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Clinical Standard Operating Procedure (SOP)

Patient Safety Standards in India, ed 1.0 IN

[Link to Procedural Information Release Note](#)

Purpose:	The purpose of this Standard Operating Procedure (SOP) is to provide a detailed description of local procedures for ensuring adequate safety reporting according to the relevant Global SOPs, International Procedures (IPs) and local regulatory requirements.
Complies with:	Drugs and Cosmetics Act and Rules, Ministry of Health and Family Welfare, Government of India
Applicable to:	All AstraZeneca Pharma India Limited (AZPIL) personnel who encounter AE and PQC arising from any AstraZeneca product. This may include staff in Clinical Research, Medical Affairs, Regulatory Affairs, Marketing, Sales and other personnel who are involved in the handling of AZ drugs and devices in India.
Summary:	This SOP describes local processes and procedures for recording, processing, following up of AEs from spontaneous and solicited sources and SAEs from local interventional clinical studies and local noninterventional studies, including pregnancy, overdose, lack of effect, medication errors and reports of misuse and abuse whether or not associated with AEs or product quality complaint reports. The SOP also describes the responsibilities of the local Patient Safety unit.

SUMMARY OF CHANGES TO THIS SOP SINCE THE PREVIOUS EDITION**What has changed:**

Section 1: e-room was replaced with SharePoint site.

Section 2.2: Sections 2.2 & 2.3 of the previous edition of this SOP were merged into one section, 2.2. Changes were incorporated to reflect current legislation and process.

Sections 3, 3.1 to 3.4, 4.1 to 4.3 and 7.2: Changes incorporated to reflect current legislation and process.

Section 7.1: Off label use was included. Attachment of source documents in Jasper and tracking of all follow-up attempts in Jasper was included. Expedited reporting of a copy of SUSARs associated with marketed products to Pharmacovigilance Programme of India was included. Quality assurance agreement was changed to quality assurance agreement or safety agreement.

Section 9: Annual review of safety agreements was changed to biennial review.

Section 10.1: GLMS was changed to AZLearn. Training related to SAE reporting in clinical studies managed by AZPIL was included.

Section 10.3: Deleted quarterly requests for new hires from Human Resource department.

Section 10.4: MC Procedural Document matrix was changed to CQF Overall Training Grid.

Section 12: Indexed journals in Indian languages were specified to Medical/Pharmaceutical journals.

Section 13: Reference to local Procedure for Management of Core Product Information was included replacing the reference to OPI Review and Management of Prescribing Information for Branded Generics.

Section 19: Auto update of Sapphire ID for the cases submitted via Jasper was included.

Section 19.1: Requirement for reconciliation of reports sent to DES was deleted.

Section 19.2: Process associated with the use of PQC Excel spreadsheet was deleted.

What is the reason for the change(s):

Changes incorporated to reflect current legislation, processes and procedures. The local SOP need to be published in LDMS as Clinical SOP.

Process Owner: Patient Safety Manager, AstraZeneca Pharma India Limited

Process Group: Clinical Quality and Compliance

Topic: Patient Safety Standards

Supersedes: AZRA SOP "Patient Safety Standards in India, ed 2.0 IN" Effective Feb.2, 2012

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1. GENERAL PRINCIPLES

This Standard Operating Procedure (SOP) describes how adverse event (AE) data as well as pregnancy, lack of efficacy, suspected transmission of infectious agents, overdose, abuse and misuse and medication error reports associated with an AstraZeneca (AZ) product, are locally collected, managed and reported within AstraZeneca Pharma India Ltd. (AZPIL), to ensure the compliance with Global SOPs and Local requirements relating to the reporting of adverse event data in India as per the Schedule Y of Drugs and Cosmetics Act and Rules, Ministry of Health and Family Welfare, Government of India (<http://www.cdsco.nic.in/Drugs&CosmeticAct.pdf>).

The current version of the “Patient Safety Standards” Global SOP and current versions of other relevant Global and Local SOPs should be referred to at all times for further details and in case of any uncertainty. The purpose of this local SOP is to describe the safety reporting process in Marketing Company (MC) AZPIL to ensure safety reporting standards defined in Global SOPs and the local regulatory requirements defined in Schedule Y of Drugs and Cosmetics Act and Rules are followed.

In this document responsibilities are mentioned by job titles. In the absence of the Patient Safety Manager (PSM), the Patient Safety Manager Deputy (PSMD) is responsible for performing all applicable tasks described in this SOP and vice versa. The AZPIL Local Study Delivery team includes Local Study Delivery Team Leader, Monitors and Study Coordinators. Contract Research Organisation (CRO) study delivery team includes CRO Study Delivery Team Leader, Monitors and Study Coordinators. The AZPIL normal business hours are from 09.00 am to 06.00 pm Monday to Friday.

For the purposes of reporting cases received by AZPIL to the Patient Safety Data Entry Site (DES), the AZPIL aware date is the date that the first AZPIL personnel became aware of the report. AZPIL personnel include employees of AZPIL, those employed by an organisation having contracted arrangements with AZPIL such as CRO, licensee, licensor or market research agency.

The local tracking database used by AZPIL is called JASPER. The database is used when applicable for case data entry, submission of reports to DES, extraction of Council for International Organizations of Medical Sciences (CIOMS) reports and periodic Suspected Unexpected Serious Adverse Reactions (SUSARs) line listings for submission to local Health Authority, Institutional Review Boards (IRBs)/Ethics Committees (ECs) and Investigators and tracking. Access to the relevant Global Patient Safety databases can be obtained via the Global Patient Safety Info space and Global MC SharePoint site.

The PSM supports Nepal, Bhutan and Sri Lanka with respect to AE reporting to local health authorities in these countries. Training regarding AE and Product Quality Complaint (PQC) reporting is provided by the PSM for the sales and marketing staff supporting the marketing in Nepal and Bhutan. However, Sri Lanka has its own marketing team and trainings are conducted locally. The AEs from these countries are received by the PSM,

entered in JASPER. The CIOMS reports posted in JASPER are submitted to the local health authorities in these countries by the PSM.

