1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the process for initiating, managing, and completing Serious Adverse Event (SAE) reconciliation between the clinical database (CDB) and the safety database (SDB). SAEs from clinical studies are stored in both the CDB and the SDB. Therefore, a procedure is required to make sure SAEs are accounted for in both databases.

2. SCOPE

2.1 This SOP applies to all clinical trials sponsored by BeiGene for which BeiGene or a selected Functional Service Provider (FSP) are responsible for all Data Management activities. This SOP would not apply to studies where the Data Management services are fully outsourced to a Contract Research Organization (CRO) which will be specified in Data Management Plan/Serious Adverse Event Reconciliation Plan.

3. ABBREVIATIONS AND DEFINITIONS

3.1 **Clinical Database (CDB):** The complete set of data for a clinical trial including CRF data housed in an EDC system (or other relational database application) and external data (e.g., data received from electronic data transfers).

3.2 **Safety Database (SDB):** A transactional database containing serious adverse event information designed to manage reporting and pharmacovigilance for investigational products. Applies to both internal and external vendor systems, where appropriate.

3.3 **Serious Adverse Event Reconciliation Plan**: This plan describes the database/report fields that will be reconciled and the timing and/or frequency of SAE reconciliation efforts, to ensure that the pre-defined key data elements in the CDB are consistent with the SDB.

3.4 **Serious Adverse Event Reconciliation Log:** A list of key pre-defined data discrepancies resulting from a comparison of SAEs reported in the CDB against those reported in the SDB. It is a cumulative running log reflective of each reconciliation at the time the reconciliation occurred and is maintained for each clinical trial.

3.5 **Serious Adverse Event Reconciliation Approval Form:** The form is used to collect signatures that indicate agreement with the assessment and disposition of reconciliation discrepancies recorded in a clinical trial's Serious Adverse Event Reconciliation Log when there is a key milestone or final database lock.

3.6 **AE:** Adverse Event

3.7 **AWS**: Amazon Web Services

3.8 **CO:** Clinical Operations

3.9 **CRF:** Case Report Form

3.10 **EDC:** Electronic Data Capture

3.11 **GPS:** Global Patient Safety

3.12 **ICSR:** Individual Case Safety Report

3.13 **LDM:** Lead Data Manager

3.14 **MC:** Medical Coding

3.15 **MedDRA:** Medical Dictionary for Regulatory Activities

3.16 **MM:** Medical Monitor

3.17 **PT:** Preferred Term

3.18 **RSG:** Rave Safety Gateway

3.19 **SAE:** Serious Adverse Event

3.20 **sFTP:** secure File Transfer Protocol

3.21 **TMF:** Trial Master File

4. RESPONSIBILITIES

4.1 Lead Data Manager (LDM) or designee

4.1.1 Leads the overall process of creating the Serious Adverse Event Reconciliation Plan with the support of GPS, MM, CO and MC and coordinates the overall process of SAE reconciliation between CDB and SDB as per the Serious Adverse Event Reconciliation Plan.

4.1.2 Ensures all tasks leading to SAE reconciliation are performed according to the frequency documented in the Serious Adverse Event Reconciliation Plan. The minimum frequency requirement is monthly.

4.1.3 Ensures the completion of SAE reconciliation and consistency between CDB and SDB, including the resolution of all SAE reconciliation issues prior to database lock and any key milestone.

4.2 Global Patient Safety (GPS)

4.2.1 Manages data in the SDB as per GPS procedures.

4.2.2 Determines the schedule for regular reconciliation of studies in consultation with LDM or designee.

4.2.3 Schedules SDB data extractions/coordinate the automation data extraction as needed for regular or milestone reconciliation.

4.2.4 Provides corrective action recommendations regarding discrepancies between CDB and SDB as required. May consult with MM, MC and/or LDM or designee.

4.3 Clinical Operations (CO)

4.3.1 Liaises with site personnel to assist with resolution of outstanding queries and/or unreported events or events that require updating in either CDB (including transmitting the data to SDB for RSG studies) or SDB.

***Note**: For RSG studies, when an SAE cannot be entered in EDC, the paper process should be followed to report these events to safety.*

4.4 Medical Monitor (MM)

4.4.1 Provides medical advice and/or recommendations to LDM or designee, GPS and MC as needed for issue resolution.

4.4.2 MM may delegate SAE reconciliation tasks to Clinical Scientist(s).

4.5 Medical Coding (MC)

4.5.1 Reviews and provides recommendations regarding discrepancies between the coding of the event in the CDB and the SDB. May consult with MM and GPS.

5. PROCEDURE

5.1 Creating and Approving SAE Reconciliation Plan

5.1.1 LDM or designee will work with GPS, MM, CO and MC to ensure that a Serious Adverse Event Reconciliation Plan is created based on the Template *Serious Adverse Event Reconciliation Plan* (VV-QDOC-00205).

5.1.2 Reconciliation frequency and fields of the CDB and the SDB/Report will be specified in the Serious Adverse Event Reconciliation Plan.

