

Review of Case Report Tabulation (CRT) packages

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ABSTRACT

The FDA requires all new drug applications (NDAs) be submitted electronically. For Statistics and Programming this involves creating the Case Report Tabulation (CRT). In this paper, we describe the process we follow at GSK when carrying out review of CRT packages.

Covering both SDTM and ADaM deliverables, we aim to highlight the issues we have encountered with the content of the CRT package itself along with the challenges faced with packages received from a CRO. We will also highlight common issues we have encountered during the review. Finally, we are providing some hints and tips for an effective review based on our experience and give you our proposal for a better CRT experience.

INTRODUCTION

One of our core principles at GSK is to focus on quality culture, governance and compliance. To support this principle, we have been performing thorough, in-depth reviews of the CRT packages. This paper aims to give an insight into how we carry out the reviews of both SDTM and ADaM CRT packages at GSK to produce what we consider a quality package.

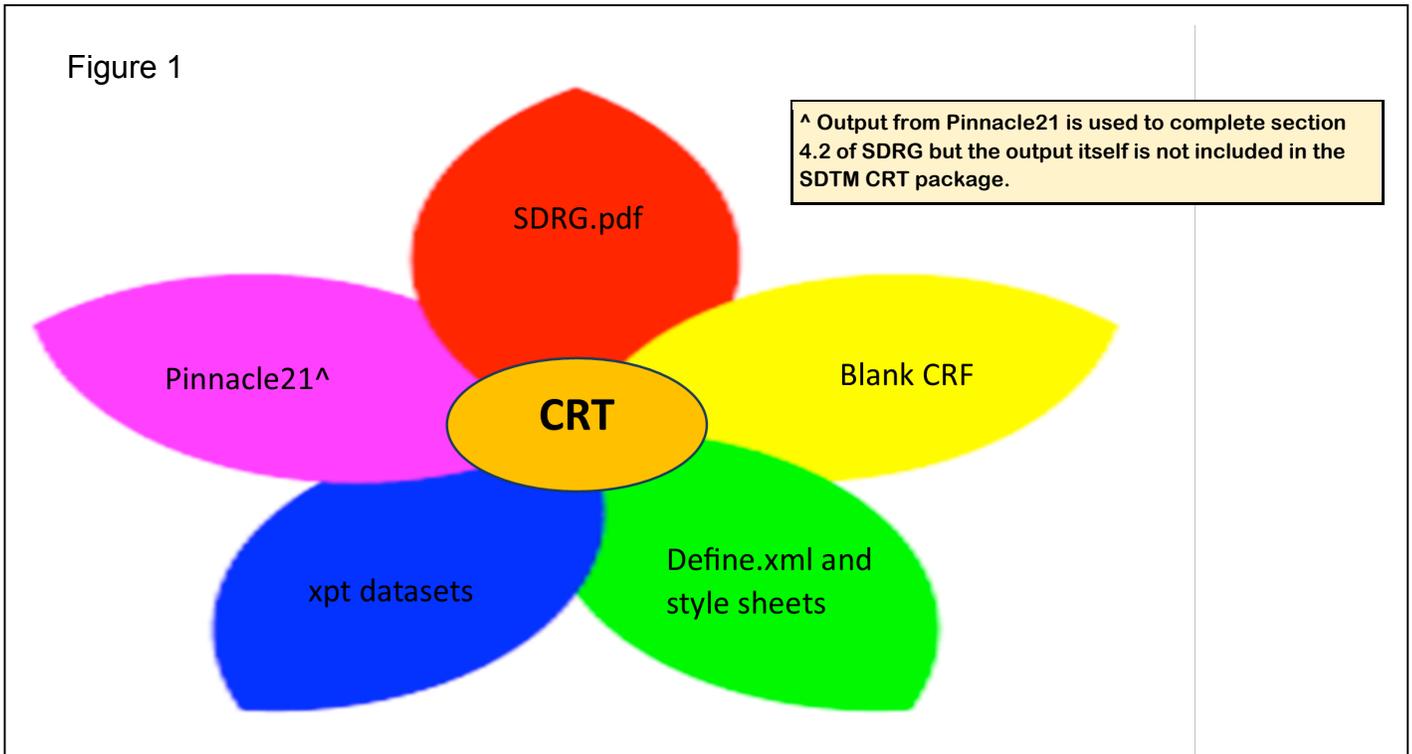
DISCLAIMER

The scope of this paper is to present an insight into how GSK carries out the review of CRT packages and as such any opinions, views or suggestions stated within this paper are those of GSK, and they are not necessarily correct.

It is understood that a review of this paper may invoke a reaction of 'that's not how to review it.' Hopefully it will also invoke a debate / discussion of our procedures.

REVIEW OF SDTM CRT PACKAGE

