they can be added or removed during the trial without the lengthy process of a migration. All potentially necessary data points will be programmed at the trial start, but will be hidden at Go-Live. Using this methodology, updates to the trial design can be made available much faster than when using the traditional migration process.

We will share our experiences on how building an adaptive trial design can influence the general processes and which operational changes are needed. More importantly, we will evaluate the benefits and merits of future-proofing the eCRF to proactively cope with updates due to flexible designs during the trial. The most important criteria are no time lost and budget efficiencies by investing in the protocol and trial design phase.

INTRODUCTION

Per FDA Guidance for Industry[2], an adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. The term prospective here means that the adaptation was planned (and details specified) before data were examined in an unblinded manner by any personnel involved in planning the revision.
The range of possible study design modifications that can be planned in the prospectively written protocol (or a separate, but also prospective, statistical analysis plan (SAP), if used) is broad. Examples include changes in the following:

- study eligibility criteria (either for subsequent study enrollment or for a subset selection of an analytic population)

- randomization procedure
- treatment regimens of the different study groups (e.g., dose level, schedule, duration)
- total sample size of the study (including early termination)
- concomitant treatments used
- planned schedule of patient evaluations for data collection (e.g., number of intermediate time points, timing of last patient observation and duration of patient study participation)
- primary endpoint (e.g., which of several types of outcome assessments, which time point of assessment, use of a unitary versus composite endpoint or the components included in a composite endpoint)
- selection and/or order of secondary endpoints
- analytic methods to evaluate the endpoints (e.g., covariates of final analysis, statistical methodology, Type I error control)

This paper will demonstrate implementation options for changes to the "planned schedule of patient evaluations for data collection (e.g., number of intermediate time points, timing of last patient observation and duration of patient study participation)" using Medidata Rave®.

Medidata Rave® is an industry-leading electronic data capture and management platform for the capture, management and reporting of clinical, operational and safety data. Implementation of adaptive trial design concepts in other EDC-systems is possible but will require other technical implementation strategies.

RAVE® AMENDMENT MANAGER

To set the scene, let's quickly review the traditional process for applying a Mid-Study Update in Rave® via Amendment Manager[5]. Amendment Manager is a module within Architect that enables users to migrate existing subject data from one CRF version to another. The migration process is made up of five parts:

Figure 1 – Rave® migration process flow chart

Mid-Study Updates can have limited to wide impact on the eCRF. The typical turn-around time for implementing a limited change, e.g. adding 1 existing form in a new visit (folder), is 10 working days. As explained later on, smart but robust alternative implementation concepts can shorten the implementation time for adding additional e.g. PK sample time points, assessments in existing visits, or new visits.

PUBLISH CHECKS

The Publish Checks tool is designed to publish changes to edit checks, custom functions, or derivations within an existing Rave® CRF version outside of the migration process. The typical turn-around time for going through a complete publish check process is 2 working days.

THE INNOVATIVE APPROACH EXPLAINED

Traditional eCRF builds perfectly reflect the Time & Events schedule in the Clinical Trial Protocol; i.e. the specified visits, assessments and data points are made available via the EDC-system for data entry by the site staff. Additional visits, assessments and data points that need to be added after eCRF go-live require a migration process in Rave®.

To speed-up the release of the updated eCRF - after agreement of the study team – based on the updated Time & Events schedule, it is possible to already foresee extra visits, assessments and data points behind the scene at the time of the initial build, but no yet showing these extra eCRF items to the end-user. E.g. in case the original protocol defines a visit on 'day 1', 'day 2', 'day 3', 'day 4' and 'day 8', and the study team anticipates that a 'day 5' might need to be added later on, this 'day 5' can already be configured in the Rave® design environment. Within this 'day 5' visit a set of expected eCRF forms can be loaded. Later on, when the 'day 5' needs to be added, Rave® checks can trigger the extra 'day 5' visit with the selected eCRF forms from the list of pre-loaded forms.