5.1.3 LDM or designee will circulate the Serious Adverse Event Reconciliation Plan to study team members, including the study safety lead, MM, CO, MC, and ICSR management team or drug safety vendor representative for review and obtain signature approval.

5.1.4 LDM or designee will file the final approved Serious Adverse Event Reconciliation Plan in the TMF.

5.1.5 If the study Serious Adverse Event Reconciliation Plan is required to update, repeat steps 5.1.1 - 5.1.4.

5.2 SAE Reconciliation Process

5.2.1 The SAE reconciliation process will be initiated after the first SAE has been reported in the CDB and/or the SDB. The SAE reconciliation process will occur via a regular frequency specified in the study Serious Adverse Event Reconciliation Plan. The minimum frequency requirement is monthly.

5.2.2 The full BeiGene study SAE listing will be extracted from SDB to AWS directly via a daily basis, and the listing will be filtered and posted into the individual study folders automatically under bdata/udata in AWS by a splitting script.

5.2.3 A programmed reconciliation listing will be generated from an extract directly from the CDB in addition to the SDB listing from step 5.2.2 and posted into the individual study folders in AWS.

***Note**: This step may be superseded by a manual process whereby the LDM or designee will generate a cumulative listing from the CDB containing all variables to be reconciled, as per the schedule specified in the Serious Adverse Event Reconciliation Plan, or as needed.*

5.2.4 LDM or designee performs reconciliation of key data as defined in the Serious Adverse Event Reconciliation Plan.

5.2.4.1 LDM or designee will record reconciliation findings on the study specific Serious Adverse Event Reconciliation Log with the Template *Serious Adverse Event Reconciliation Log* (VV-QDOC-00206).

5.2.4.2 If no discrepancies are identified, this will be documented in the Serious Adverse Event Reconciliation Log. Reconciliation is considered complete until the next round of SAE reconciliation.

5.2.4.3 If discrepancies exist, this will be documented in the Serious Adverse Event Reconciliation Log and procedure steps 5.2.6 to 5.2.8 will be followed.

5.2.4.4 LDM or designee will post the Serious Adverse Event Reconciliation Log in an internal central location for GPS and MM to access. LDM or designee will communicate new or updated discrepancies in the Serious Adverse Event Reconciliation Log to GPS and MM as required.

5.2.5 GPS provides the recommendations for corrective actions for CDB as required and/or takes corrective actions for SDB. All recommendations and actions taken are to be documented in the Serious Adverse Event Reconciliation Log. GPS may consult with the MM for corrective action recommendations.

5.2.6 If there are any coding discrepancies, LDM or designee will share the Serious Adverse Event Reconciliation Log with MC.

5.2.7 MC will work with GPS and/or MM to provide resolutions, as appropriate.

5.2.7.1 Mismatches of PT due to MedDRA version differences between the CDB and SDB will be reviewed and accepted as appropriate and documented in the Serious Adverse Event Reconciliation Log as such. All final decisions regarding discrepancy resolutions will be made by MM.

5.2.8 LDM or designee will issue queries in the CDB for site follow-up and resolution. Corrective action queries will be documented and tracked in the Serious Adverse Event Reconciliation Log.

Notes: *The LDM or designee may issue queries in the CDB to clarify direct data point discrepancies prior to receiving corrective action feedback from GPS, MM or MC.*

All discrepancies that require GPS, MM, or MC feedback and/or recommendation will be actioned when GPS, MM, or MC have provided feedback.
Example: Coding discrepancies

5.2.8.1 LDM or designee will share and escalate the discrepancies that require CO follow-up with the site.

5.2.8.2 CO team will follow up with sites to ensure the discrepancies/queries are resolved.

5.2.8.3 For discrepancies/queries requiring expedited review, LDM or designee will escalate to study safety lead to further follow up.

5.2.8.4 GPS will update the SDB where appropriate (i.e., clarification or correction received from the sites on an SAE form or equivalent form). For RSG studies, sites will update the data in CDB and transmits it to safety database. An updated cumulative listing of the SDB containing all variables to be reconciled may be sent to LDM or designee via the method in step 5.2.2.

5.2.8.5 When medically equivalent matches are not possible, LDM or designee, MC and/or GPS will consult with MM to clarify any mismatches and ensure that terms are 'medically compatible'.

5.2.8.6 If all methods to reconcile data have failed, LDM or designee will consult with GPS, MM and/or MC for a final decision. All final decisions regarding discrepancy resolutions will be made by MM.

5.2.8.7 LDM or designee will update the Serious Adverse Event Reconciliation Log for each discrepancy resolved.

5.2.8.8 Events will be considered reconciled when all required data points reconcile between both CDB and SDB databases. If there are any exceptions agreed upon with the study team, the information should be specified in the Serious Adverse Event Reconciliation Plan. Sites need to follow up the protocol defined rule of SAE collection for SDB and CDB post collection.

After CDB lock, new or updated SAE data will be captured only in the SDB.