Figure 1 shows a beautiful flower to represent the complete SDTM CRT package, with each constituent part represented by a petal. These are the five constituents of the SDTM CRT package which includes Study Data Reviewers Guide (SDRG.pdf), Pinnacle21 report, Blank CRF (contains SDTM variable mappings. This is also known as aCRF), XPT datasets (transport files created from SDTM datasets), Define.xml and style sheets. Note that the required naming convention for FDA submissions is now cSDRG.pdf



In GSK, accountability for SDTM falls under Data Management (DM), and they are responsible for ensuring data quality and compliance with CDISC standards. The creation of SDTM within GSK is currently outsourced to a 3rd party vendor who maps the aCRF data to STDM standards, and the review is a collaboration between DM, Data Quality Lead (DQL) and statistical programming. If the SDTM CRT package is created by a CRO, the Clinical Data Acquisition and Delivery (CDAD) provides further technical support on reviews.

The main checks are being performed by DM, DQL and CDAD which includes review of hyperlinks, derivations, bookmarks, source, reviewer's guide (SDRG) and Pinnacle21 report. However, the programming group will support the review a SDTM CRT package to insure the package is "submission ready" and that there will be no surprises when the package is sent to the regulators (i.e, FDA).

Figure 2 on page 4 shows the flow diagram of the review process we follow with the collaboration between DM, DQL and Programming.

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The programming review consists of two parts:

1. Validate the package – please see beige boxes in Figure 2:
We import the whole SDTM CRT package (define.xml, xpt datasets, aCRF, SDRG etc..) into our in-house reporting systems called HARP and this import performs a series of validation checks. This is the list of ERRORS that HARP helps to identify which need to be addressed by vendor or CRO:
 - CRF page is listed twice for the same variable
 - Duplicate entry within a Controlled Term
 - TYPE for a variable not missing

