Paper SD11

Quarterly Safety Reporting: Timely Analysis of Clinical Safety Data Using Qlik Sense Software

Yvonne Denkins, PhD
IQVIA Biotech, Morrisville, NC, USA

ABSTRACT

FDA guidance strongly recommends a process for reviewing, evaluating, and managing accumulating safety data within the clinical data base at appropriate intervals (21 CFR 312.32(c)(1)(i))[1, 2]. To meet client requests for review of safety data per agency guidelines, Clinical Scientists (CS) at IQVIA Biotech created and developed a robust process for quarterly safety reporting. Clinical Science and other team members review study data quarterly using a validated Qlik Sense software platform. The resulting Quarterly Safety Report (QSR) is prepared as a stand-alone document showing case report form safety data using tables and graphics. Any anomalies, trends, and safety signals found are reported to the client and if needed, regulatory agencies.

The IQVIA Biotech Qlik Sense software platform is a visual tool that incorporates data from multiple sources into a user-friendly, interactive, dashboard environment. With drill-down capability mimicking eCRF design, this visual platform promotes easy access for the review of clinical safety data.

INTRODUCTION

IND Safety reporting is required under 21 CFR 312.32 and FDA guidance[1, 2] strongly recommends "a process for reviewing, evaluating, and managing accumulating safety data from the entire clinical trial database at appropriate intervals." (A.3.c.). Because it is critical that a drug product's risks be adequately assessed during development, sponsors should ensure that they have in place a systematic approach for safety surveillance. Clinical Scientists (CS) at IQVIA Biotech produce the Quarterly Safety Report (QSR), a stand-alone document which reviews the clinical data base – via summary tables, graphics, and a report summary – and outlines trends in the data. Clinical Scientists work closely with biostatisticians to prepare specifications for tables to be included in the report. As these are tables that may also be used in the Clinical Study Report, efficiencies are gained. The QSR evolves with the study to include study adaptations various study phases (e.g. a trial moving from phase 1 escalation to phase 2 expansion).

Clinical Scientists also review the data quarterly using IQVIA Biotech's validated data visualization dashboard Clinical Data Review (CDR) – a platform build upon the software Qlik Sense. The department of Clinical Science oversees the creation of the CDR platform directing its specification, implementation and validation. The CDR platform provides clinical trial data on a project or program level in visual and tabular form and is designed so that the user may obtain both details and analytics of patient demographics, disposition, adverse events, labs, including eDISH (evaluation of Drug-Induced Serious Hepatotoxicity plot) analysis of liver enzymes to indicate Hy's Law laboratory criteria, and vital signs. The platform also includes access to patient profiles, eliminating the need to develop them separately. Following report completion, anomalies and safety signals found are reported to Medical Monitoring and the Safety Department in a timely manner required by and appropriate for reporting to the regulatory agencies. Sponsor access to the platform can be obtained via a separate license.

The QSR provides safety data in visual and tabular form so Sponsors/Customers may fulfil an FDA recommendation and streamline the safety data review process.

PROCESS

The process developed for QSR is a cross functional venture that provides the sponsor with an overview of key safety data obtained from the clinical data base. The steps needed to create, develop, implement, and maintain a Quarterly Safety Report (QSR) are shown in Figure 1 and the participating functions and responsibility are noted below.

Process Scope:

The QSR includes adverse events, safety labs, and vital signs from the clinical database and consist of a review on a project (single study) and/or program level (multiple studies evaluating the same compound). The report is produced using a data analytic platform that streamlines the safety data output and programmed, validated tables.

Upon adding the QSR to the scope of work (SOW) QSR activities are led by CS and the Project Manager (PM) who assures that the staff assigned to a project are familiar with the required scope of work and implementation plan.