As a result, no Rave® migration process is needed but instead a publish check process can be used, reducing the implementation time with 8 days (2 working days for publish checks versus 10 working days for a migration process).

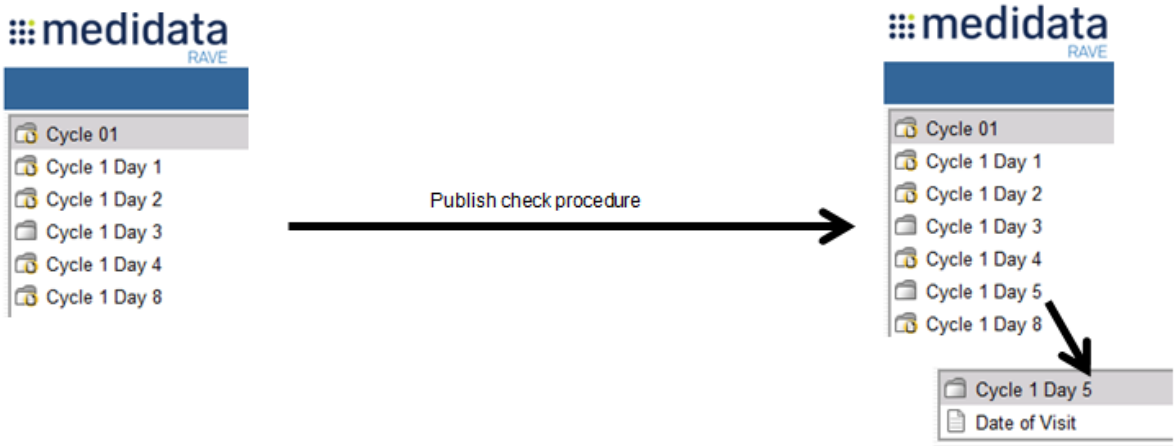

Figure 2 – Adding the 'day 5' visit with a selection of pre-loaded eCRF forms to the eCRF via the Publish check procedure

Similar dynamic behavior is possible for defining the PK sample time points in the eCRF. A Custom Function can add the PK sample time points for the applicable visits as needed starting from a single eCRF page design. The Custom function code snippet below figure 3 adds the planned time points for visit "DAY1" as shown in the upper screenshot of below figure.

