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This paper focuses on how CDISC® SDTM standards can be leveraged (using SAS® software and TIBCO Spotfire®) to create a user friendly, highly visual and interactive environment, where any clinical trial that is generating SDTM data, can quickly access and efficiently review their data on an ongoing basis, for example to support areas such as safety review, identifying data issues, supporting dose escalation and identifying trends. Our Preclarus® Patient Data Dashboard (Preclarus PDD) has been deployed on over 70 studies within PPD® and growing. This paper is a great opportunity to share our experiences and challenges when using CDISC SDTM standards in this way and the huge advantages that these visualisations are bringing the monitoring and ongoing review of our clinical data.

Visual analytics platforms, advances in data warehousing and the increase in CDISC SDTM availability provide the perfect landscape for the quick and cost effective review of clinical trial data as a clinical trial is running. This is a true opportunity to save lives and reduce costs. For example, a medic, using our Preclarus Patient Data Dashboard, identified an increase in infections which then contributed to discussions towards a protocol amendment. We have also seen a reduction in the development, and therefore costs, of patient profiles as the Preclarus Patient Data Dashboard is both better suited to the task and less costly to implement.

Our goal was to introduce an environment where practitioners could effectively interact with the full set of clinical trial data collected without the need for customised reports, as the trial runs, to isolate subjects of interest and then comprehensively drill down into those subjects to ascertain why. An important challenge for our industry is the timely and cost effective delivery of systems for clinical data review on any given clinical trial, regardless of therapeutic area or how that data was collected, e.g. electronic data capture (EDC), central labs or diaries - all this while ensuring that these systems remain intuitive, interactive and comprehensive.

As CDISC SDTM becomes increasingly available across studies and more timely, this can be best achieved through leveraging standards. This paper shows how we have met this challenge through deploying a comprehensive and scalable data review environment built on the foundation of an established industry standard, CDISC SDTM.

Table 1: ECG Test Results

Study Identifier	Domain Abbreviation	Unique Subject Identifier	ECG Test or Examination Short Name	Numeric Result/Finding in Standard	Baseline Flag	Visit Name	Date/Tim ECG
DEMO-DEMO	EG	DEMO-003-0012	QT	300.00	Y	DAY 1	2013-01-01
DEMO-DEMO	EG	DEMO-003-0014	QT	300.00	Y	DAY 1	2013-01-01
DEMO-DEMO	EG	DEMO-587-0005	QTC				
DEMO-DEMO	EG	DEMO-587-0005	QTC				
DEMO-DEMO	EG	DEMO-291-0008	QT				
DEMO-DEMO	EG	DEMO-686-0005	QTC				
DEMO-DEMO	EG	DEMO-686-0005	QTC				
DEMO-DEMO	EG	DEMO-686-0005	QT				
DEMO-DEMO	EG	DEMO-686-0005	QTC				
DEMO-DEMO	EG	DEMO-686-0005	QT				
DEMO-DEMO	EG	DEMO-153-0010	QT				
DEMO-DEMO	EG	DEMO-670-0001	QT				
DEMO-DEMO	EG	DEMO-670-0001	QT				
DEMO-DEMO	EG	DEMO-670-0001	QT				
DEMO-DEMO	EG	DEMO-670-0001	QT				
DEMO-DEMO	EG	DEMO-021-0004	QT				
DEMO-DEMO	EG	DEMO-021-0004	QT				
DEMO-DEMO	EG	DEMO-021-0004	QT				
DEMO-DEMO	EG	DEMO-036-0002	QT				
DEMO-DEMO	EG	DEMO-036-0002	QT				
DEMO-DEMO	EG	DEMO-036-0002	QT				
DEMO-DEMO	EG	DEMO-003-0012	QTC				
DEMO-DEMO	EG	DEMO-638-0001	QT				
DEMO-DEMO	EG	DEMO-638-0001	QT				

ECG Results Box Plot - Change from Baseline

This box plot shows the change from baseline in standard units (non-SDTM) for QTC and MS. The y-axis ranges from -120 to 60. The x-axis shows the change from baseline in standard units (non-SDTM) for QTC and MS. The plot includes a legend for Reference points (Average, Median, Lines and curves, Horizontal Line, Horizontal Line, Horizontal Line) and a table of statistics.

Statistic	QTC	MS
Max	80.01	120.00
Min	-29	63
Outliers	0	10

ECG Results - Numeric Results/Findings over Study Timeline (Color by Subject)

This scatter plot shows the change from baseline in standard units (non-SDTM) for QTC and MS over the study timeline. The y-axis ranges from -350 to 100. The x-axis shows the change from baseline in standard units (non-SDTM) for QTC and MS. The plot is color-coded by subject.

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Through CDISC SDTM standards, powerful data review systems can be designed before any data is collected on a study.

The use of standards delivers many solutions to today's challenges, for example **scalability** as the same platform can be deployed on any study that has CDISC SDTM data. Standards also deliver a **comprehensive and intuitive** package as its reproducibility allows a centralised and specialist investment that gets the system right. Through economy of scale we get a **cost-effective solution** as there is no requirement for study specific customisation and cost, so it is effectively free where SDTM is already available and furthermore reduces cost, for example the reduction in study specific safety review listings. The dashboard is also **quick to deploy** as the Preclarus Patient Data Dashboard is built on CDISC SDTM standards in advance, not designed from study data. To use, the PPD study team simply uploads new SDTM data into the system.

The following sections explore the dashboard itself, review support for specific therapeutic areas and focus on some of the challenges that we faced when constructing the Preclarus PDD.

DEPLOYING CDISC SDTM DATA FOR MONITORING AND REVIEW

Strong visualisation based environments are made up of many technical components, each designed for their intended purpose within the overall product. The Preclarus Patient Data Dashboard is no different. For the user interface, we use TIBCO Spotfire, which is an ideal tool for user interaction, user friendly reporting and deployment via a web browser.