This Local SOP relates to the following Procedural documents:

- Patient Safety Standards (LDMS_001_00070878)
- Adverse Event Reporting in Clinical Studies (LDMS_001_00066992)
- Obtaining Follow-up Information on Adverse Event Reports (LDMS_001_00079285)
- Handling of Adverse Drug Reaction Reports from the Published Literature (LDMS_001_00079282)
- Patient Safety After Hours Procedures (LDMS_001_00075444)
- Handling of Reports of Product Quality Complaint/Product Security with associated Adverse Events, Lack of Effect, or Medication Error (LDMS_001_00095610)
- Management of Safety Agreements [6-P6-(current version)-X]
- Pharmacovigilance Quality Programme (8-P97-cv-X)
- The Principles of the Clinical Quality Framework (LDMS_001_00056600)
- The Product Master list [8-P87-(current version)-X]
- Requirements for collection of adverse event during organised data collection programmes [7-P23-(current version)-X]
- Requirements for Reporting of Adverse Events arising from Digital Listening Activities [7-P25-(current version)-X]
- Expedited and Periodic Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARS) to Investigators and Ethics Committees in Asia Pacific (LDMS_001_00085881)
- Expedited Reporting of Adverse Events (LDMS_001_00068866)
- Define Procedural Information Training Requirements (LDMS_001_00079250)
- Management of Product Quality Complaints in India (LDMS_001_00123161)
- Procedure for Management of Core Product Information (INDRAD/007)
- Product Recall (LDMS_001_00157185)

1.1 Accountabilities and responsibilities

Table 1 summarises the main job roles and their accountabilities and responsibilities relating to the processes described in this SOP.

Table 1 Accountabilities and responsibilities

Who	Accountability / responsibility
Patient Safety Manager/Deputy Patient Safety Manager	<ul style="list-style-type: none"> Responsible for patient safety matters covering data from both clinical studies and marketed use of AstraZeneca products described in the section 4.5.2 of the SOP 'Patient Safety Standards (LDMS_001_00070878)'. Responsible for the local Marketing Company (MC) overarching responsibilities for relevant Pharmacovigilance processes described in Table 1 of the International Procedure 'Pharmacovigilance Quality Programme (8-P97-cv-X)'.

2. ADVERSE EVENT REPORTING IN CLINICAL STUDIES

2.1 Serious Adverse Event (SAE) Reporting in Clinical Studies managed by AZPIL

The Investigators report the SAEs in clinical studies using the Web Based Data Capture (WBDC) system or paper based SAE form within 24 hours to the AZPIL. The reporting of the SAEs to the DES is done either by Local Study Delivery team / Patient Safety personnel to ensure reporting within the required timeframe in the absence of one.

2.2 SAE reporting process

The Investigator completes SAE details in the WBDC system. On completion a "New SAE alert email" is sent to Patient Safety, India Mailbox from the clinical study database. The Local Study Delivery team reviews the SAE in WBDC system and if needed liaise with the site to complete any missing information.

Upon review, the monitor enters the 'AZ aware date' and ticks 'send e-mail alert to Drug Safety' check box against appropriate event on AZ Aware of SAE form. The reporting is done within required timelines (refer to SOP Adverse event reporting in clinical studies). A second e- mail alert is sent from WBDC system to Patient Safety, India Mailbox, which confirms the reporting to the DES.

In the clinical studies using paper Case Record Form (CRF), the investigator enters the details of the SAE in the clinical study in the paper based SAE form. The site personnel send the SAE form through FAX or scanned copy of the SAE form by e-mail to the AZPIL Local Study Delivery team. The AZPIL Local Study Delivery team reviews the completeness of the form and if needed liaise with the site to complete any missing information. If the AZPIL Local Study Delivery team does not have the case worker/case

approver account in JASPER patient safety database, the AZPIL Local Study Delivery team sends the completed SAE form to the PSM.

The AZPIL Local Study Delivery team/PSM enters the SAE in the JASPER patient safety database and submits to the DES within the required timeline as per table 1-1 of the Adverse Event Reporting in Clinical Studies SOP. The paper copy of the SAE report is filed in the Clinical Study- specific file by the AZPIL Local Study Delivery team.

An e-mail is received by the PSM through 'Patient Safety, India Mailbox' from SAPPHIRE confirming the receipt of SAE report by DES.

The study monitor contacts the investigator site and sends the following information to Patient Safety, India Mailbox within 6 calendar days of occurrence of SAE (where possible), but no later than 6 calendar days of AZ aware date.

- Duly filled Appendix XI of Schedule Y signed by the investigator
- Investigator's assessment of clinical trial related injury at his/her own discretion
- Initial/Follow-up information
- Study information (protocol title, study code, Clinical Trial Registry of India (CTRI) registration number, sponsor and sponsor's address with contact number and e-mail address).
- Details about the investigator (study centre, study site number and e-mail address of investigator)
- Details about the ethics committee (name and address of the IRB/EC, name and address of the chairman of IRB/EC with contact number and e-mail address)
- Detail of the Head of the Institution where the trial has been conducted (name and address with contact number and e-mail address, and confirmation if the investigator is the Head of the Institution)
- Causality Assessment (Related/Unrelated) by Investigator
- Details of compensation provided for injury or death. In case no compensation has been paid, reason for the same.
- Laboratory investigation report/Discharge summary (if available and applicable)
- Post-mortem report (if applicable and available) Clinical trial approval letter

3. REPORTING TO REGULATORY AUTHORITY, HEAD OF THE INSTITUTION AND IRB/EC

3.1 Local Regulatory Requirement

Schedule Y of Drugs and Cosmetics Act and Rules, Ministry of Health and Family Welfare, Government of India (<http://www.cdsc0.nic.in/Drugs&CosmeticAct.pdf>) requires the sponsors to report to all concerned (Chairman of the IRB/EC, Head of the Institution where the trial has been conducted and Regulatory authority) of all SAEs in an expedited manner.