5.3 Final SAE Reconciliation Documentation Prior to CDB Lock and/or Key Milestone

5.3.1 LDM or designee will use the Form *Serious Adverse Event Reconciliation Approval Form* (VV-QDOC-00194) to document reconciliation completion prior to CDB lock or prior to any key milestone requiring SAE reconciliation. LDM or designee will circulate the Serious Adverse Event Reconciliation Approval Form and obtain study team approvals.

5.3.1.1 The Serious Adverse Event Reconciliation Approval Form will not be completed for recurrent reconciliations as per the Serious Adverse Event Reconciliation Plan.

5.3.2 LDM or designee will file Serious Adverse Event Reconciliation Log(s) and Serious Adverse Event Reconciliation Approval Form(s) in the TMF. All study documents will be filed in accordance with the study specific TMF Management Plan what is followed with Template - *Trial Master File (TMF) Management Plan* (VV-QDOC-00276).

6. REFERENCES

6.1 Controlled Documents

6.1.1 VV-QDOC-00194 - Form - *Serious Adverse Event Reconciliation Approval Form*

6.1.2 VV-QDOC-00205 - Template - *Serious Adverse Event Reconciliation Plan*

6.1.3 VV-QDOC-00206 - Template - *Serious Adverse Event Reconciliation Log*

6.1.4 VV-QDOC-00276 - Template - *Trial Master File (TMF) Management Plan*

6.2 Regulatory References

6.2.1 N/A

6.3 Other References

6.3.1 N/A

7. APPENDICES

7.1 N/A

8. DOCUMENT HISTORY PAGE

Version	Effective Date	Brief Description of Change
1.0	11JUN2018	Original SOP
2.0	13NOV2019	Re-formatted 3.1 Abbreviations list. Updated 3.2 Definitions. Updated 4.0 Responsibilities. Updated and clarified 5.0 Procedure into three main sections (5.1 Creating and Approval of SAE Reconciliation Plan, 5.2 SAE Reconciliation Process and 5.3 Final SAE Reconciliation Documentation Prior to CDB Lock and/or Key Milestones). Added recommended SAE Reconciliation frequency and when SAE Reconciliation to be initiated, 5.2.1. Added clarification that LDM may issue SAE queries for direct data point discrepancies prior to receiving feedback/log from other functional teams, 5.2.9. Added that LDM to escalate trends of concern with CO, 5.2.10. Updated SOP to include process for expedited review, 5.2.12. Clarified in SOP that if cross functional agreement cannot be reached in SAE reconciliation, final decision maker will be MM, 5.2.15. Clarified SAE reporting in CDB after protocol collection period, 5.2.17. Added process clarification for completing SAE Reconciliation Approval Form, 5.3.1 and 5.3.2
3.0	20 Aug 2021	• Re-formatted and re-ordered abbreviation list in section Abbreviations and Definitions. • Updated Responsibilities in general language and added the scenario for RSG. • Updated the process in section 5.2.2 and 5.2.3 per the method change to transfer the safety data from SDB to AWS directly. • Added the scenario for RSG in section 5.2.8.4. • Clarified monthly is the minimum frequency requirement in section 4.1.2 and 5.2.1. • Updated with 'LDM or designee' in the whole document. • Administrative updates.

Document Approvals

Approved Date: 10 Aug 2021

Task: SME Approval Verdict: Approve changes & release	Xiaojuan Qu, (xiaojuan.qu@beigene.com) Document Owner 13-Jul-2021 04:30:44 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Hongwei Wang, (hongwei.wang@beigene.com) Functional Area Representative 13-Jul-2021 05:58:21 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Wazir Woods, (wazir.woods@beigene.com) Functional Area Representative 13-Jul-2021 14:59:53 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Jean Ohara, (Jean.Ohara@beigene.com) Functional Area Representative 14-Jul-2021 00:11:37 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Lillian Chau, (lillian.chau@beigene.com) Functional Area Representative 14-Jul-2021 14:36:27 GMT+0000

Task: SME Approval Verdict: Approve changes & release	CJ Delgra, (cj.delgra@beigene.com) Functional Head 21-Jul-2021 15:51:36 GMT+0000

Document Approvals

Approved Date: 10 Aug 2021

Task: SME Approval Verdict: Approve changes & release	Kelly Shart, (kelly.shart@beigene.com) Functional Area Representative 27-Jul-2021 21:58:51 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Yong (Ben) Ben, (ben.yong@beigene.com) Functional Head 30-Jul-2021 00:42:03 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Melika Davis, (melika.davis@beigene.com) Functional Head 30-Jul-2021 04:12:27 GMT+0000

Task: SME Approval Verdict: Approve changes & release	Jane Huang, (jane.huang@beigene.com) Functional Head 09-Aug-2021 23:39:08 GMT+0000

Task: QA Approval Verdict: Approve changes & release	Khosheh Sanglaji, (khosheh.sanglaji@beigene.com) QA Approval 10-Aug-2021 16:36:29 GMT+0000