The management of the data, that underpins TIBCO Spotfire, is carefully transformed via SAS, to ensure that TIBCO Spotfire's best features are showcased, to ensure that data is processed quickly and to ensure a seamless integration with our already established systems. Within PPD, our SDTM data sets are developed within a tightly controlled SAS based platform. A mixture of already established and new technologies provides the perfect foundation on which to build such a system.

Another very important consideration is low cost and fast implementation at the study level. The Lead Programmer, who is responsible for SDTM creation, runs pre-developed SAS macros to format their SDTM and then transfer this data into an upload folder, where TIBCO Spotfire automatically loads the data using Automation Services, a service provided with the software.

To ensure that the centrally developed systems remain current, these are enhanced by a central team following a six-monthly release cycle, based on enhancement requests from the users and the SDTM documentation from CDISC, without any need to know the clinical data in advance.

We provide some scope for the Lead Programmer to customise their dashboard via SAS, however this is not required and is rarely used.

The following sections explore some of the useful features that we have made available within the dashboard.

ADVERSE EVENTS

Adverse events (AEs) are a key focus of any safety review, for example the ability to quickly locate and isolate relevant AEs. In this example, we show how a very comprehensive set of visualisations can be designed to suit any clinical trial, before the data is collected. We recommend that the dashboard developer remains aware of which SDTM data are required, expected or simply permissible within the standard. This ensures universal compatibility as only data that is required or expected should be made necessary for the dashboard to function. In the case of expected variables, it should be considered how these should be handled if a study does not collect this data. This approach ensures the maximum scalability of the system as new trials are loaded.

Below is one of our AE displays, where users can select SDTM labels to populate the tree map (as in this example, grouped by "Sex" and "Body System or Organ Class"). In this way, users can focus on individual AE groups that are of interest to them.

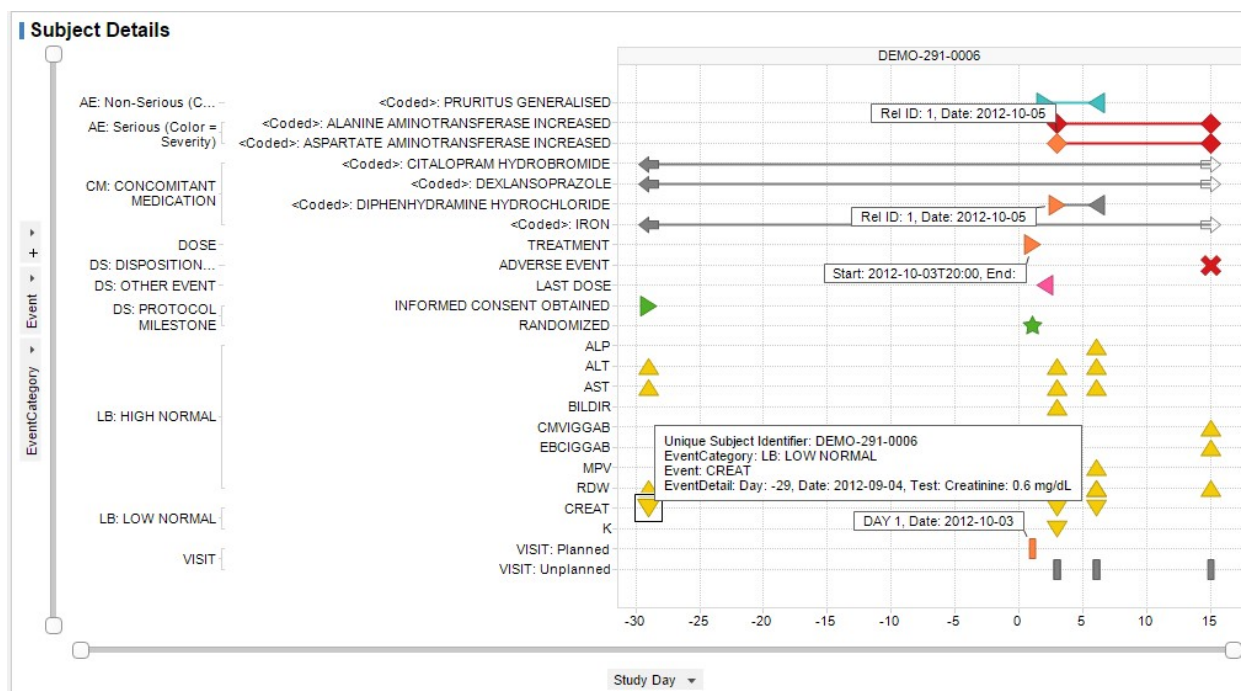
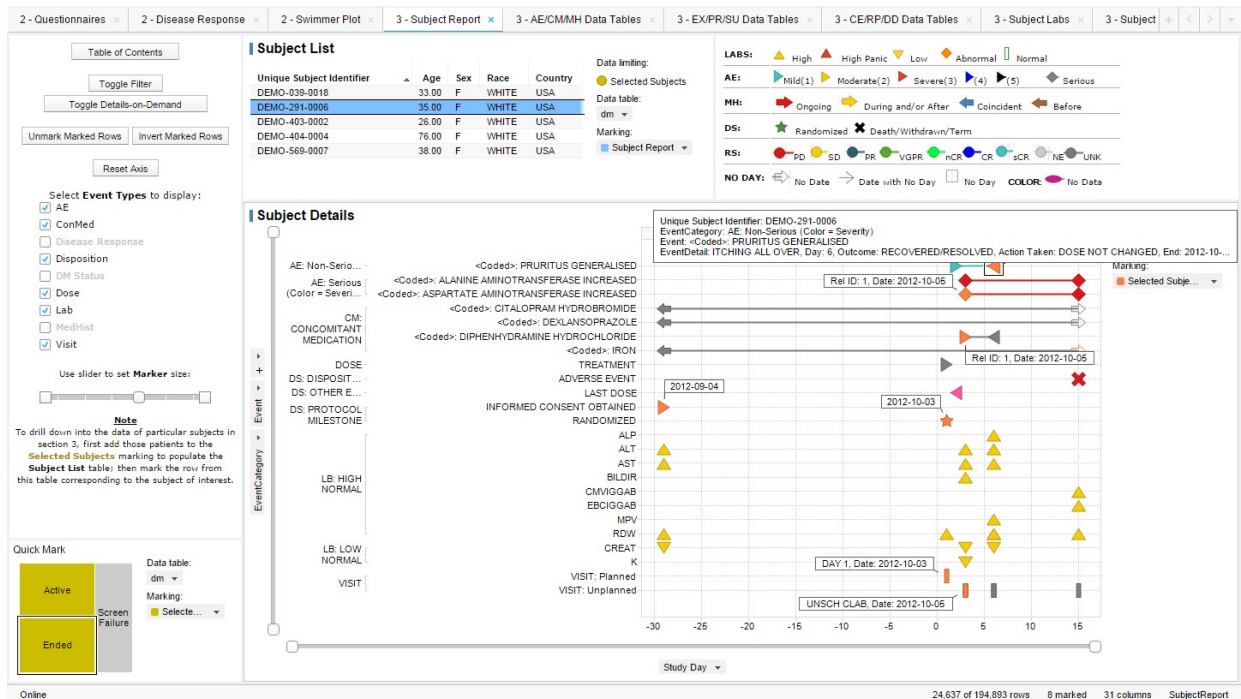
For maximum compatibility, the list of SDTM labels (for selection below), can be pulled from a data set generated by SAS, to ensure that only SDTM labels available on the study are made available to the user.