Process Flow Chart

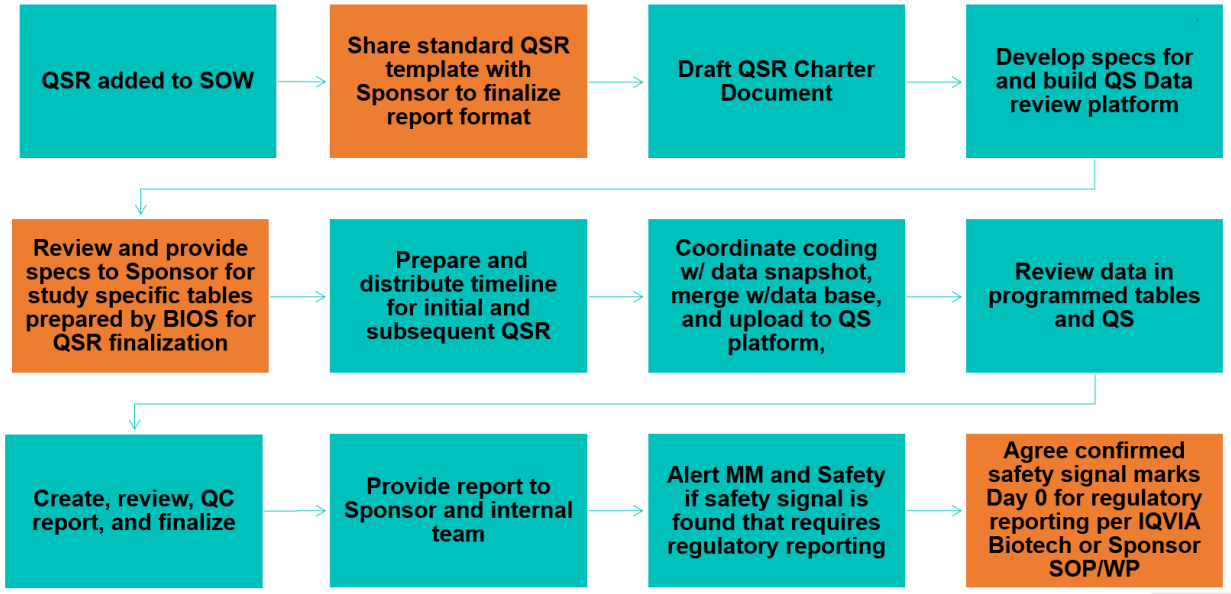

Figure 1 QSR Process Flow Chart

Responsibilities:

The active participants in the process are responsible for the following:
The CS is responsible for overseeing QSR creation, review, and finalization. After a thorough review of the protocol the CS prepares a QSR Charter specific to the study for sponsor review.

Clinical Scientists also provides specifications to IT and oversees the build and QC of a study specific data visualization platform using the QS CDR tool. Additionally, CS provides study specific table shells to Biostatistics (BIOS) for review and programming. Many of the tables will also be used in the Clinical Study Report – thus efficiencies are gained. Using the programmed tables and graphics from the CDR tool the CS reviews the report comparing it to data from the previous quarter. The CS writes a draft summary for the report data for the quarter and report any anomalies or safety signals found within the data to Medical Monitoring and the Safety Department in a timely manner required by and appropriate for reporting to the regulatory agencies.

The QSR Coordinator creates, reviews, and revises the report per CS requests. In addition, the coordinator executes timeline providing functional group participants with calendar reminders appropriately. The coordinator is responsible for preparing the graphics chosen by the CS for the report from the CDR and placing them and tables and listings within the report.

Project Management serves as the point of contact for the sponsor. The PM develop and distributes the timelines (Table 1) that hold tasks for the internal team and the abbreviated timeline which holds associated dates for the sponsor. In addition, PM schedules any meetings needed between the internal team and the sponsor.

Information Technology (IT) is responsible for programming and building the QS CDR platform needed for QSR graphics and review. They upload data into the dashboard per sponsor and IT agreed timelines using data extracted from the IQVIA Biotech data warehouse. They make any necessary changes to the application that may occur due to additional sponsor requests and protocol amendments.