In addition, the SAEs of death are required to be expedited to Chairman, Expert Committee for Examination of Reports of SAEs constituted by the Licensing Authority. The reporting requirements are also communicated by the regulatory authority in the clinical study approval letter. The expedited reporting to regulatory authority should include the data elements described in Appendix XI of Schedule Y and pre-screening checklist for submission of SAE report (<http://goo.gl/Y8GbmQ>). The SAEs are posted in JASPER as CIOMS forms for expedited reporting.

3.2 Reporting to Regulatory Authority

All SAEs are forwarded within 10 calendar days of occurrence of SAE (where possible), but no later than 10 calendar days of AZ aware date to the Drugs Controller General of India (DCGI). The SAEs of death are forwarded within 10 calendar days of occurrence of SAE (where possible), but no later than 10 calendar days of AZ aware date to the Chairman, Expert Committee for Examination of Reports of SAEs constituted by the Licensing Authority.

The PSM extracts the produced unblinded CIOMS forms, if available from JASPER. PSM completes the pre screening for submission of SAE report. Where CIOMS forms are available, page numbers in the pre screening checklist will be referred to the sections in CIOMS forms. Where CIOMS forms are not available, page numbers in the pre screening checklist will be referred to the sections in signed Appendix XI provided by the investigator.

For the SAEs wherein investigator assessed causality is 'Related/Unrelated' and injury is 'No', injury assessment assigned by investigator is considered for expedited reporting. A default statement explaining lack of sponsor causality assessment and reference to Company Clinical Comment is included for expedited reporting.

For the SAEs wherein investigator assessed causality is 'Related/Unrelated' and injury is 'Yes', the PSM shall obtain the Sponsor's injury assessment and causality statement/company clinical comment from the Global Safety Physician with 8 calendar days of occurrence of SAE (where possible), but no later than 8 calendar days of AZ aware date for expedited reporting.

PSM forwards all SAE reports to Regulatory Affairs Manager located in Delhi for submission to Drugs Controller General of India (DCGI). PSM forwards the SAE reports of death to Chairman, Expert Committee for Examination of Reports of SAEs constituted by the Licensing Authority.

A copy of the SAE report along with a cover note is filed for records along with the acknowledgment copy or speed post/courier receipt, if applicable.

All SAE report submissions to DCGI and Chairman, Expert Committee for Examination of Reports of SAEs constituted by the Licensing Authority are tracked in JASPER. In the event of any delay in forwarding SAE reports to regulatory authority, the reason for delay is determined by PSM and documented with corrective and preventive action in JASPER. The reason for delay is also communicated to regulatory authority, if requested. Appropriate

preventive measures should be taken by the PSM to avoid any delay in the future due to the same reason.

3.3 Reporting to the Head of the Institution and Chairman, IRB/EC

All SAEs are forwarded within 10 calendar days of occurrence of SAE (where possible), but no later than 10 calendar days of AZ aware date to the Head of the Institution where the clinical trial is conducted and the Chairman of the IRB/EC which accorded the approval for conduct of clinical trial at the investigator site.

The expedited reporting of SUSARs to the Head of the Institution and the Chairman of the IRB/EC is done by Warsaw Hub. The PSM responsible for expedited reporting of non SUSARs to the Head of the Institution and the Chairman of the IRB/EC.

A copy of the report prepared for submission to Regulatory Authority as described in Section 3.2 of this SOP will be used for submission to Head of the Institution and Chairman, IRB/EC. A copy of the SAE report along with a cover note is filed for records along with the speed post/courier receipt.

All SAE report submissions to Head of the Institution and Chairman, IRB/EC are tracked in JASPER. In the event of any delay in forwarding SAE reports to Head of the Institution and Chairman, IRB/EC, the reason for delay is determined by Warsaw Hub/PSM and documented with corrective and preventive action in JASPER. Appropriate preventive measures should be taken by the Warsaw Hub/PSM to avoid any delay in the future due to the same reason.

3.4 Periodic SUSAR Line listing

There is no local requirement in India to submit the Periodic SUSAR Line Listing to Regulatory Authority, Investigators or IRBs/ECs. Hence the Periodic SUSAR Line Listings posted in JASPER are discarded by PSM.

4. REPORTING FOR STUDIES INVOLVING CONTRACT RESEARCH ORGANISATION (CRO)

4.1 SAE Reporting in Clinical Studies managed by CRO

When AstraZeneca uses CRO for the purpose of conducting clinical studies, it is the responsibility of Study Delivery personnel of the CRO to ensure that processes for handling AEs are in accordance with SOP “Adverse event reporting in clinical studies”. As the CRO acts on behalf of AstraZeneca, the AZ aware date is the date when any employee of that CRO becomes aware of a SAE.

The Investigators report the SAEs in clinical studies using the Web Based Data Capture (WBDC) system or paper based SAE form to the CRO. The reporting of the SAEs to the DES is done by CRO study delivery team. The PSM is responsible for expedited reporting to the DCGI and Chairman, Expert Committee for Examination of Reports of SAEs

constituted by the Licensing Authority. The PSM and Warsaw Hub are responsible for expedited reporting to the Head of the Institution and Chairman, IRB/EC.

The Investigator completes SAE details in the WBDC system or sends the completed paper based SAE form to the CRO study delivery team. The CRO study delivery team to review the SAE in WBDC system or the paper based SAE form and if needed liaise with the study site to complete any missing information.