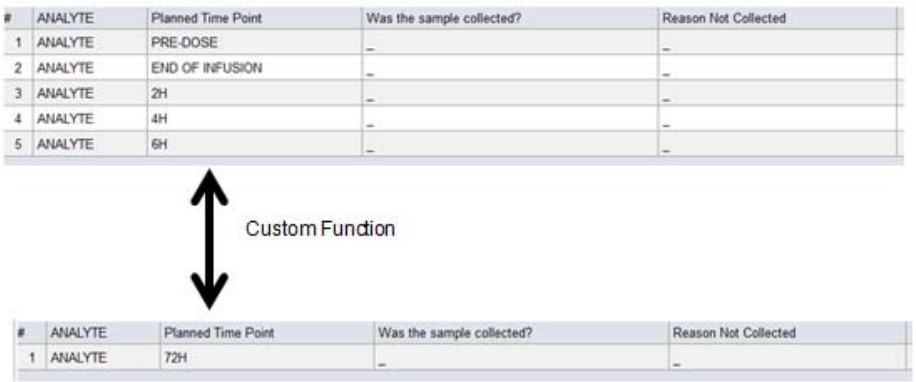

Figure 3 – 2 PK eCRF forms with sample time points as defined in a Custom Function

```
object[] TObject = (object[]) ThisObject;
Subject subject = TObject[0] as Subject;
DataPoint dpAction = TObject[1] as DataPoint;
string parentFolder = (string) TObject[2];
string childFolder = (string) TObject[3];
int numberOfLogLines = (int) TObject[4];
int studyPart = (int) TObject[5];
Instances insAllParents = dpAction.Record.Subject.Instances;
DataPages dgsPC = new DataPages();
foreach (Instance insParent in insAllParents)
{
    if (insParent.Folder.OID == parentFolder)
    {
        Instances insAllChilds = insParent.Instances;
        foreach (Instance insChild in insAllChilds)
        {
            if (insChild.Folder.OID == childFolder)
            {
                DataPage dgPC = insChild.DataPages.FindByFormOID("PC");
                if (dgPC != null)
                {
                    dgsPC.Add(dgPC);
                }
            }
        }
    }
}
if (dgsPC.Count > 0)
{
    foreach (DataPage dg in dgsPC)
    {
        if (numberOfLogLines > 1)
        {
            for (int i = 1; i < numberOfLogLines; i++)
            {
                dg.AddLogRecord();
            }
        }
        if (studyPart == 1)
        {
            if (parentFolder == "C1")
            {
                if (childFolder == "Day1")
                {
                    for (int i = 1; i < dg.Records.Count; i++)
                    {
                        Record rd = dg.Records[i];
                        DataPoint dpPCTPT =
rd.DataPoints.FindByFieldOID("PCTPT");
                        if (i == 1)
                        {
                            dpPCTPT.UnFreeze();
                            dpPCTPT.Enter("PRE-DOSE", string.Empty, 0);
                        }
                        else if (i == 2)
                        {
                            dpPCTPT.UnFreeze();
                            dpPCTPT.Enter("END OF INFUSION", string.Empty, 0);
                        }
                        else if (i == 3)
                        {
                            dpPCTPT.UnFreeze();
                            dpPCTPT.Enter("2H", string.Empty, 0);
                        }
                        else if (i == 4)
                        {
                            dpPCTPT.UnFreeze();
                            dpPCTPT.Enter("4H", string.Empty, 0);
                        }
                        else if (i == 5)
```

visit definition

time point definitions

```
                        {
                            dpPCTPT.UnFreeze();
                            dpPCTPT.Enter("6H", string.Empty, 0);
                        }
                    }
                }
            }
                ...
        }
    }
}
return null;
```

NEXT STEPS?

The approach of using publish checks for making additional visits, assessments and data points is valid and can be used for both trial adaptive protocols and non-trial adaptive protocols, but when building very large study designs Rave® is requiring much more time for some steps of the publish check process which might lead to system time-out issues - i.e. just adding a very wide range of potential visits, assessments and data points is to be avoided. It is therefore important that the clinical study team discusses the eCRF requirements with the technical staff to come to an eCRF build that is ready for future study design changes within the technical Rave® boundaries.

CONCLUSION

The concept of adaptive trials is being supported by regulatory authorities[1,2,3] for quite some time now. The challenge of implementing an adaptive trial methodology is however still work in progress, as it requires both the proper technology and a set of strong, unified processes and last but not least good teamwork[4]. Adaptive trials are complex and require a great deal of planning and diligence to complete. Executed correctly, adaptive trials can save sponsors millions of dollars in drug development costs by streamlining the trial conduct process. The earlier you can determine that a drug is not effective, the earlier you can either drop an arm in favor of a more promising one or the earlier you can stop a trial altogether. Some key points around adaptive trials to remember are:

- Adaptive trials represent the best opportunity to reverse the current productivity trend and will be used at scale in our industry moving forward. Sponsors and vendors who have prepared will be the ones who are most successful.
- Working closely with all stakeholders in the clinical development process to plan the road-map for adaptive trial implementation is a critical element of success.
- Don't forget – it's not just technology! It's also processes and organizational impact that need to be addressed.

REFERENCES

1. European Medicines Agency (EMA) – Reflection Paper on Methodological Issues In Confirmatory Clinical Trials Planned With An Adaptive Design (October 2007)
2. US Food and Drug Administration (FDA) – Draft Guidance – Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)
3. US Food and Drug Administration (FDA) – Draft Guidance – Guidance for Industry Adaptive Design for Medical Device Clinical Studies (May 2015)
4. Anne Kulak, Adaptive Trials Are Here… Are You Ready?, Geeks Talk Clinical (October 2014)
5. Medidata Rave®, Amendment Manager Training Manual (May 2013)

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