Clinical Reporting includes BIOS, Statistical Programming, and Data Programming. The biostatistician drafts QSR table shells and specifications. BIOS evaluates newly programmed tables to ensure they are programmed according to specifications and they review programmed tables that contain quarterly data before each QSR. Statistical Programming programs and validate QSR tables per BIOS specifications and they generate validated tables for each QSR. Data Programming converts laboratory results to standard units and calculate Common Terminology Criteria for Adverse Events (CTCAE) grades for input into the CDR. Additionally they integrate medical coded terms with Case Report Form (CRF) data and uploads CRF data to the Data Warehouse for the QS CDR platform following the quarterly data cut. Following preparation and review, Quality Control (QC) is performed on the completed report.

The report is then forwarded to the Medical Monitor (MM) for review and preparation of a short summary that provide medical interpretation of findings. If during review a potential safety signal is found by CS, it is reported to and discussed with MM. The study MM and PM, without undue delay, arranges a discussion with the sponsor and Safety. If, after the report is finalized, there is a potential safety signal found, at that time that team will decide:

- Whether there is a true safety signal,
- When the reporting clock starts, and
- What the action plan will be for reporting.

If the Sponsor confirms that the safety events identified meet the criteria as a reportable event, the date that the study team agrees a safety signal has been confirmed becomes Day 0 for regulatory reporting purposes and the safety department responsible for this activity begins their process for reporting as per SOP to ensure that the following requirement is met:

> "If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made." [1]

Charter:

The purpose of the Charter is to define the steps necessary to create, develop, implement, and maintain a QSR – a document that provides the sponsor with an overview of key safety data obtained from the clinical data base.

Clinical Science works closely with all team members who retain a responsibility for the creation and development of the report. The QSR Charter is drafted by CS and presented to the Sponsor for discussion prior to the first QSR report. The Sponsor may request changes to the Charter prior to the first meeting. Team members will follow IQVIA Biotech Working Practice Quarterly Safety Report Preparation and Completion for report preparation, dispensation, and follow-up to ensure confidentiality and proper communication to the sponsor and regulatory reporting agencies.

The purpose of this Charter is threefold:

1. To describe the roles and responsibilities of the participants who prepare QSR.
2. To outline communications and interactions between the QSR preparers and the study sponsor, and
3. To outline procedures to safeguard the integrity of the study data.

The Charter describes the QSR participants (described above) and their responsibilities, meetings and processes, the QSR process, report, and timeline.

Table 1. Standard Timeline for the initial and subsequent QSRs

Project Safety Review	Projected Timespan
IT programs QS	15 weeks
CS prepares shells of initial tables and discusses with BIOS. **BIOS prepares sponsor-ready table shell document.** **Statistical Programmers program initial tables. Tables reviewed by BIOS and CS – Corrections made**	5 Months (initial QSR) – Subsequent occurs 4 weeks prior to report due date
Extract data for Data Snapshot	4 weeks prior to report due date
Statistical Programmers Produce Tables	4 days (all other QSRs) – occurs 4 weeks prior to report due date
Review Data in conjunction with the table output to ensure accuracy. **Review data in QS to determine which graphic output should be included in the report.**	3.5 weeks (prior to report due date)
Create, review and revise report	2 weeks (prior to report due date)
Post report to secure site for Sponsor	Report due date

Data Visualization (QS CDR):

Clinical Scientists create a standard, visual, user-friendly, interactive, dashboard environment for clinical safety data in the CDR using the IQVIA Biotech approved and validated software – Qlik Sense. Data Visualization via Qlik Sense provides the capability of daily data base review with drill-down capability mimicking eCRF design in a visual platform allowing easy access and completion of data review or summary.
The sheets within the application include the following:

- **Home page**: In a platform review of data this page lists Sponsor studies and allows the reviewer to choose one or more studies of interest for review. Once chosen, the sheet displays the site subject population and the selected study is locked across all pages of the visualization platform so that the user reviews only that study's or set of studies' data. The Home page also allows the reviewer to choose the sheet – amongst Demographics, Disposition, AEs, Labs, Vitals, and Patient Profiles – on which to start their review. (Figure 2)

- **Demographics**: Reviews study/subject demographic values including cohort race, gender, age, disease stage and other pertinent information according to study needs.