SUBJECT REPORT

An important display in any dashboard is a patient profile type view where all of a subject's medical detail can be viewed together on a timeline. In this display, different areas of interest, e.g. AEs, labs, study drug, concomitant medication, visit schedule etc. can be selected at the left as required and plotted against the day on which it occurred within the subject's progress through the study.

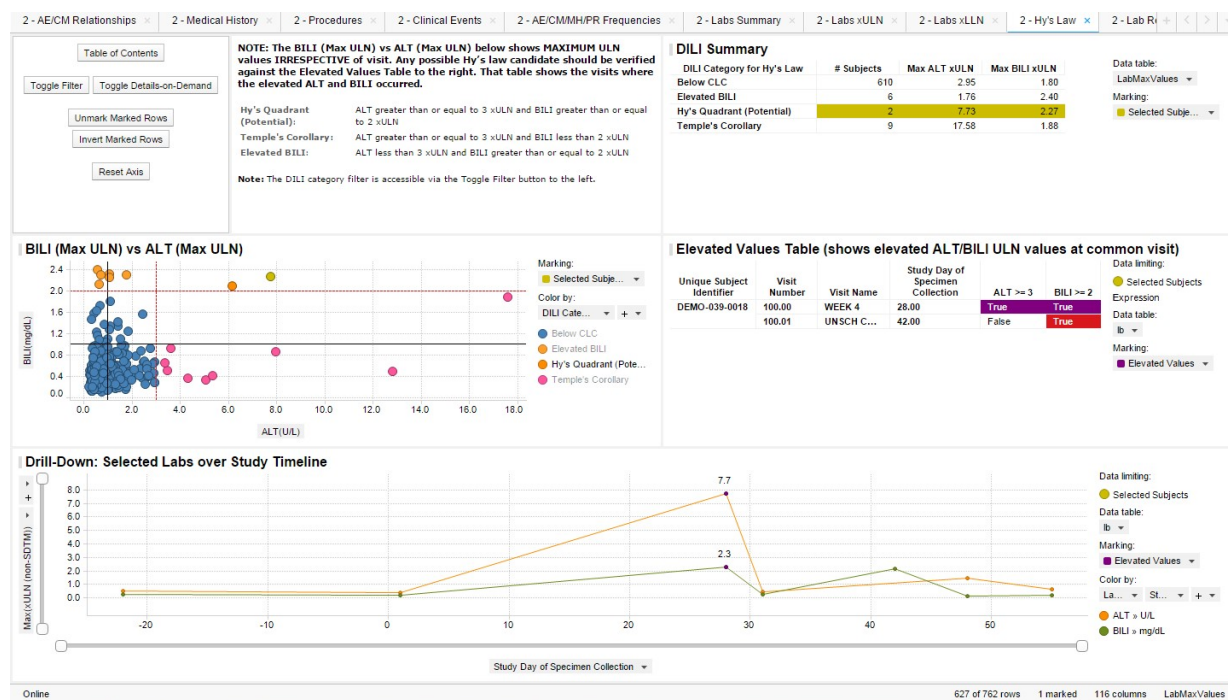
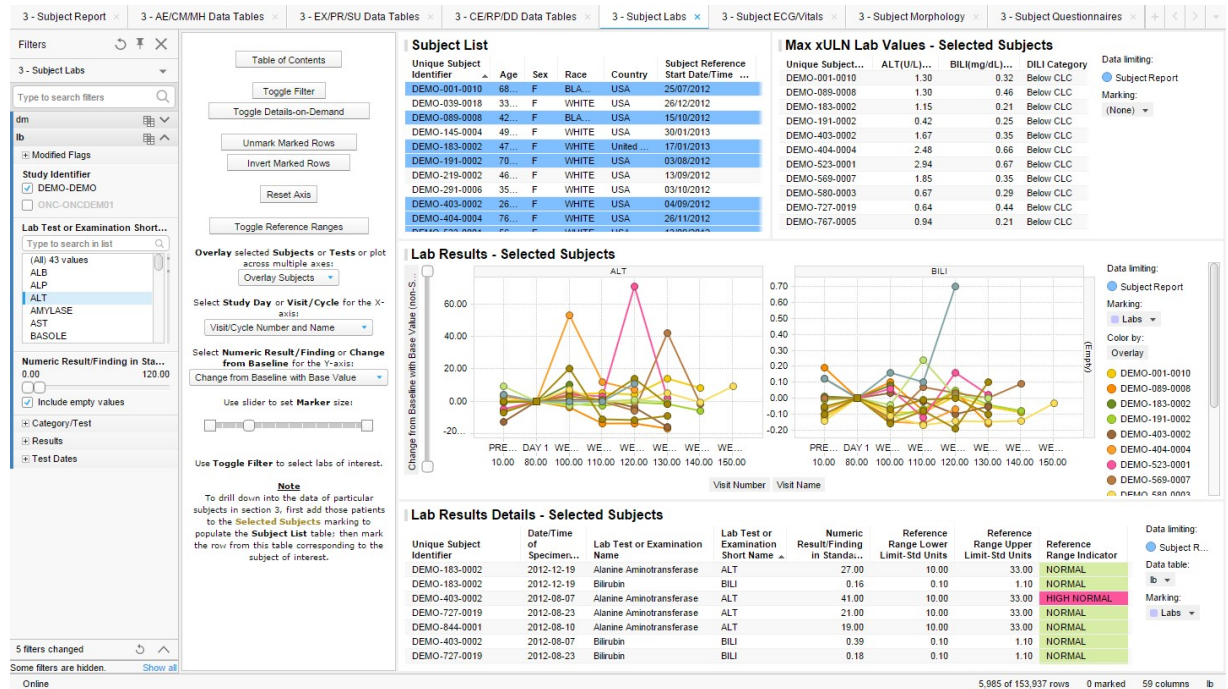
This is a good opportunity to consider some challenges. While SDTM, and its design of the RELREC domain, make it difficult to display explicit links between study data held across different domains, the user can view potential links when different data are plotted together using universal variables, such as study day. In some cases, RELREC can be used, for example to show explicit relationships between Adverse Events and Concomitant Medications. This can be seen in this example via the marker label. The use of TIBCO Spotfire marker labels (extra information shown for elements that are clicked) and tooltips (shown when the mouse is hovered over an item) can greatly enhance the user experience.