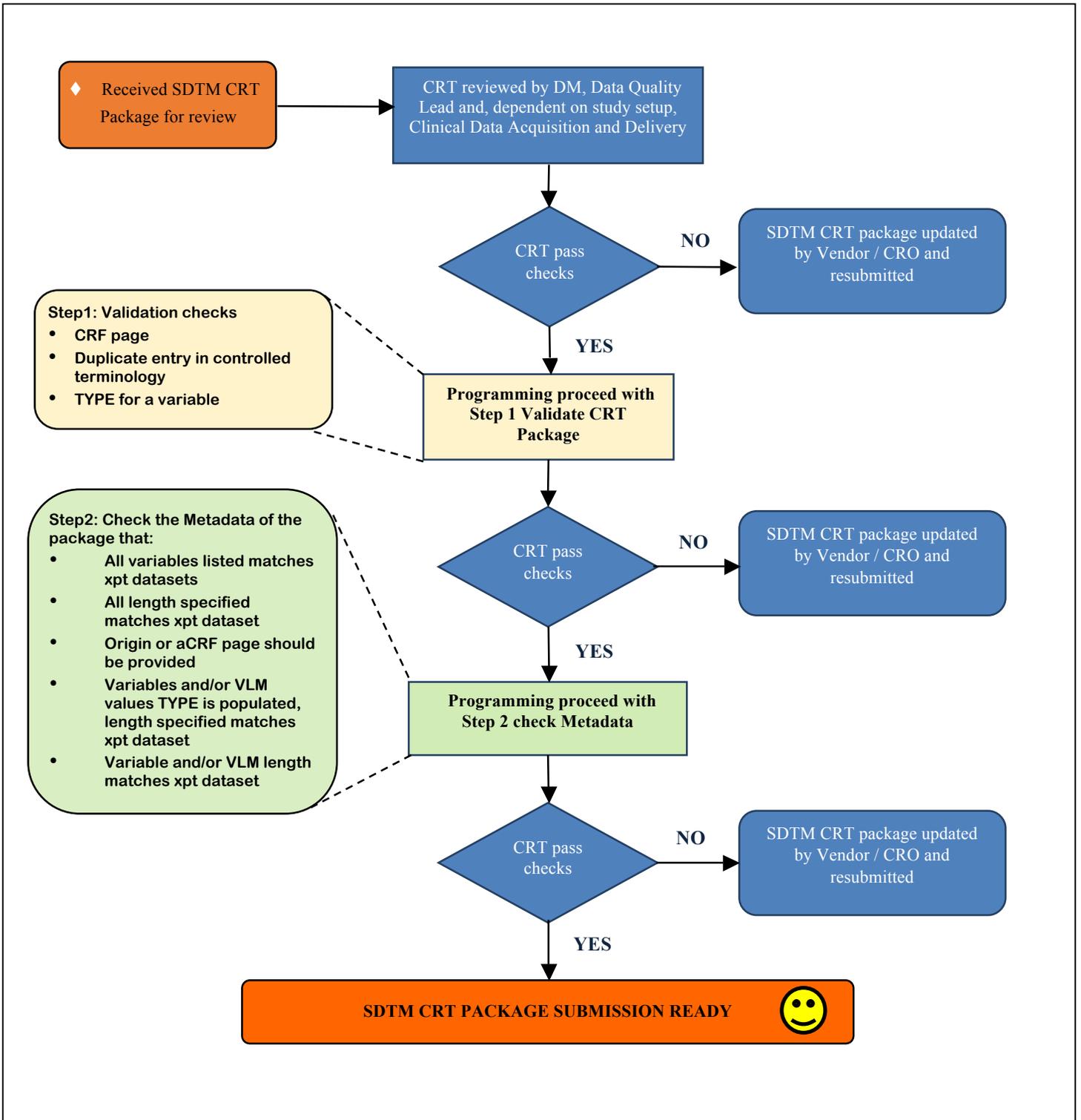
If the first review step was successful, proceed to the second step.

2. Check the Metadata – please see green boxes in Figure 2:
This is the list of ERRORS that HARP helps to identify which need to be addressed by vendor or CRO:
 - One or more variables contained in the actual dataset that are not in the define.xml
 - Length specified does not match what is in the actual dataset
 - Origin or aCRF page is not provided
 - Variables and/or VLM the value of TYPE is not TEXT, INTEGER or FLOAT. LENGTH is not provided or LENGTH does not match the length of variable in actual dataset.
 - Variables and/or VLM has a LENGTH of 0

Any ERRORS are fed back to DM, DQL and CDAD so that they can be reported back to the vendor/CRO to address. A new CRT package is received from the vendor/CRO and the process will be repeated to (1) validate the package and (2) check the metadata.

If both these tasks complete successfully and DM, DQL and CDAD confirms the quality is in place then the SDTM CRT is submission ready.

