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Supporting End to End Standards in Study Set Up

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ABSTRACT

Ensuring consistently high level compliance to data standards in studies is a challenge. Embedding standards from protocol development to eCRF set up and through to submission is a positive way to ensure the benefits of standards are realized at all stages of the clinical trial.

In Roche Pharma Research and Early Development (pRED), Clinical Data and Information Sciences (CDIS) are developing tools to support 'end to end standards'. One such tool is an eCRF specification, at the variable level, that is created directly from a new protocol schedule of assessments tool using global library standards. The aim of the tool is to promote and encourage the use of standards. As well as being used for eCRF specification, the tool will also be able to directly load the agreed standards into Medidata Rave® to start eCRF build.

INTRODUCTION

In Pharma Research and Early Development (pRED) at Roche a new tool was developed in 2012 to support protocol writing. The outcome was a single set of Synopsis and Protocol Templates that can be used for all pRED clinical studies. These templates allow for therapy area specific text to be added at the touch of a button. They also ensure that standard wording for assessments are used across all studies/therapy areas which will further simplify the database set up. In addition, to support the data collection, a tool to create an optimized schedule of assessments (SoA) tool was also produced, ensuring that scientific and operational needs were reflected. The SoA tool is in excel format which also uses standard definitions for assessments.

Once approved the data from the SoA is translated into an eCRF design specification which the study data manager provides to the Clinical Database Programmer to use to build the study in Medidata Rave®. The important aspect is that the specification has a clear relationship to the assessment names in the eCRF standards, helping compliance to CDISC-CDASH standards. During the development of the SoA tool an opportunity to further assist standards compliance was identified

The idea was to enhance the SoA tool to provide variable level specifications which can then be uploaded into Medidata Rave® Architect using the Architect Loader. Using this enhancement to the tool will not only reduce set up time via uploading the specification rather than copying in each variable from the global libraries, but it will also improve standards compliance up front. Improved standards compliance in set up will reduce the need for additional extraction/mapping program updates to create the SDTM data sets at the end of the study.

In addition, using the tool will bring forward the discussion on standards therefore allowing more time in the study setup cycle for any deviation requests to be submitted and discussed if required. By agreeing to standards earlier in the process it will allow for study specific assessments to be the focus of eCRF review meetings, and less chance of last minute change requests slipping through. The intention is that the end result from using the tool will be that standards are seen as the time saver/quality enhancement they should be rather than an obstacle for studies, especially experimental/adaptive design studies, and the reason for delayed UAT due to late change requests.

EMBEDDING STANDARDS DURING PROTOCOL DEVELOPMENT

During the authoring of the protocol, data standards were not often considered a priority and it was only when it came to the eCRF set up and review meetings that deviations to standards were requested due to the protocol

requirements and the way it was worded. Sometimes these deviations could have been avoided if the impact on standards had been discussed during the protocol review. As a result of the protocol template initiative updates were made to ensure that the data we collect complies with industry standards.

The single protocol template produced by the initiative can now be used for all pRED studies and this helps to ensure that the basic standard safety and therapeutic assessments are described in a consistent manner which makes data collection and eCRF setup more straightforward (see Fig 1).

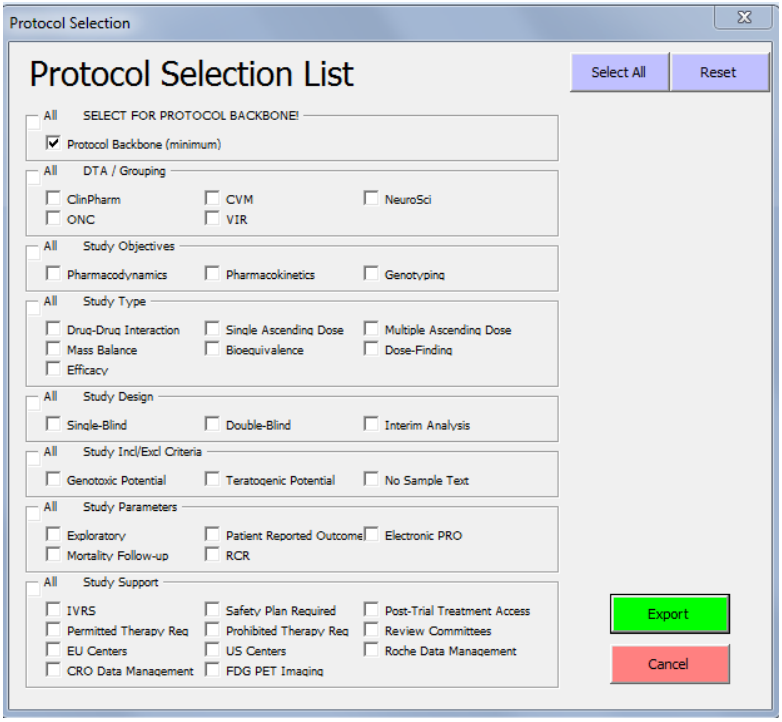


Figure.1: Protocol selection

THE SCHEDULE OF ASESSSMENT TOOL (SoA)