- **Disposition**: Relays subject enrollment status within the study with drill down access to detailed information (Figure 3).

- **Adverse Events (AE)**: Reviews the number of AEs experienced by a subject or group of subjects by exploring relationship to study drug, action taken, grade, and occurrence over time. Also, by shared-space tab manipulation, evaluates AEs by unique subject highest grade, interrelationships between selected AEs, and AE evolution through grade and duration.

- **Labs**: Allows the reviewer to choose one analyte and compare it across the study by cohort, grade, dose, cycle Length, visit, group or individual subject. Tabular lab details are shown as on scrolls down the sheet.

- **Labs – Multiple Analytes**: Allows the reviewer to select one or more analytes to compare across cohort, grade, dose, cycle Length, visit, or individual subject. Lab details are also shown.

- **Liver Enzymes – Treatment**: Delivers the baseline values of liver enzymes (ALT, AST, Total Bili, APL) for cohort, grade, dose, cycle Length, visit, or individual subject. The sheet also displays subjects who might have experienced DILI (Drug Induced Liver Injury) through eDISH graphs which plot peak liver enzyme (ALT or AST by Total Bili) values and normal lab by category quadrant (Normal, Templar's Corollary, Cholestasis, and Hy's Law). The Change from Baseline Graph provides the reviewer a view of subject liver enzyme over time (Figure 4)

- **Vitals**: Plots subjects' vital signs over the current length of the study.

- **Patient Summary** Provides a graphic depiction of an individual subject's study drug, AEs by grade with any concomitant medication, and occurrences over time. This patient profile home page also displays subject labs and vital signs over time. The reviewer may choose AE's, labs, or vitals of interest from this page.

- **Patient Summary Tables –**: This sheet displays listings of tabular data that includes Patient Information, Disease History, Prior Systemic History/Prior Cancer Radiation, ECOG Performance Status, Study Drug Administration, Adverse Events, Labs, Labs Summary, Vital Signs, Pregnancy, Dose Limiting Toxicity, Urinalysis, Treatment Discontinuation, Study Exit, and Survival Status.