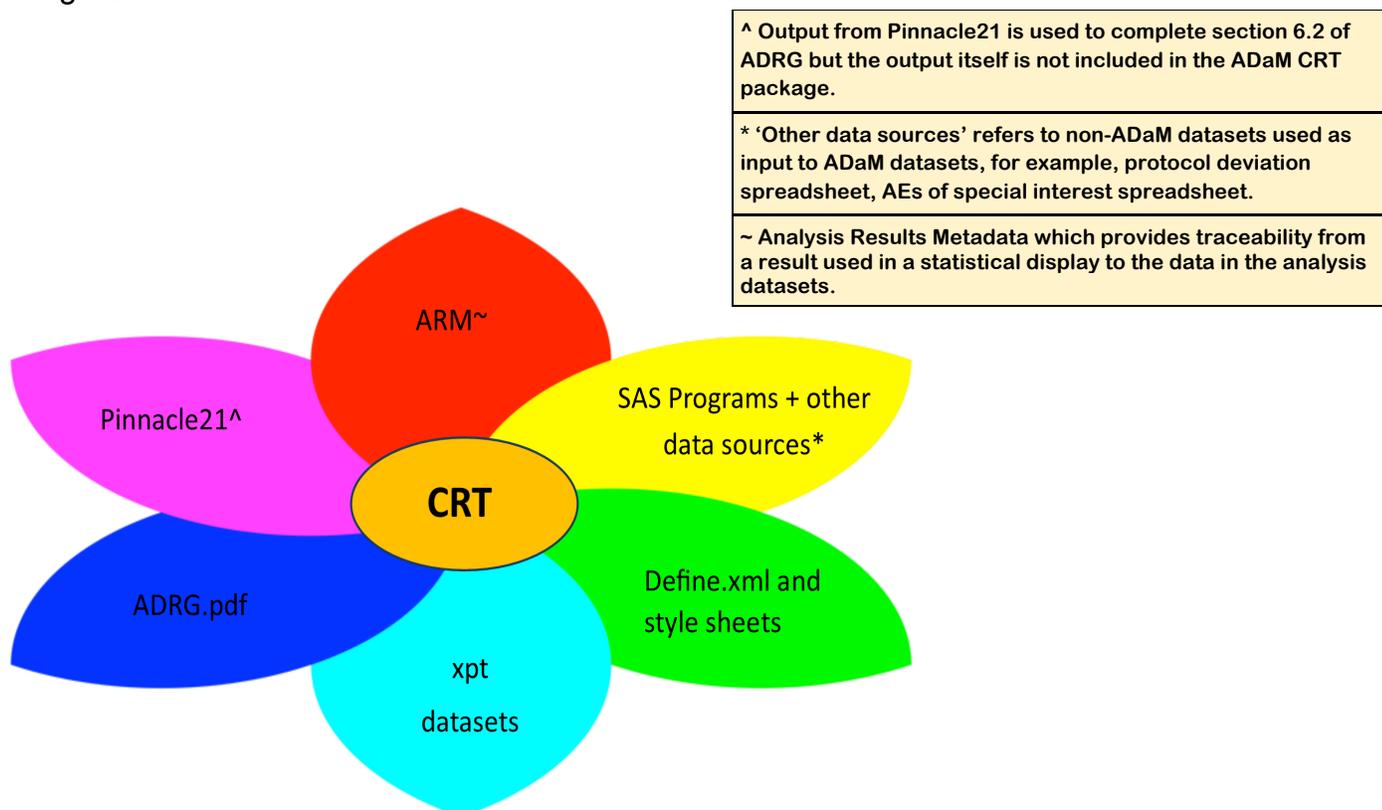
FIGURE 2 - FLOW DIAGRAM OF REVIEW PROCESS FOR SDTM CRT PACKAGE



REVIEW OF THE ADaM CRT PACKAGE

Figure 3 shows another beautiful flower this time to represent the complete ADaM CRT package, with each constituent part represented by a petal. These are the six constituents of the ADaM CRT package which includes Analysis Data Reviewers Guide (ADRG.pdf), Pinnacle21 report, XPT datasets (transport files created from ADaM datasets), Define.xml and style sheets, SAS programs included in the package and other data sources (non-ADaM datasets used as an input to an ADaM dataset) and Analysis Results Metadata (ARM), which provides traceability from display (table, figure or listing) to an ADaM dataset. Note that the required naming convention for FDA submissions is now ADRG.pdf.