The SoA tool, designed alongside the protocol template, further supports the use of standards. It is pre populated with the standard safety and therapy area assessments. The therapeutic assessments that appear at the study level will depend on the library selected in the selection sheet (see Fig. 2).

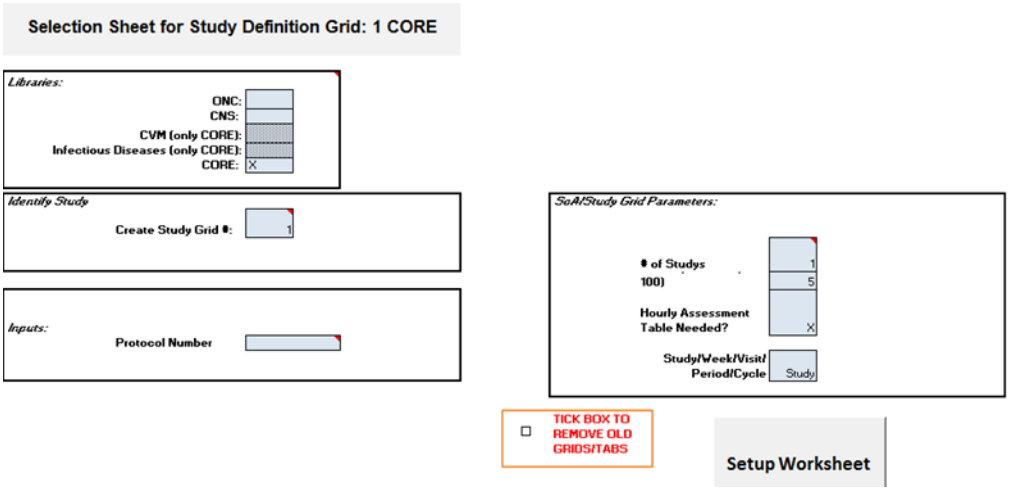
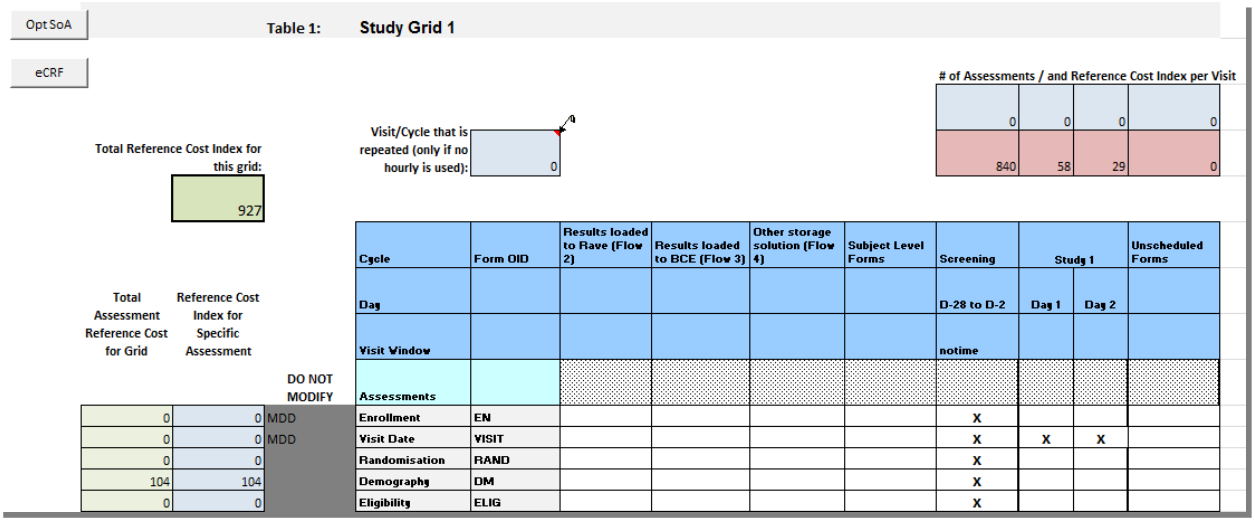


Figure 2: Selection sheet for study grid (SoA)

The next step is that the study scientist can then select which of these assessments are required for the study and assign them to the appropriate visits and time points (see Fig.3). It also provides a total cost estimate for the assessments selected. The study data manager can provide assistance to the study scientist with the SoA set up. By being involved at this early stage the study data manager can ensure that the standards assessments are not changed unless absolutely necessary, and that sufficient information is present to enable the building of any

additional study specific eforms. The important point here is that even study specific eforms need to be mapped in to SDTM and this needs to be considered during the eCRF build.