LABS

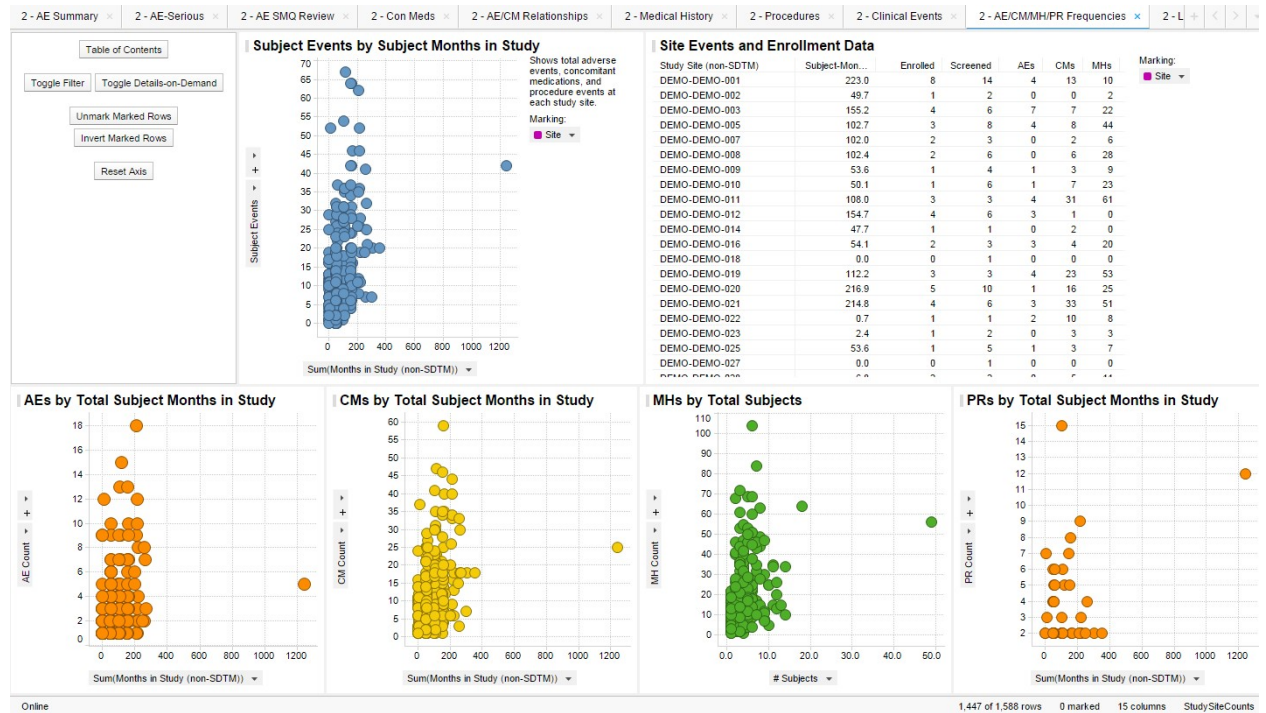
Any drug safety review system would not be complete without a solid emphasis on labs, where individual subjects can be examined, who perhaps had a concerning AE, or select multiple subjects that exceed a predefined range. Specialist pages also help, for example a Hy's Law page to assist with assessing drug toxicity via the liver function tests. The examples below focus on numerical labs where data is plotted continuously. To add flexibility for the user, functionality is provided for overlaying subjects or tests on the same axis. In addition, simple derivations can be included, for example the addition of non-SDTM variables such as change from baseline or the establishment of maximum values for the review of Hy's Law.

In these cases, very careful planning is required to ensure that any derivation considers all possibilities allowable in SDTM, e.g. the impact of the SDTM variable LBDRVFL (Derived Flag) when calculating change from baseline. Filtering is also an important feature, where users can open and close filter panels to select data of interest, for example to choose which lab tests to view or to set the drug ranges of interest to plot.



ASSESSING RISK

With the regulatory focus on risk based monitoring (RBM), a useful feature in any data review system is the identification of risks within our clinical trials, so that resources can be redirected to areas that have the greatest risk. With our focus on CDISC SDTM data, our system is ideally suited to look for risks evident within the collected clinical trial data. One such opportunity is to compare the relative rates of reported events or interventions at each investigator site, to identify outlying sites. We are interested in both sites that over report or under report. These investigator centres may indicate higher risk and therefore require additional monitoring attention.