Upon review, the CRO study delivery team sends the SAE report to the DES by e-mail with the 'AZ aware date'. The PSM or Patient Safety, India mailbox is copied on this e-mail. The reporting is done within required timelines (refer to SOP Adverse event reporting in clinical studies). A confirmatory e-mail regarding the receipt of SAE by DES is received by the PSM through 'Patient Safety, India mailbox' from SAPPHIRE.

The CRO study delivery team contacts the investigator site and sends the following information to Patient Safety, India Mailbox within 6 calendar days of occurrence of SAE (where possible), but no later than 6 calendar days of AZ aware date.

- Duly filled Appendix XI of Schedule Y signed by the investigator
- Investigator's assessment of clinical trial related injury at his/her own discretion
- Initial/Follow-up information
- Study information (protocol title, study code, Clinical Trial Registry of India (CTRI) registration number, sponsor and sponsor's address with contact number and e-mail address).
- Details about the investigator (study centre, study site number and e-mail address of investigator)
- Details about the ethics committee (name and address of the IRB/EC, name and address of the chairman of IRB/EC with contact number and e-mail address)
- Detail of the Head of the Institution where the trial has been conducted (name and address with contact number and e-mail address, and confirmation if the investigator is the Head of the Institution)
- Causality Assessment (Related/Unrelated) by Investigator
- Details of compensation provided for injury or death. In case no compensation has been paid, reason for the same.
- Laboratory investigation report/Discharge summary (if available and applicable)
- Post-mortem report (if applicable and available)
- Clinical trial approval letter

4.2 Reporting to the Regulatory Authority

The SAE reports are expedited to local regulatory authority following the process described in section 3.2 of this SOP.

4.3 Reporting to Head of the Institution and Chairman, IRB/EC

The SAE reports are expedited to Head of the Institution and the Chairman of the IRB/EC following the process described in section 3.3 of this SOP.

5. FOLLOW-UP OF SERIOUS ADVERSE EVENTS IN CLINICAL STUDIES

As much information as possible is obtained when the SAE is first reported. Follow-up may be necessary to obtain data required for medical evaluation of the case. The type and extent of follow-up undertaken is in response to the nature, severity and medical significance of the report and determined for each individual case. Follow-up is undertaken as applicable by the AZPIL Local Study Delivery team or the CRO study delivery team with guidance as appropriate from the Patient Safety Unit, see the SOP 'Obtaining follow-up information on Adverse Event Reports'. All attempts of follow-up with the investigator or reporter are documented.

In some cases, long-term follow-up is required, for example to determine the final outcome or sequelae of the event. For clinical studies, follow-up of SAEs may continue beyond the end of the study. When follow-up is complete or the AZPIL Local Study Delivery team /CRO study delivery team cannot obtain any further information the AZPIL Local Study Delivery team /CRO study delivery team communicates this to the DES and the case is considered closed.

In paper-based studies, the AZPIL Local Study Delivery team /CRO study delivery team contacts site staff using appropriate data query forms to obtain an answer to any follow-up queries. The AZ representative should actively follow-up on any incomplete or missing information not reported through with the initial SAE report to DES.

If the study is being conducted using a web-based data capture (WBDC) system, queries will be raised directly with site staff using the system query functionality. AZPIL Local Study Delivery team /CRO study delivery team may raise follow-up queries in the WBDC system.

When becoming aware of follow-up to a SAE in a paper-based study, or in a WBDC study when modules other than AE or SAE have been updated, the AZPIL Local Study Delivery team /CRO study delivery team will review the data entered by the Investigator/Site Staff and capture the clock start date (AZ aware date).

The AZPIL Local Study Delivery team /CRO study delivery team sends the follow-up information to DES within the required timeline as per table 1-1 of the Adverse Event Reporting in Clinical Studies SOP.

6. UNBLINDING IN CLINICAL STUDIES

The PSM and all Investigators have access to the Unblinding tool kit. There is one Unblinding kit at each Investigational Site and the other with the PSM. The details of code breaking are always kept in secure place accessed by the PSM. During medical emergency where appropriate management of the subject depends on the treating physician's knowledge of the treatment allocation, either the Investigator/ PSM are authorised to carry out the code break. In the event that Investigator/ PSM breaks a treatment code, the AZ Patient Safety DES should be informed.

In case the study uses Interactive Voice Response (IVR) or Interactive Web Response (IWR) system, the unblinding should be performed as per the study specific IVR/IWR manual/worksheets. In the event of unblinding, the AZ Patient Safety DES should be informed.

7. SAFETY REPORTING FOR MARKETED PRODUCTS

7.1 Safety Reporting and timelines for Marketed Products

Schedule Y of Drugs and Cosmetics Act and Rules, Ministry of Health and Family Welfare, Government of India requires all cases involving serious unexpected adverse reactions to be reported to the licensing authority within 15 days of initial receipt of the information.

Safety reporting for marketed products in India includes spontaneous reports. A spontaneous report is an unsolicited communication including pre-publication manuscripts, by a healthcare professional or consumer that describes one or more adverse drug reactions (ADRs) in a subject who was given one or more AstraZeneca marketed products and that does not derive from a study or any organised data collection scheme. This also includes:

- Outcomes of the use of AstraZeneca products during pregnancy
- ADRs during breastfeeding/drug exposure via breast milk
- Paediatric data (ADRs in neonates, infants or children)
- Lack of efficacy
- Suspected transmission of infectious agents
- Overdose, abuse, off label use and misuse
- Medication errors

Post marketed adverse event report form can be found with PSM/PSMD, in DELTA (database used by marketing team at AZPIL) and on the AstraZeneca India website (<http://www.astrazenecaindia.com/>).

In the event of a spontaneous report associated with marketed products, the treating Physician/Reporter sends the report to the PSM by Fax or E-mail

(patientsafety.india@astrazeneca.com). Spontaneous reports received by the “The Medinfo” e-mail (med.info3@astrazeneca.com) are forwarded by Medical Information Associates to the PSM. In case the spontaneous reports are received through medical information toll free number (1800 425 2031), the medical information associate attending the toll free number receives and communicates the spontaneous report to the PSM. If the spontaneous report is received by phone or letter, the PSM obtains the complete information from the reporter. All spontaneous reports received by phone are documented by the PSM.