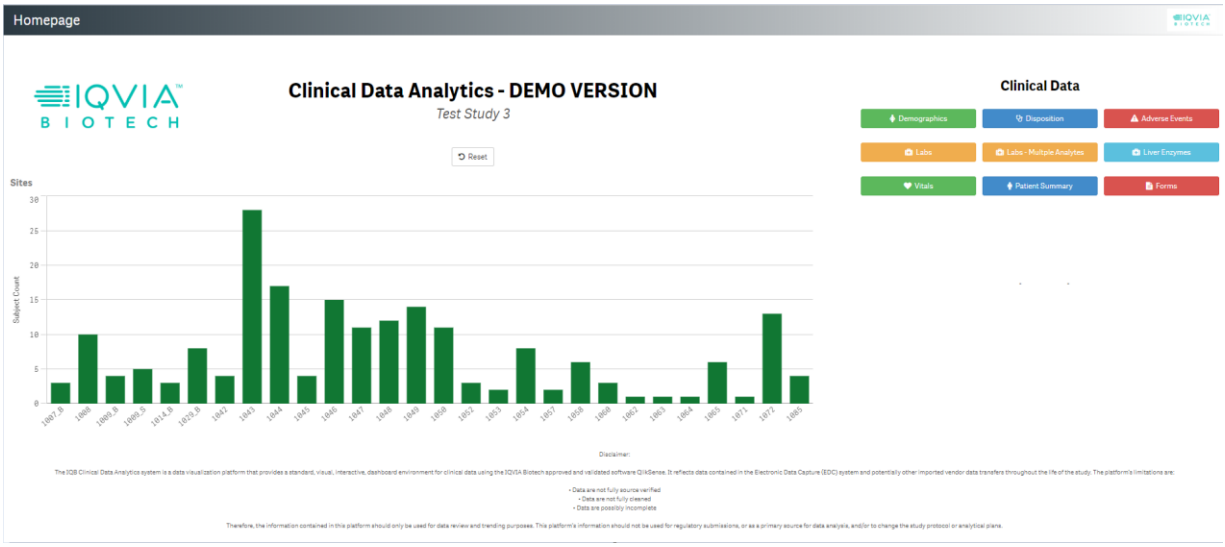

Figure 2 Home page: In a platform review of data this page lists Sponsor studies and allows the reviewer to choose one or more studies of interest for review. Once chosen, the sheet displays the site subject population and the selected study is locked across all pages of the visualization platform so that the user reviews only that study's or set of studies' data. The Home page also allows the reviewer to choose the sheet – amongst Demographics, Disposition, AEs, Labs, Vitals, and Patient Profiles – on which to start their review

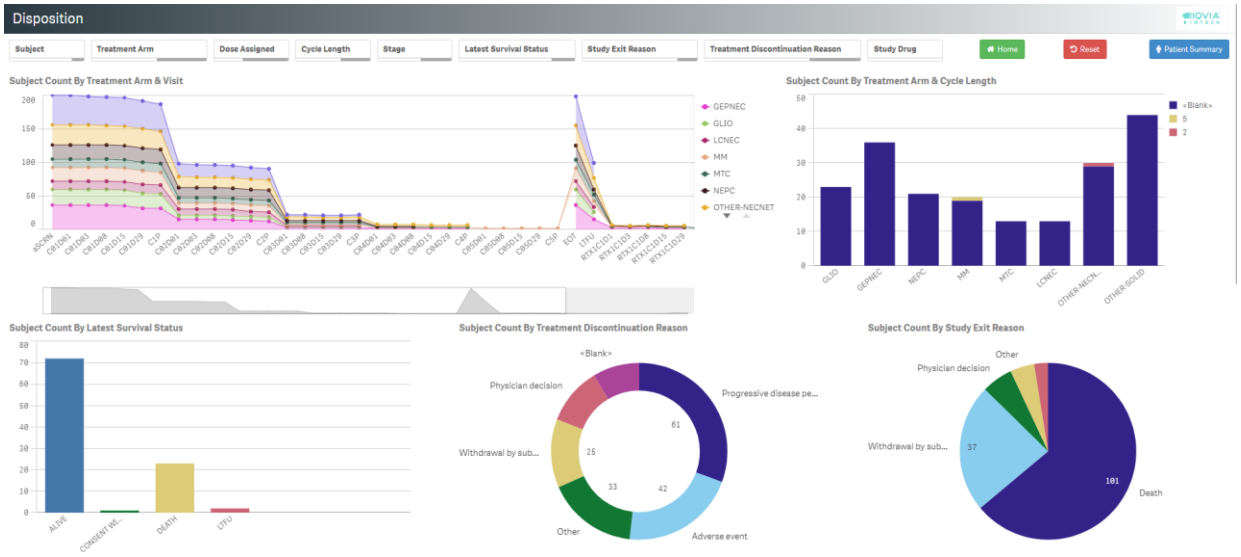

Figure 3 Disposition: Relays subject enrollment status within the study with drill down access to detailed information.

Figure 4 Liver Enzymes – Treatment: Delivers the baseline values of liver enzymes (ALT, AST, Total Bili, APL) for cohort, grade, dose, cycle Length, visit, or individual subject. The sheet also displays subjects who might have experienced DILI (Drug Induced Liver Injury) through eDISH graphs which plot peak liver enzyme (ALT or AST by Total Bili) values and normal lab by category quadrant (Normal, Templar's Corollary, Cholestasis, and Hy's Law). The Change from Baseline Graph provides the reviewer a view of subject liver enzyme over time.