THERAPEUTIC AREA SUPPORT

Many clinical data review systems focus on drug safety, which is centred around generic SDTM domains applicable to all studies, for example Adverse Events (AE) and Labs (LB). Another very important area for review are data collected that are Therapeutic Area (TA) specific. The ability to make progress in this area was greatly assisted by the CFAST initiative.

To quote, "CFAST is an initiative formed to accelerate clinical research and medical product development by creating and maintaining data standards, tools and methods for conducting research in therapeutic areas that are important to public health. CFAST was initiated as a partnership between CDISC and the Critical Path Institute (C-Path)."¹

At PPD, we established TA Working Groups, with experts in each field, to enhance the Preclarus Patient Data Dashboard specifically for TAs based on the CFAST Therapeutic Area User Guides (TAUGs). These guides provide detail on how therapeutic specific data should be recorded in the standards.

The following section provides a list of TAUGs already published through CFAST as well as PPD's TA experience. I then focus on some of the enhancements we have added to support TA specific needs.

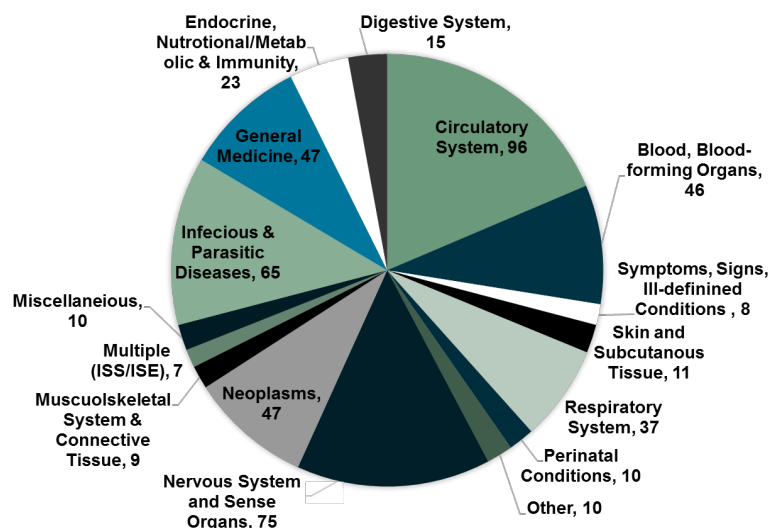
USER GUIDES PUBLISHED VIA CFAST

Therapeutic Area User Guides (TAUGs) published via CFAST define new approaches to populating existing SDTM domains, as well as new domains, specifically to support individual therapeutic areas such as oncology, neuroscience, cardiovascular and vaccines.¹

Project	Publication Date	Project	Publication Date
Alzheimer's Disease v1	September 9, 2011	Schizophrenia v1	June 9, 2015
Tuberculosis v1	June 29, 2012	Dyslipidemia v1	June 19, 2015
Pain v1	August 7, 2012	Virology v2	September 30, 2015
Virology v1	December 6, 2012	Traumatic Brain Injury v1	December 14, 2015
Parkinson's Disease v1	December 18, 2012	COPD v1	January 26, 2016
Polycystic Kidney Disease v1	February 26, 2013	Tuberculosis v2	February 26, 2016
Asthma v1	November 26, 2013	Breast Cancer v1	May 16, 2016
Alzheimer's Disease v2	December 16, 2013	Rheumatoid Arthritis v1	November 14, 2016
Multiple Sclerosis v1	May 2, 2014	Kidney Transplant	October 31, 2016
Diabetes v1 (ADaM Supplement)	September 11, 2014 (December 18, 2015)	Major Depressive Disorder v1	December 5, 2016
Cardiovascular Endpoints v1	October 17, 2014	Diabetic Kidney Disease v1	December 13, 2016
Influenza v1	November 25, 2014	Pain v1.1 (update)	December 13, 2016
QT Studies v1	December 12, 2014	Ebola v1	December 19, 2016
Chronic Hepatitis C Virus v1	May 8, 2015	Malaria v1	January 9, 2017