All AZPIL personnel are trained to collect and report the spontaneous reports to the PSM within 24 hours of their awareness. The PSM reviews the spontaneous report. If needed, PSM shall liaise with the Physician/Reporter to complete any missing information. The spontaneous report is entered in JASPER and submitted to DES by PSM within the required timelines as per table 1 of the Patient Safety Standards SOP. The source documents are attached in the local tracking screen in JASPER, the paper source documents are filed in the AZPIL Patient Safety file. The follow-up of spontaneous reports are conducted as per the SOP ‘Obtaining Follow-up Information on Adverse Event Reports’. Any additional information received is entered in JASPER and submitted to DES within the required timelines as per table 1 of the Patient Safety Standards SOP. All follow-up attempts are tracked in JASPER.

If the spontaneous report is SUSAR, the CIOMS form is posted in JASPER. The PSM downloads the CIOMS from JASPER and submits to the Local Regulatory Authority within 15 days of AZ aware date with a copy to The Senior Scientific Officer, National Coordinating Centre, Pharmacovigilance Programme of India. A copy of the CIOMS report and cover letter is filed in the AZPIL Patient Safety file along with the speed post/courier receipt. In the event of any delay in reporting to regulatory authority, the reason for delay is determined and documented by PSM. The delay is also communicated to DCGI, if requested. Appropriate preventive measures should be taken by the PSM to avoid any delay in the future due to the same reason.

For the products wherein the AZPIL has a quality assurance agreement or safety agreement signed with the vendor, the adverse event reporting will be handled as per the safety agreement or safety clause of the quality assurance agreement. If AZPIL is responsible for reporting the spontaneous reports to regulatory authority, the spontaneous report is entered in JASPER and submitted to DES by PSM. The CIOMS forms of the spontaneous reports posted in JASPER are extracted by PSM and expedited to DCGI. If the vendor is responsible for reporting the spontaneous reports to regulatory authority, the spontaneous report is sent to the vendor, entered in JASPER and suppressed by PSM.

7.2 Product Quality Complaints

The PQCs are managed as per the local SOP ‘Management of Product Quality Complaints in India (LDMS_001_00123161)’ The PQCs from the Physicians, patients or other sources received by Sales, Marketing, Medical and Manufacturing Operations personnel are communicated to the PSM or PSMD. The details of the PQC, contact details of the

complaint originator and any additional information pertaining to the PQC/complaint sample (if available) will be collected from the complaint originator. .

Within one day of complaint receipt by PSMD/PSM, the PSMD/PSM shall enter the PQC in Global Complaints Management (GCM) and submit it to the supplying site for investigation. PSMD/PSM shall send the complaint sample (if available) to the supplying site for investigation.

When a PQC indicates that it was associated with an AE, lack of effect, actual or potential medication errors, off-label use and misuse, the report is entered in two databases - the GCM and JASPER. Data entry in GCM and JASPER is performed by the PSMD/PSM. The PSM enters the GCM number associated with the PQC in JASPER (PQC tick box should be checked and GCM number added) and submits the report to the Data Entry Site as per timelines specified on Table 1 of the Patient Safety Standards SOP. When the report is incomplete, the PSM or PSMD conducts follow-up to obtain the complete information from the reporter. The follow-up is conducted as per the SOP 'Obtaining follow-up information on Adverse Event Reports'.

On a monthly basis, PSM runs the applicable Business Objects report in SAPPHIRE. This report highlights cases reported to DES as PQCs with no associated GCM complaint ID number captured. During the review, if no GCM number is spotted for the cases reported to DES as PQCs, the PSM is responsible for extracting the GCM complaint ID number and forwarding this information to the DES as soon as possible.

7.3 Periodic Safety Update Reports

According to the Local Regulatory requirements, the Periodic Safety Update Report (PSUR) to be submitted every six months for the first two years after approval of the drug is granted to the applicant. For the next two years, the PSURs to be submitted annually. The Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSUR due for the period must be submitted within 30 calendar days of the last day of reporting period.

For global AstraZeneca products when the PSUR is posted in GEL, the AZPIL regulatory affairs team receives a notification regarding the posted PSUR. AZPIL regulatory affairs team extracts the PSUR from GEL. The AZPIL regulatory affairs team is responsible for submission of the PSURs to the local health authority and filing a copy of the submitted PSUR with the cover letter in the AZPIL regulatory affairs files. AZPIL regulatory team is also responsible to coordinate with Global Submission Management Group to track the submission of PSUR in the Global Electronic Library/Submission Lifecycle Management.

For Products of Local Opportunity (PoLOs) which are marketed by AZPIL in India, if AZPIL is required to submit the PSURs to local health authority, AZPIL regulatory affairs team is responsible for scheduling, preparation, review, finalisation, approval and sign-off and follow-up of PSURs using the templates/guidance documents associated with International Procedure Periodic Safety Update Reports and Related Reports. The AZPIL regulatory affairs

team is responsible for submission of PSURs for PoLOs to the local health authority, archiving and tracking of submission.

For PoLOs wherein AZPIL has a Quality Assurance agreement signed with vendors, the PSUR submission to local health authority will be handled as per the safety clause in the Quality Assurance agreement.

8. PROCESS FOR PATIENT SAFETY MANAGER BACKUP

In the event the PSM is on leave, business travel or sick etc. the PSM should inform the Medical Director and PSMD. The PSMD will take the responsibility to perform the activities of the PSM. The PSMD shall contact the PSM in case of any clarifications are required related to the PSM activities.

9. LOCAL SAFETY AGREEMENTS

Local Safety agreements are a part of the quality assurance agreements and are created with inputs from the PSM, Legal and Regulatory departments.