Opt SoA | Table 1: Study Grid 1

eCRF

# of Assessments / and Reference Cost Index per Visit

0	0	0	0
840	58	29	0

Total Reference Cost Index for this grid: 927

Visit/Cycle that is repeated (only if no hourly is used): 0

Total Assessment Reference Cost for Grid	Reference Cost Index for Specific Assessment	DO NOT MODIFY	Cycle	Form OID	Results loaded to Rave (Flow 2)	Results loaded to BCE (Flow 3)	Other storage solution (Flow 4)	Subject Level Forms	Screening	Study 1		Unscheduled Forms
			Day						D-28 to D-2	Day 1	Day 2	
			Visit Window						notime			
			Assessments									
0	0	MDD	Enrollment	EN					X			
0	0	MDD	Visit Date	VISIT					X	X	X	
0	0		Randomisation	RAND					X			
104	104		Demography	DM					X			
0	0		Eligibility	ELIG					X			

Fig. 3: Optimised study grid (exported to SoA for protocol appendix)

For both the SoA tool, and protocol template, cross-functional teams were set up. Having the input and buy in from the various stakeholders was critical. Once the template and SoA were rolled out and used in studies, ongoing feedback from users commenced. Since the roll out updates have been made to both tools to provide further improvement based on user feedback.

THE STANDARDS SPECIFIC ENHANCEMENT

Currently the SoA is translated to the eCRF design specification at the assessment level (e.g. Vital signs, Urine sampling) and the Clinical Database Programmer refers to the protocol, footnotes and standards guidance documents to decide which data collection variables to include in the eCRFs. They then rely on study team meetings/eCRF review discussions for the agreement on what to include in the final eCRF. With this method it can result in decisions being made at a late stage and last minute requests for deviations from standards. This can impact study timelines, which often comes as a surprise to study team members as they do not realize the impact a relatively minor change could have on study set up as well as extraction/mapping programs further downstream.

The solution proposed was to further enhance the SoA tool to create a variable level detail for an eCRF Design Tool which can also then create a file that can be uploaded in to Rave® Architect via the Architect loader (see Fig 4.). The upload would perform the first stage of study set up, adding all the standard folders, eForms and field edit checks required for the study.

The tool will contain all the standards available in the pRED Rave® global library volumes. Currently this is the core safety standards (compliant to CDASH and SDTM) and Oncology and CNS specific standards that comply with SDTM mapping requirements.

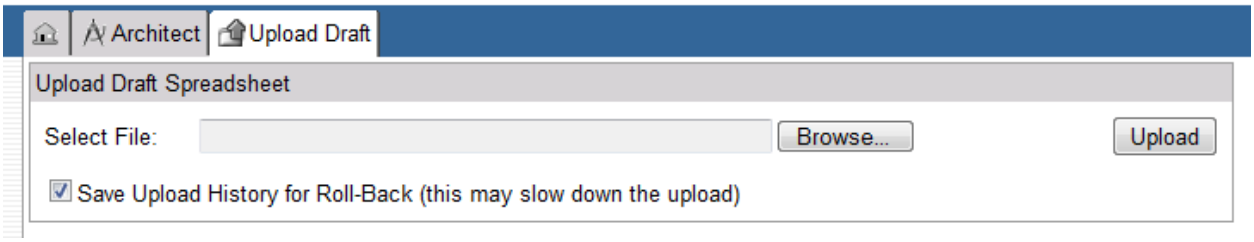


Fig.4 Rave® Architect Loader

ECRF DESIGN TOOL

Once the SoA has been approved this can be extracted into a word document that can be inserted in to the protocol. The next step would be to select a button on the optimized study grid for eCRF worksheets to appear. This will then list all assessments selected as required for the study and will provide all the associated standard variables available in the global libraries. This means that when it comes to reviewing standards the study team will only need to look at standards applicable to the study rather than the full deck in the pRED Rave® global libraries. The study data

manager can then select the variables required for each assessment (eCRF). Each variable will also have guidance on their use. (See fig 5)