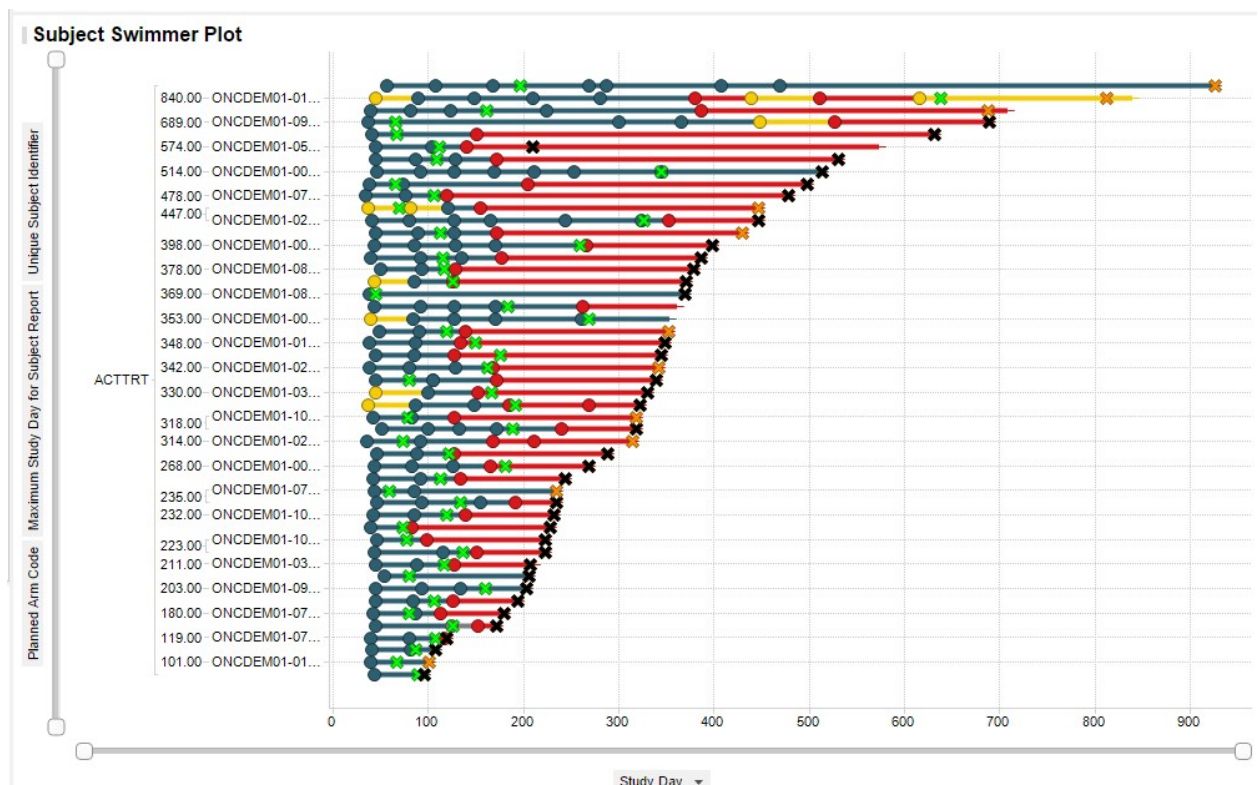
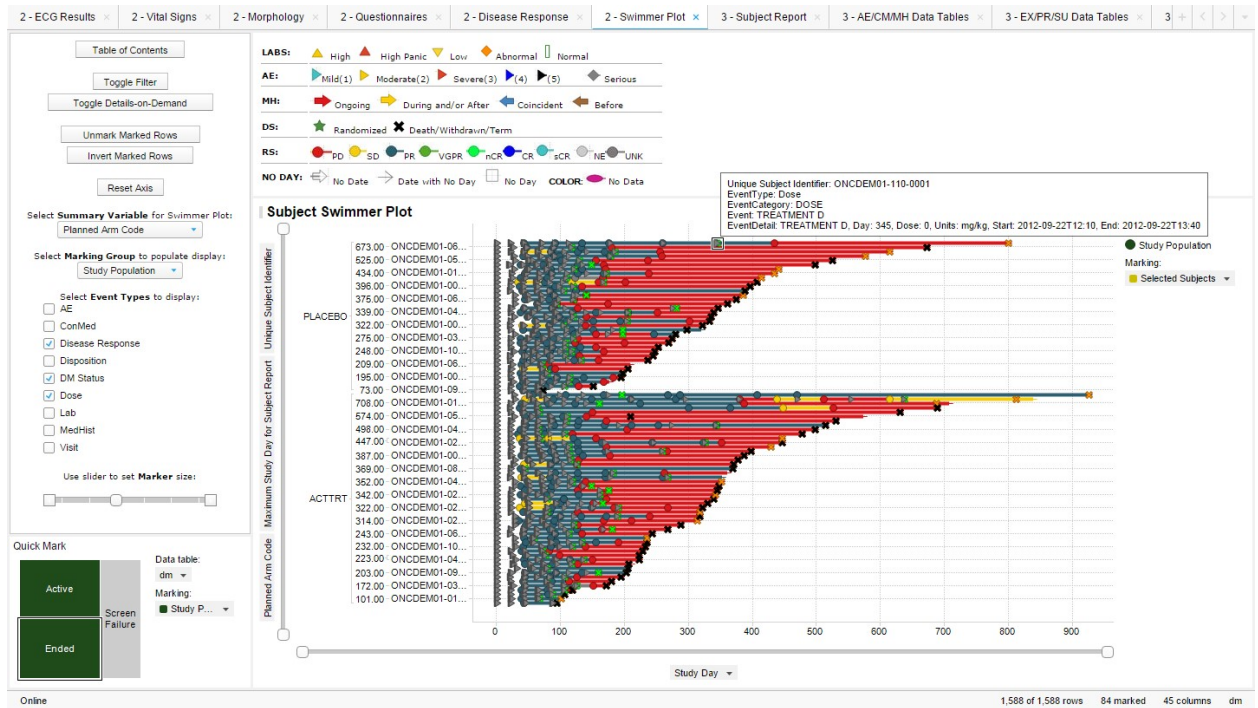
This, combined with PPD's extensive therapeutic area experience, has provided an ideal platform to enhance our dashboards further, to increase the value add across our portfolio of studies.