The PSM communicates details of local licensing agreements to Patient Safety Processes & Standards team as applicable. The agreements are reviewed biennially and change if any communicated to the Global Patient Safety team. These reviews and changes related to the agreements are documented by PSM.

10. TRAINING

The PSM is responsible for Adverse Event and PQC Reporting training. All classroom trainings provided by PSM are documented in the 'Classroom Training Signature List (LDMS_001_0026809)' and filed. All trainings completed through AZLearn are documented in AZLearn. Training completed through WebEx and Teleconference are documented in MC Patient Safety file.

10.1 Clinical study delivery team

New member in the AZPIL Local Study Delivery team undergo training in the SOP "Adverse Event Reporting in Clinical Studies" through the AZLearn. The PSM to ensure the training is complete and clarifies doubts if any. The PSM should provide the training to the new member in the AZPIL Local Study Delivery team on SAE reporting in clinical studies managed by AZPIL. The clinical study delivery team should also complete the training as described in section 10.3.

10.2 CRO study delivery team

The External Provider Management Team (EPMT) Study Delivery Lead is accountable and responsible for the execution of the training and will provide the training material to the

CRO. By using the Train the Trainer concept, the CRO identifies super trainers or equivalent within the CRO organization, who are responsible for performing ongoing training for the CRO staff.

10.3 Employees of AZPIL

Training on ‘Adverse event and product quality complaint awareness’ for the new employees is provided by the PSM in their induction program or through AZLearn. The Adverse Event Report form and a “Wallet Card” on Adverse Event reporting are made available to all trainees at the end of the training session. All employees complete their annual refresher training in the sales and marketing strategy brief meetings or through AZ Learn. For the new employees who do not have access to the AZLearn, the refresher training is provided through classroom training. PSM provides the adverse event and product quality complaint awareness training to the line managers of the employees who do not have access to computers or AstraZeneca e-mail, these line managers train their reportees who have no access to AstraZeneca e-mail or computers.

10.4 Patient Safety Manager

The Global Patient Safety team are communicated of any new patient safety starters in AZPIL. The new starter should complete the MC Safety Manager – New Starter Training Checklist. Any new starter is responsible for ensuring that their training records are updated at all times as per the Global Clinical Quality Framework (CQF) Overall Training Grid. This requirement is also mandatory for any current patient safety staff. The CQF Overall Training Grid can be found in the Product Knowledge Transfer (PKT) Library (<http://pktlib.ta.astrazeneca.net/index.jsp?id=090082f181f8eed4&action=view&format=native&latest=true>). If the new starter is not sure whether a global Core procedural document is applicable to their role or not, they should contact the MC Medical director or designee. An exemption procedural form should be signed in this case and kept on the individual's local training folder. Updated, signed and dated copies of their CV and Job description should also be kept in this folder. Training on global and local Patient Safety procedural documents should be recorded in the AZLearn. Any additional training that cannot be recorded in AZLearn should be kept in the individual's training folder. Assistance on training on global procedural documents can be provided by the Global Patient Safety Marketing Company & Partner Interfaces team upon request. For new starter, a competency assessment is performed by the MC Medical Director or a designate. Competency is assessed with respect to submission of AE reports to DES, regulatory authority, periodic reporting to regulatory authority, safety surveillance, literature review, local quality control and local licensing agreements.

New starters and current patient safety staff is also responsible for ensuring that they have self read and understood all applicable local health authority regulations in their country. Training records related to this training should be kept in their training folder.

11. AFTER HOURS PROCESS - PATIENT SAFETY PERSONNEL CONTACT DETAILS

PSM is responsible for adequate after hours process(es) for situations such as requests for emergency unblinding for AZ sponsored studies or requests for safety information by local regulatory authority or healthcare professionals or patients.

11.1 Clinical Studies

For any afterhours needs, in AZ sponsored clinical studies, the nominated AstraZeneca representatives (AZPIL Local Study Delivery team member/PSM/PSMD) are to be contacted for the concerned studies. The list of after hours contacts can be found in the Business Continuity Plan (BCP) file at the PSM desk and AstraZeneca Pharma India Ltd.

11.2 Marketed Products

For any emergency related to marketed products and any compassionate use of AZ products, PSM have to be contacted. The contact details are incorporated in the AstraZeneca Pharma India Ltd., telephone contact board number.

The caller during afterhours is directed to dial the PSM extension number. The call from the PSM extension number is auto transferred to PSM's mobile number. For the calls received during afterhours, the date and time of after hours calls, person requesting the information, person contacted and details of the conversation are documented by the PSM.

12. LITERATURE SEARCH

DCGI does not require or expect Pharmaceutical companies to perform local literature reviews for the purposes of identifying ADRs related to AZ products marketed in India. Additionally, there are also no Indexed Medical/Pharmaceutical Journals in Indian languages and the relevant Indian English Journals are routinely reviewed by the global patient safety literature search team. Therefore, no active literature search is performed at AZPIL for any global products or Product of Local Opportunity (PoLOs) marketed by AZ in India or anywhere else in the world. PSM reviews at least annually the list of Indian journals searched by DES. Any case reports identified from other publications/media/non-indexed journals will be reported within the required timelines to the Data Entry Site through JASPER within the required timelines as per table 1 of the Patient Safety Standards SOP.

13. PRODUCTS OF LOCAL OPPORTUNITY (POLOs)

If AZPIL is responsible for submitting the required reports to the regulatory authority, any spontaneous reports received are entered in JASPER and submitted to DES by PSM as per timelines described in table 1 of the Patient Safety Standards SOP. If the report is a SUSAR, the PSM expedites the report to DCGI with the data elements of Appendix XI of Schedule Y of Drugs and Cosmetics Act. The respective therapy area Medical Affairs

Manager is responsible for performing the medical review and writing the company clinical comment for SUSARs; these should be submitted to the DES before the CIOMS is generated.