Figure 3



When starting to review the ADaM CRT package make sure you have the following in addition to the ADaM CRT components: Protocol, Reporting and Analysis Plan (RAP)/Statistical Analysis Plan (SAP), SDTMs, Pinnacle21(P21) report and PhUSE ADRG template and completion guidelines. Other potentially useful information can be the annotated CRF and SDTM mapping specifications.

Check sections 1 to 4 of the ADaM Data Reviewer's Guide (ADRG) for content and accuracy. At GSK, we use the PhUSE ADRG template as a starting point so we check all sections are present and correct. All bulleted questions in the template should be included and answered accurately. For example, if date imputation is different for adverse events and concomitant medications the method should be described under the individual analysis dataset description (ADRG section 5.2.x) and not under section 3.6 Imputation/Derivation Methods as this is for methods used across multiple analysis datasets.

Review ADRG section 5 Analysis Dataset Descriptions in conjunction with define.xml. Crosscheck the Inventory of Analysis Datasets in ADRG section 5.2 with page 1 of define.xml. The dataset names, labels,

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class and structure should match up. The Keys on page 1 of define.xml should show the unique key for that ADaM.

Review each analysis dataset specification in define.xml along with the corresponding section in ADRG section 5.2 Analysis Datasets. Ask yourself the question 'Could I reproduce this dataset with the information provided in define.xml and ADRG?'. To be able to do this, the derivations in define.xml for each variable within an ADaM should contain enough information to create it. If it doesn't look for further information in ADRG as the derivation may have been too complex to include in the small box available. If there is still not enough information suggest a more detailed explanation is provided in ADRG or perhaps a computational method is added to define.xml.

If sections of the RAP/SAP have been specified check these are accurate. Similarly, if a derivation from the RAP/SAP has been followed but the section is not referenced or it states 'See RAP/SAP for more detail', suggest the specific section is added as this can save the reviewer a lot of time.

SPECIFIC CHECKS FOR ADRG

The following section details the information I have found useful in the ADRG when reviewing.

Has the source SDTM(s) of the ADaM been specified? It saves a lot of time for reviewers if they know where the data has come from.

How does the number of observations in the ADaM compare with the main source SDTM? If there are more observations in ADaM this might be due to derived records or new parameters. If less observations this might be because only a subset of the SDTM was required. Check an explanation is provided. If you can't work out how the ADaM has the number of records it does it could be highlighting a lack of transparency. For example, if the RAP/SAP states 'if there are multiple results on the same date, use the latest result' the ADaM would ideally retain all the data and use an analysis flag to show which result was used.

Ideally all data used in the ADaMs will use SDTM as the source data. This is the FDA's preference. However, occasionally non-SDTM sources may be required, for example, a spreadsheet of protocol deviations leading to exclusion from the per-protocol population, or a spreadsheet containing the preferred terms of adverse events of special interest. Define.xml should mention the name of any non-ADaM source data as part of the variable derivations. Check ADRG has a detailed description of the source data under section 1.4 Source Data Used for Analysis Dataset Creation.

If analysis flags are included in the ADaM a description of them detailing their purpose should be provided under ADRG section in 5.2, unless the derivation of the flag is consistent across all ADaMs, in which case the description should be included under ADRG section 4.4 Variable Conventions.

Any derivations that deviate from the RAP/SAP or additional data handling techniques not included in the RAP/SAP should be defined and a reason given.

Look at the P21 report created on the ADaM datasets. All issues that cannot be resolved should be listed under ADRG section 6.2 Issues Summary. Check the explanations provided.

Check the table of contents matches the Phuse ADRG template and that all the hyperlinks work. Use the Phuse ADRG completion guidelines to check what information is useful to include for each section.

Note that the required naming convention for the reviewer's guide for FDA submissions is now adrg.pdf.