CONCLUSION

Sponsor request for Quarterly Safety Reporting is increasing within the pharmaceutical and biopharmaceutical industry. Federal regulations hold clinical trial sponsors with accountable for patient safety and for evidence that the responsibility has been up held. Clinical Research Organizations (CRO) provide support services to companies that develop new drugs or devices for human health. CRO are obligated to anticipate the needs of sponsors and provide services that will fill the need.

The request from sponsors for Quarterly Safety Reporting has increased within the organization over the last 5 years. As such, the Clinical Science Department created a process to deliver QSR within a project or over a platform of studies. The process drives delivery of a robust report that analyzes clinical trail data from the clinical data base from 3 months after first subject into the trial or per sponsor designation until the close of the data base. The process described is one that uses validated tables and listings, and graphics from a validated output (CDR). The efficiencies gained by employing the QSR include a targeted review of data from the clinical data base at appropriate intervals per agency recommendation.

The CDR is a tool used to review data from the clinical data base on a quarterly basis. Review processes which included data gathering/manipulation by DM and biostats to create SAS TLGs on demand, or data analysis set review via Excel or JReview proved to be costly (as time spent by Biostats programming validated TLGs for unclean data) and cumbersome (as training required to manipulate Excel files and create JReview reports is tedious and user-unfriendly). Platforms that incorporate disparate data into a user-friendly interactive dashboard environment have become more commonplace in the clinical research industry. The CDR programmed in Qlik Sense is IQVIA approved software that has been built to IQVIA Biotech Clinical Science specifications and that is modified to fit client need.

The CDR tool initially affected those involved with QSR – including the internal team CS, Medical Monitoring, Project Management, and Information Technology and the external team of the sponsor. However, the platform has been built-out to include on-going data review by additional internal team members within both clinical science and clinical operations. Moreover, this tool has been provided to customers to view their data on an on-going basis.

The tool brings together disparate data sources under a set user-friendly visual platform for data review. Users are able to open the application and view all areas of subject safety data (including but not limited to Demographics, Disposition, Labs, Vitals, AE, Drug Administration) and explore possible drug-induced organ injury (e.g. for liver (e.g. Hy's Law) and/or kidney) on an overall population level. The platform has drill down capability that allows various stages of subject detail review with the click of a button on areas of the graphic to the level of patient profile analysis. Additionally, the system is auditable and thus able to provide detailed information regarding entry by users – a feature that is needed to maintain accurate safety records for data review in the event of sponsor request or regulatory agency audit.

The efficiencies gained by the use the CDR in preparing QSR allows for both report completion in a timely and efficient manner, and for increased capacity to provide this service to more customers.

REFERENCES

1. 21 CFR 312.32 (c)(1) Title 21 Food and Drug Administration Code of Federal Regulations, April 1, 2019

2. Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), December 2012

ACKNOWLEDGMENTS

I thank Joe Donaghy for helping me realize the completion and widespread distribution of this tool, and for providing me with a stellar development team, including Michelle Dunston, James Carter, and Stewart Taylor. I thank my colleagues for their service and dedication to the CDA tool's preparation/build, distribution, and training including Vidya Muthukumar and Elise Collins. I also thank members of the QSR team who help on a consistent basis with the preparation and QC of the report including Khushboo Parmal and Safoora Mulla. Finally, I thank members of the Clinical Science Department for their encouragement and advise in the creation and development of the tool for corporate distribution including Dr. Julie Horan and Dr. Ijeoma Agunanne.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:
Author Name: Yvonne Denkins, PhD
Company: IQVIA Biotech
Address: 7100 Perimeter Drive
City / Postcode: Morrisville, NC 27560
Work Phone: 805 490 8375
Email: ydenkins@novellaclinical.com
Web: www.iqviabiotech.com