If the vendor is responsible for expedited reporting to regulatory authority as per the safety reporting section of the quality assurance agreement, all spontaneous reports received by AZPIL are sent to the vendor within the timelines specified in the safety clause of the Quality Assurance agreement, they are tracked in JASPER but not sent to DES.

The prescribing information of the PoLOs will be reviewed as per the local Procedure for Management of Core Product Information.

14. LOCAL PRODUCTS LIST

The PSM quarterly requests from the Regulatory Director or a designate an updated list of AZPIL products marketed in India. Any relevant updates for PoLOs marketed in India are immediately communicated to the MPL manager. Refer to The Product Master List 8-P87-(current version)-X International Procedure for additional information.

15. PRODUCT RECALL

A product shall be recalled from the market when a Product Quality Issue presents a serious risk to the health of the consumer, may adversely impact AstraZeneca (e.g. due to a Good Manufacturing Practice compliance or licensing failure), when a notification is issued by the local health authority to recall the product, or when there is suspected/actual tampering by a third party. Any Product Quality Issue that is brought to the attention of the PSM by external customers or health authority is immediately communicated to the AZPIL Recall Coordinator and Medical Director. Further information on the local recall process can be found in the local SOP 'Product Recall (LDMS_001_00157185)'.

16. CHANGES IN PATIENT SAFETY STAFF

Any changes in PSM staff and AZPIL Patient Safety procedures should be communicated as soon as possible to the Global Patient Safety team by the PSM or Medical Director.

17. NOTIFICATION OF POSSIBLE LITIGATION AND URGENT SAFETY CONCERN

The PSM is notified immediately of any threatened, possible or actual legal action concerning an AE or other safety issue associated with an AZ marketed product or the named patient use / compassionate use of an AZ product in India. The PSM informs the Medical Director. The AZ Global and local Legal departments are immediately notified

and actions taken, as appropriate. Notification is documented and retained with the other case information.

In the event of an urgent safety concern that poses a real, impending and important threat to patients, a product or the business, or one where the company does not have full control but seeks to limit its impact, the PSM informs the Medical Director and the Global Patient Safety team of the urgent safety concern. In consultation with the Global Patient Safety, the PSM ensures immediate notification of urgent safety concern to local health authority.

18. MARKETING ACTIVITIES

Respective therapy area Medical Affairs Managers should inform the PSM of any marketing activities in their therapy area such as organized data collection programmes, patient support and disease management programmes, registries, market research, digital listening activities, surveys of patients or healthcare professionals, which may result in adverse events (including lack of efficacy, drug exposure during pregnancy, drug overdose, drug misuse, medication errors, suspected drug interactions, PQC reports, and suspected transmission of infectious agent) that might be identified during the course of the activity, whether actively sought (i.e. as a solicited report) or simply reported on a voluntary basis to AstraZeneca (i.e. as 'stimulated' or 'spontaneous' reports). PSM should review such activities and incorporate the process to ensure appropriate collection of spontaneous and PQC reports. Further information on collection of safety information can be found in the international procedures: 7-P25-(current version)-X Requirements for Reporting of Adverse Events arising from Digital Listening Activities and 7-P23-(current version)-X: Requirements for collection of Adverse Events during Organised Data Collection Programmes.

19. RECONCILIATION OF REPORTS

All reports (initial and follow-up) submitted to DES are acknowledged by via an automated e-mail to 'Patient Safety, India' mailbox within 24 hours of submission. PSM is responsible for receiving and keeping these acknowledgements. The Sapphire case ID is added to report in Jasper. If a report is submitted and acknowledgement is not received or Sapphire case ID is added in Jasper within 24 hours, the PSM should confirm receipt of the case by checking case details in Bob Infoview or contacting DES.

19.1 Clinical Studies

Serious adverse events from clinical studies are sent for data entry onto SAPPHIRE. All information is also stored in the clinical study database. It is important that data is consistent in both databases.

For global studies, there is a global process to ensure data is reconciled in the two databases and is done by the global study team. For local studies, consistency checks between the

databases are performed by the local study delivery team at least monthly to ensure data is reconciled.

The following fields are required to be consistent in both the SAPHIRE and clinical databases:

- Case identifiers
- SAE, preferred term
- Causality assessment to investigational product and study procedure
- Outcome
- Serious criteria

It is the responsibility of the local study delivery team to ensure that a reconciliation process is in place for each study and to ensure that this is documented. Reconciliation must be performed on at least a monthly basis during the study with a final reconciliation performed at the end of the study. All reconciliation activities must be documented even when no SAEs have been found.

Study Teams can run Reconciliation Report from SAPHIRE Bob {Cases Clinical Events in Clinical Trials (list of cases)} themselves which they can then use to perform reconciliation. If the study delivery team members do not have access to SAPHIRE, Reconciliation Report from SAPHIRE Bob can be requested from the PSM.

19.2 Marketed Products

The Medical Information Associates (MIAs) for all therapy areas are trained on local reporting process for spontaneous reports. All queries received by the MIAs from any sources (Med info mailbox, their AstraZeneca email, phone, letter or medical information toll free number) are captured in the medical information tracking log. This tracking log is maintained by the MIAs and saved in the shared medical folder ([\\inblmsfp01\medical\MEDICAL AFFAIRS 2009\Queries\Query Tracking Log](#)). The PSM is responsible for reviewing the log monthly to ensure that all reports have been appropriately reported to local Patient Safety.

The PSM should perform the reconciliation of the adverse event reports at least annually for the local marketing activities and digital listening activities ongoing for more than one year and reconciliation is considered necessary. Reconciliation will be done by comparing the supplier/agency list of reported cases received with those entered onto the AstraZeneca global safety database and any missing cases will be requested from the supplier/agency.