SPECIFIC CHECKS FOR ADAM DEFINE.XML

The following section details specific areas of the define.xml I have found useful to check.

Look at the ADaM dataset. Overall, does it look like it is following CDISC standards for the class of dataset stated on page 1 (P21 also checks this)?

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For variables that include controlled terminology (CT), crosscheck the values in define.xml with the ADaM dataset. Ideally if the derivation of, for example PARAMCD states 'decoded version of PARAM' the Code Value in the CT will show all the values of PARAMCD and the Code Text will be the values of PARAM. This shows how the variable was mapped. If the CT is for a variable with entries pre-populated on the CRF, the preference is for all possibilities to be listed in the CT not just the ones that exist in the ADaM dataset.

For datasets other than ADSL, check the CT specified for the variables copied from ADSL matches that specified in ADSL.

Check any Value Level Metadata (VLM) has been used appropriately and the information is accurate. Under the VLM the Value column usually shows PARAMCD and the Label column usually shows PARAM. VLM can be very useful if there are different derivations of AVAL/AVALC for each new parameter in an ADaM.

Check all the hyperlinks work correctly.

COMMON ISSUES

- Incorrect, missing or duplicate controlled terminology in define.xml.
- TYPE for a variable in the define.xml is not defined as: 'Num', 'Char', 'Text', 'Integer', 'Float', 'Date', 'Datetime'.
- One of more variables in actual dataset are not in define.xml.
- Length specified in define.xml does not match actual data or is missing.
- For VLM values and dataset variables a 'TYPE' of TEXT, INTEGER or FLOAT, LENGTH should be provided.
- For variables other than RFICFDTC in DM and QVAL in SUPP, Origin or aCRF page should be provided.
- Incorrect or incomplete derivations in define.xml
- Incorrect use of VLM in define.xml (applying VLM's to PARAM, PARAMCD)
- Dataset structure on Page 1 of define.xml doesn't match section 5.2 Analysis Datasets in ADRG and incorrect unique key on Page 1 of define.xml

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HINTS AND TIPS

- Create and review detailed ADaM specifications prior to ADaM creation at study start and maintain throughout the study. Mandate QC of the ADaM specifications for pre-programming. This will reduce the time needed to review define.xml at the end of the study when CRT package is usually created.
- If possible, make notes of which ADaM datasets contain screen failures and which ADSL variables are common to other ADaM datasets as this information is needed for ADRG.
- ADRG is a living document. Start writing it at any time throughout the study, it doesn't have to be left until the end.
- Rerun and check the P21 report through the course of the study on both SDTM and ADaM datasets. Make sure you are running the latest version of P21 and the controlled terminology – it is what the FDA will use.
- If time and budget permit, get the CRT package reviewed by an independent programmer. They'll see the study in the same way as the external reviewer.
- Check the keys on page 1 of the ADaM define.xml are unique by doing a PROC SORT with NODUPKEY. The log should show zero observations were deleted.
- For variables that use controlled terminology do a quick PROC FREQ on that variable in SAS for crosschecking against define.xml.
- Watch out for special characters in defin.xml, e.g. variable names can't have \ / * , ? < > | “ ‘ : % # + () { } [] and the comments section can't have “ ’ | & *
- Use the PhUSE Template!

CONCLUSION

At GSK, although the SDTM CRT package is the overall responsibility of DM, the successful production of a quality product is a collaboration between DM and Programming. Unlike ADaM, the review process for programming is quite automated as our in-house reporting system is well equipped to ensure the components of the CRT package adhere to CDISC and FDA submission requirements.

The ADaM CRT package is the overall responsibility of programming. The review process explained in this paper is almost entirely manual and occurs in addition to some of the automated checks we have in place within our in-house reporting system. It is usually performed by an independent programmer who will hopefully look at the study in the same way as an FDA reviewer. The aim is to reduce the review time required by the FDA reviewer as they will not need to send so many questions back to the sponsor.

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