PPD'S THERAPEUTIC AREA EXPERIENCE



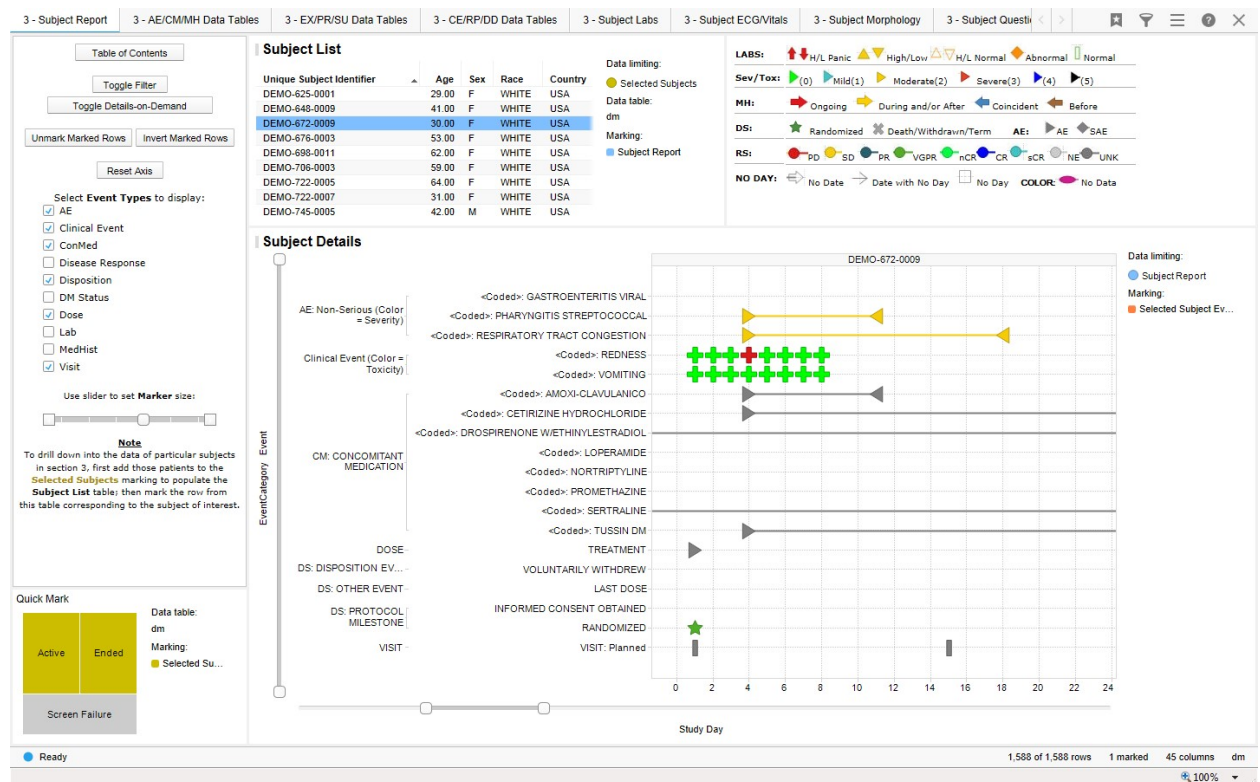
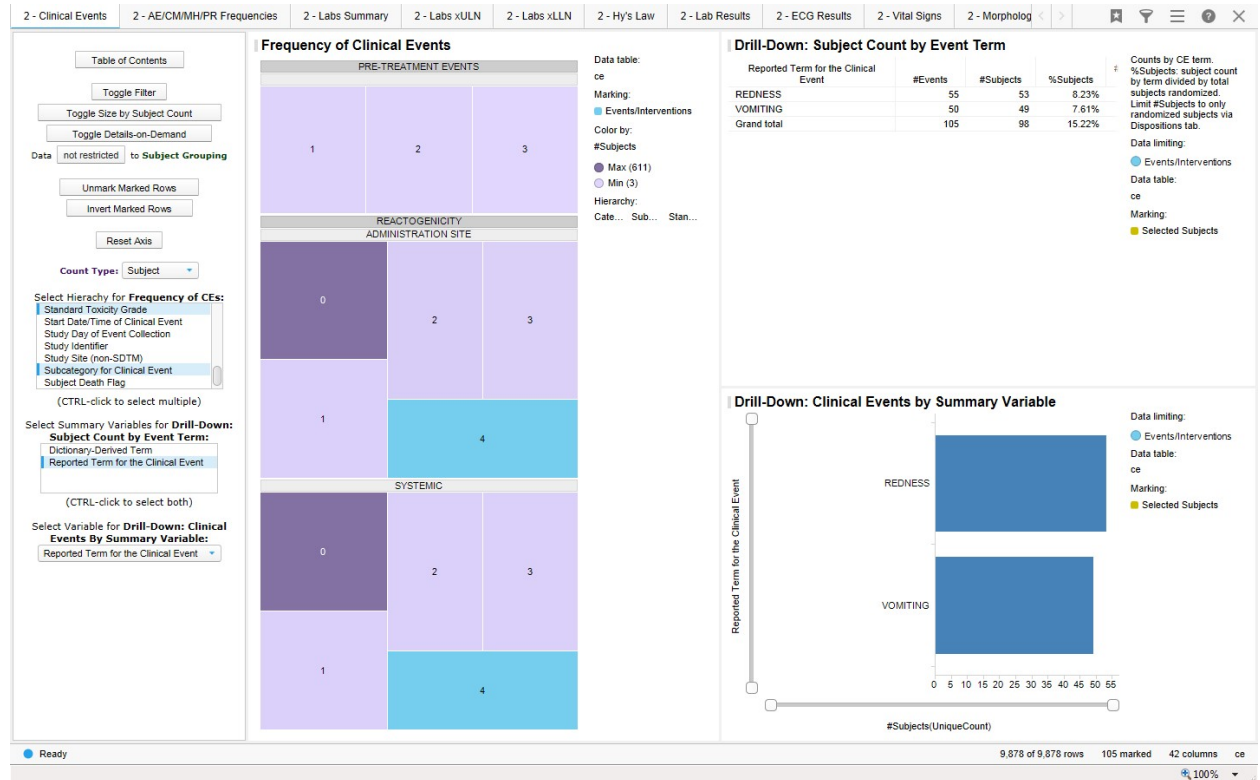
SWIMMER PLOT – ONCOLOGY

Oncology is an area where many useful visualisations can be added, using SDTM domains such as Disease Response (RS), Tumor Identification (TU) and Tumor Results (TR). The example below shows how response assessments are used together with other variables, such as Date/Time variables from the Demographics (DM) domain. SDTM has all the building blocks required to automatically generate useful swimmer plots, such as below, for oncology and other studies (if different domains are selected). Here we see the disease response changing over time, when study drug was last provided and whether and when the subject died.