Opt eCRF

	Form OID	FieldOID	PreText	Add to Form (X)	Type	In Study Grid(s)	Recommended Parameters/Units	Comment - Unique Grid Information	Justification	DSC Approved	Guidance
Demography	DM					**0**					
Demography	DM	**DSSTD_DC**	**Date of Consent**	X	**REQUIRED**	**0**	**dd mon yyyy**				**Required:** Date the patient or patient representative signed informed consent to participate in the study. Age of subject is derived from this date.
Demography	DM	**AGE**	**Age**		**REQUIRED**	**0**	**years**				**Required:** Inlcude in all pRED studies unless local country ethics dictate otherwise otherwise. The date from which age will be derived is Date of Consent. Age unit defaulted to Years. For paediatric studies refer to Data Dictionary on wiki (units are optional) Age is required for laboratory range setting. Please refer to SDM Study Planning and Set up Checklist for guidance on collection of Birth Date and calculation/collection of age.
Demography	DM	**SEX**	**Gender**	X	**REQUIRED**	**0**				No	**Required:** Subset of F and M used for pRED Core Standards Can be defaulted for single sex studies. Sex is required for laboratory range setting.

Fig 5: eCRF Design Specification

To ensure the standards essential for reporting are included in all studies, all 'Required' and 'Recommended' variables listed in the tool, as defined by a pRED Roche initiative in 2012 (with reference to the SDTM implementation and CDASH guidance documents), will be pre populated for inclusion (with an X in Add Form column). If additional optional variables are required the study data manager can populate the column with and X but will also need to enter a short justification to ensure they are only collecting data required for the study and not just because it is there for selecting.

As with the SoA once the study data manager has completed selecting the variables required for the study the worksheet can be optimized by selecting Opt eCRF button (see top left of fig 5.) which will remove any variables not needed. This will allow the reviewers to concentrate on what is selected for the study. This should avoid study teams being overwhelmed by too much data as well as reducing the likelihood of selecting variables that are not going to add value to the study.

As the document is to be used as the eCRF specification, any changes to standard labels/formats or object identifiers should also be recorded in the tool. As a result the spreadsheet is programmed to highlight any changes made by the cell turning red. The study data manager would then need to submit a change request to the standards committee and the cell affected would only go back to the original colour once confirmation that the change has been approved has been given.

The tool will incorporate all available standards (Safety and therapy specific) and also allows for the specification of additional study specific eforms if required. With another touch of a button a spreadsheet suitable for direct upload into Medidata Rave® via the architect loader can be created. Specific SAS programs will be written to ensure the data is in the correct format and suitable for uploading by the clinical database programmer. Any changes to standards made in the tool will be populated on a separate worksheet so that the programmer can make manual updates in Rave® architect after the initial upload.

With all the documentation being in one spreadsheet, all discussions around standards and any changes requested are clearly documented. The impact of changes will also be clearly visible to study teams and in theory should encourage increased compliance. This will then reduce time spent during extraction updating the programs required to map the data into SDTM for reporting.

CONCLUSION

The protocol template and SoA tool are currently being used in half of all the new pRED studies. The developers and project leaders are continuing to monitor user feedback. The feedback received so far has been vital for improving the user satisfaction. The improvements have been important in ensuring that the uptake continues to grow and the benefit of having a flexible 'one fits all' template is realised.

In order to further support the user and ensure the aim of embedding standards early in the study is not lost, the study data manager needs to be brought on to the study at an earlier point in protocol development than previously, or at least have data management support with expertise in the tool available. With this new process the discussions on data collection standards can start earlier and the pRED Data Standards Committee will receive deviation requests towards the beginning of study set up rather than after the eCRF review meetings which is sometimes very close to 'go live'.

The eCRF design and upload functionality of the tool is still in development. Once rolled out user feedback on this aspect will be equally as important. The members of science who have been shown the tool have shown a positive

interest in being able to clearly see the standards available for their study and the impact of making even small changes. If however the main users of the tool are not happy with the eCRF design and upload functionality, there is the danger they will continue with the current method of eCRF build, where building is done directly in Rave, which is harder to monitor up front. The study team need to see that ensuring standards compliance up front, rather than from monitoring via compliance reports prior to UAT, will reduce the bottle neck just before go live, as well as improving the quality of the SDTM output provided to the statistical programmers at the end of the study. This will be demonstrated during initial pilots and through the roll out of the eCRF design and upload functionality of the SoA tool across pRED studies.

CONTACT INFORMATION

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