20. COMPLIANCE MONITORING

The compliance figures for the expedited reporting of adverse events to the health authority, Head of the Institution where the clinical trial is conducted and Chairman, Ethics Committee will be generated monthly by the PSM. The compliance figures of expedited reporting of adverse events to the health authority will be communicated to the Global

Patient Safety team. Compliance figures included in the compliance data maintained by Global Patient Safety will be communicated to the Medical Director/Regulatory Affairs Director.

PSM should assess the compliance to reporting timeframes for the cases submitted to DES and local health authority. If any late cases are identified, the PSM should investigate and determine the reason for the late reporting. PSM should communicate at least monthly the reasons for late case reports to Global Patient Safety team and AZPIL Medical Director/Regulatory Affairs Director. The PSM is responsible for documenting the cases that are submitted late to DES and local health authority. The PSM is also responsible for implementing the corrective and preventive actions for late reports.

The PSM is also responsible to maintain the local Patient Safety Quality Control planner and schedule.

21. REQUESTS FOR SPONTANEOUS REPORTS FROM LOCAL HEALTH AUTHORITY

On an annual basis, the PSM requests from the health authority all spontaneous reports directly received by the health authority associated with AstraZeneca products. These requests are filed in AZPIL Patient Safety files. The reports received from the health authority, are sent to DES as per required timelines specific in table 1 of the Patient Safety Standards SOP.

22. ORGANIZATIONAL CHARTS, JOB DESCRIPTION AND CURRICULUM VITAE (CVs)

The organization chart of the Patient Safety staff should be maintained by the PSM. Job description and CVs of the Patient Safety Staff are maintained by the respective staff members in their Training and Education Files. The organizational charts, job description and CVs should to be updated when necessary and reviewed at least annually. The organizational charts of Patient Safety staff should be version controlled.

23. INVESTIGATORS BROCHURE AND LOCAL PRESCRIBING INFORMATION

The AZPIL Local Study Delivery team should send the investigator's brochure and communicate any updates to the investigator's brochure to PSM. The Regulatory Affairs Director or a designate should send the prescribing information and communicate any updates to the prescribing information for any AZ products marketed in India to the PSM.

24. LIST OF STUDIES

The PSM should request the Head of AZPIL Local Study Delivery teams for the list of all phase I to IV studies run by the AZPIL. The list should be reviewed and any updates should be communicated to PSM. The AZPIL Local Study Delivery teams should inform the PSM of any Patient Safety obligations related to any clinical study approvals by the health authority.

25. REGULATORY INSPECTIONS

In the event of any regulatory inspections by the local health authority covering Pharmacovigilance activities, the PSM should inform the Medical Director/Regulatory Affairs Director and Global Patient Safety Pharmacovigilance Inspection Support team. The Medical Director/Regulatory Affairs Director should make the necessary arrangements for the inspections with the support from Patient Safety Staff and Global Patient Safety Pharmacovigilance Inspection Support team. The PSM should complete the inspection planner and checklist before the inspection.

26. ARCHIVING

Patient Safety Manager regularly archives the following documents:

- Training file of Patient Safety Personnel
- Adverse Event training records
- SOPs/ Operational Procedural Information (OPIs)
- Serious adverse event reports in Clinical study
- Adverse events reports from marketed products
- List of Marketed products at AZPIL
- Reports to Local Regulatory Authority

All the documents archived by the Patient Safety Unit are recorded into an excel table. The records are archived for the period as per the global procedural documents and for the period as per the Global Retention and Disposal Schedule. If any documents are retrieved from the Archive facility, the PSM maintains a list of documents retrieved along with reason for retrieval. All the retrieved documents are sent back to Archive facility after the purpose of retrieval is achieved.

27. LOCAL PROCEDURAL DOCUMENT MANAGEMENT

Local Patient Safety SOPs or OPIs are only developed when required to comply with a local regulatory requirements, local industry practice and global SOP/OPI.

The PSM is the “Content Owner” of local Patient Safety SOPs and these are approved by the AZPIL Medical Director. Local Patient Safety OPIs are approved by local “Process Owner” assigned by the AZPIL Medical Director.

All local Patient Safety SOPs and OPIs are approved and stored in LDMS and viewed using ProDoc in accordance with the Principles of the Clinical Quality Framework Global SOP. The Regional Asia Pacific Clinical Procedural Information Coordinator is responsible for uploading approved versions of local Patient Safety SOPs, OPIs and templates in LDMS.

The local Content/Process Owner is responsible for ensuring that the most updated version of local Patient Safety procedural documents are used at the MC and are in compliance with the most current local and Global regulatory requirements and Global SOPs/OPIs. Local Patient Safety SOPs and OPIs should be reviewed at least once a year, however urgent reviews may be required due to business critical changes.

If new information which may result in local procedural changes is identified, these are tracked locally by the Content/Process Owner and submitted to the PSM for evaluation.

The local Patient Safety procedural document management team is responsible for evaluating change requests received and deciding what actions should be taken in a timely manner. The team is constituted of the PSM, AZPIL Medical Director and if applicable, the local process owner.

Change requests received by the local Patient Safety procedural document management team are evaluated based on the following:

- The regulatory or business-critical drivers for the change
- The impact of the change on the local process
- The impact of the change on other local departments

The following decisions could be made by the local Patient Safety procedural document management team:

- Initiate immediate development of a new local SOP/OPI due to business critical changes which immediately affect the local way of working.
- Initiate fast track update of current local SOP/OPI or development of planned deviation.
- Put on hold: Creation of new SOP/OPI or update of current SOP/OPI is required but not urgent and can be actioned at a later stage, determined by the local Patient Safety procedural document management team.
- Withdrawal of current local SOP/OPI.
- Rejection of change request.

Final decisions are tracked and actioned accordingly by the assigned local Content/Process Owners.

A list containing old and current versions of all local SOPs/OPIs versions is maintained by the PSM, updated when necessary and reviewed at least annually. A hard copy of old versions of local procedural documents are kept and clearly marked as superseded.