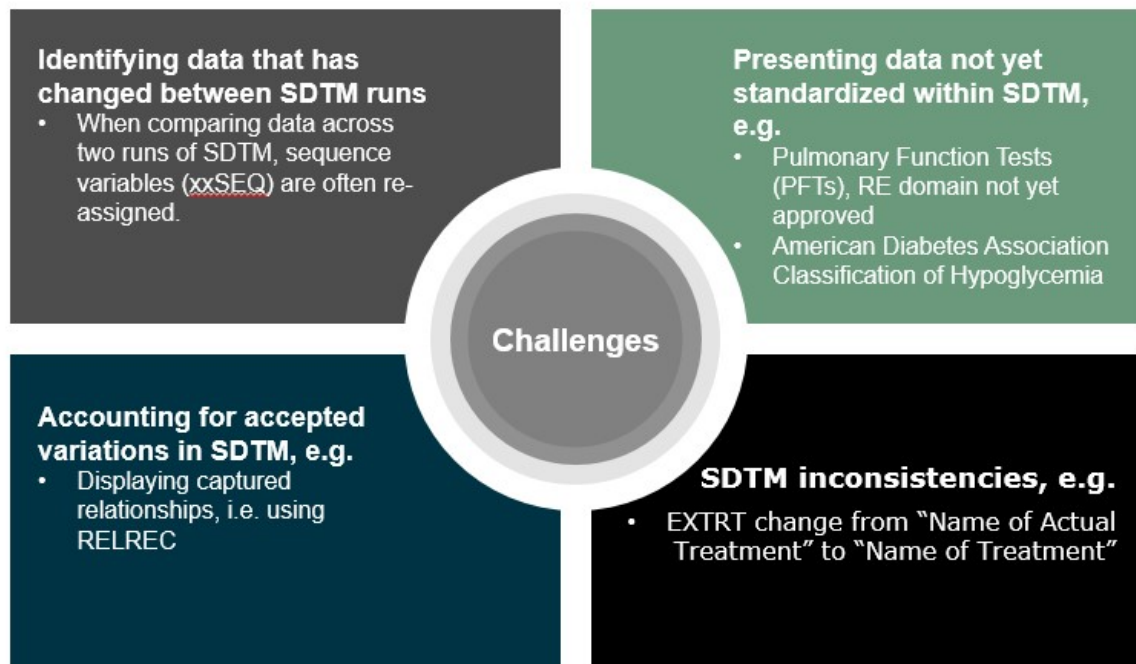
REACTOGENICITY – VACCINES

Vaccines is another growth area where there is plenty of opportunity to assist TA specific review. In this example, users can drill down into the reactogenicity gradings captured, via the diary card, during the observational period. These results can be assessed against other events that impact the subject, such as AEs and any concomitant medication taken.



CDISC SDTM CHALLENGES ENCOUNTERED

In this section, I explore some of the challenges encountered when using CDISC SDTM specifically for dashboard visualisations.



IDENTIFYING DATA THAT HAS CHANGED BETWEEN SDTM RUNS

The ability to isolate data that was previously reviewed from data that is changed or new, is a common request for dashboards that are regularly updated. SDTM data sets are not designed to be compared against previous runs of SDTM for the same trial. SDTM sequence variables (xxSEQ) are often reassigned between one SDTM run and the next, so cannot be used. We have established programs to manage this, but this is a complex business. Consideration should also be given to what data the user needs to review under these circumstances, for example only the data that has changed or all data for subjects, where any of their data has changed.

MANAGING PERMITTED VARIATIONS IN SDTM

The algorithms that drive the Preclarus PDD need to account for any permitted variations in the CDISC SDTM standard that may be encountered in the data sets. RELREC is a good example of where the standards allow multiple variations. Even in the relatively simple relationship between Adverse Events and Concomitant Medications, this can become vastly complicated, for example where xxGRPID variables are used. One answer is to set the dashboard to exclude features, where the data does not conform. This is a much better approach than the dashboard failing or even worse, surfacing erroneous data.

PRESENTING DATA NOT YET STANDARDISED WITHIN SDTM

There are various additions that we would like to add that are not yet defined within CDISC SDTM. Examples include domains that are not yet approved, such as Respiratory System Findings (RE). This is where studies would capture Pulmonary Function Test (PFT) data. Another example are standards required for capturing the American Diabetes Association Classification of Hypoglycemia. Gaps such as these, mean that data is recorded anywhere within SDTM, so we cannot locate the relevant data, to display, via our algorithms.

SDTM INCONSISTENCIES

Our system is designed to accommodate different versions of SDTM, which is largely successful due to the excellent standard management incorporated into CDISC SDTM. Care does need to be taken however, as small adjustments between versions can cause problems for algorithms. For example, the variable EXTRT, in the Exposure (EX) domain, had a label change between SDTM v3.1.3 and v3.2 from "Name of Actual Treatment" to "Name of Treatment". In another example, the QSSTRESC label, "Character Result/Finding in Standard Format", in the Questionnaires (QS) domain, breaks the 40-character rule. This means that many studies will assign an alternative label. In such cases, it is important to ensure that the dashboard continues to locate the data. It is important to make the algorithms robust to such variations by looking for and recognising these cases.

CONCLUSION

PPD's Preclarus Patient Data Dashboard has allowed PPD, and our clients, to reduce costs and identify issues more effectively.

This paper shows how far CDISC SDTM has come and how it can be effectively utilised today to greatly enhance the monitoring and review experience on clinical trials. Through the focus on standards, this paper explores how we have delivered timely visualisations for safety review through to wider therapeutic area support, as well as some of the challenges faced when designing such a dashboard.

We have found CDISC SDTM an ideal standard to develop a comprehensive dashboard that can quickly load clinical trial data for review.

- Through SDTM standards, our dashboard currently supports over 30 domains (AE, CE, CM, DD, DM, DS, DV, EG, EX, FA, IE, LB, MB, MH, MO, MS, OE, PE, PR, QS, RELREC, RP, RS, SU, SV, TA, TE, TI, TR, TS, TU, TV, VS).
- This includes over 120 visualisations across over 40 individual pages.
- Implemented on over 70 studies across over 10 clients and rising.
- Deployed for safety review/ trending.
- Deployed for dose escalation support.
- Deployed for identifying data issues.

This is a dynamic and visualisation based view of CDISC SDTM data for ongoing review and monitoring. As discussed, this approach delivers solutions that are:

Scalable: Out-of-the-box data review tool for SDTM studies.

Comprehensive and Intuitive: Centrally developed by experts.

Cost effective: Study specific cost/customisation is not required.

Quick to deploy: Simply upload SDTM into the system.

Through the Preclarus[®] PDD we have discovered what we can now achieve, compared to the limitations that our industry faced only a few years ago. I am very much looking forward to the next steps for Preclarus, particularly as our industry continues to take advantage of standards, new technologies and the better access to data in its various forms.

REFERENCES

¹ Source: www.cdisc.org/cfast-0

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